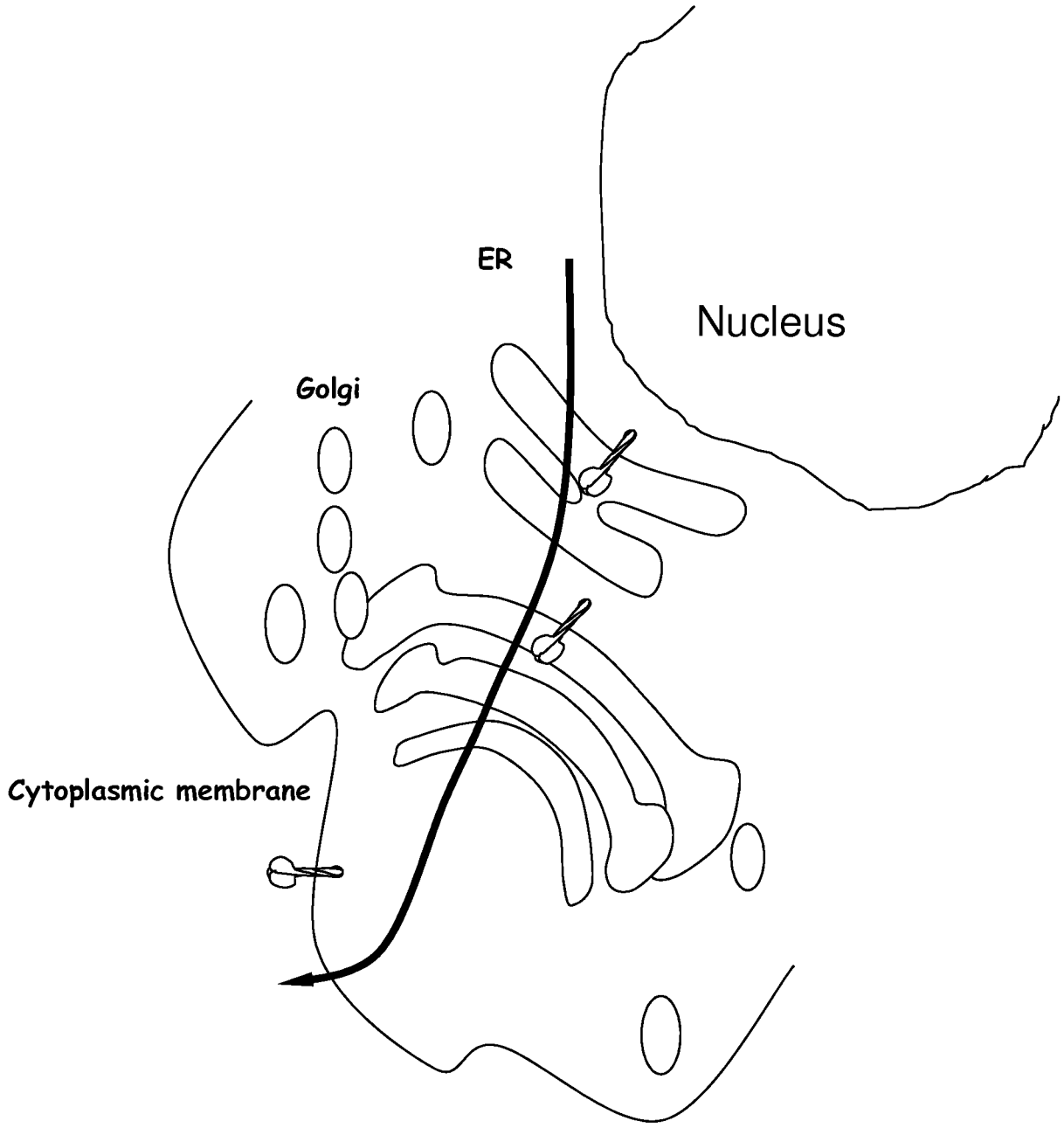
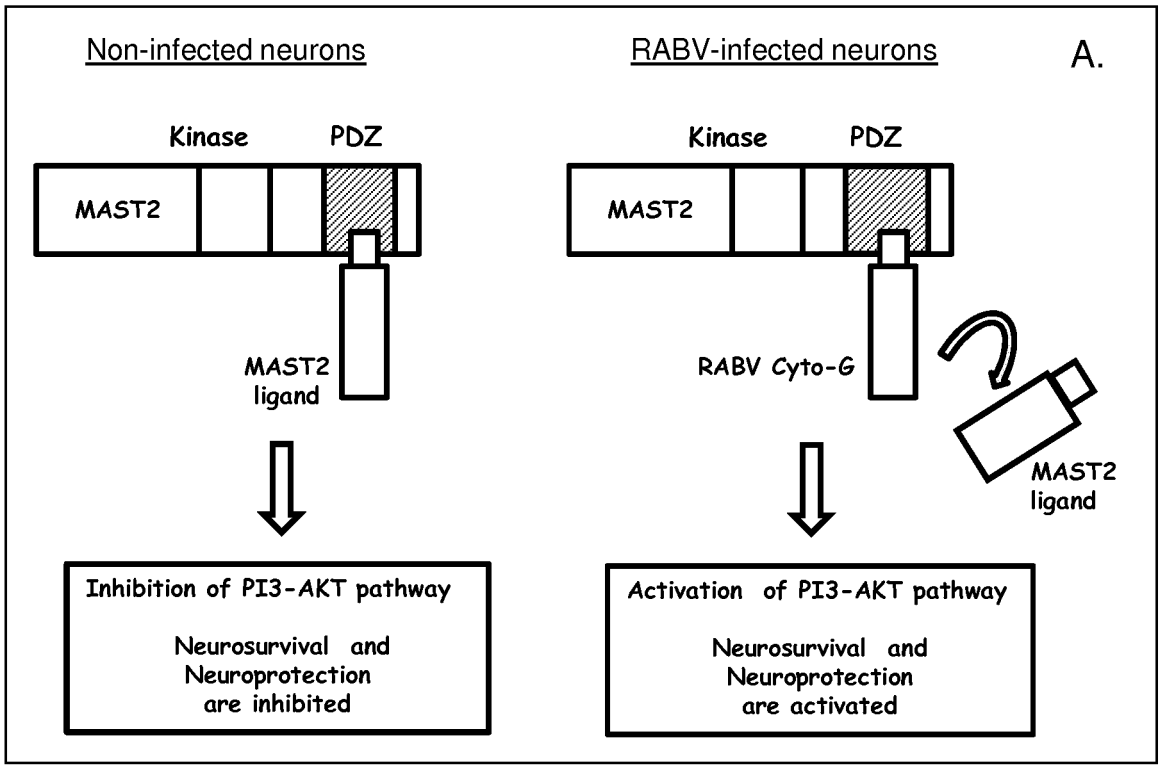


FIG. 1


Non-infected neurons
RABV-infected neurons
A.
Kinase
PDZ
MAST2
MAST2 ligand
RABV Cyto-G
Inhibition of PI3-AKT pathway
Neurosurvival and Neuroprotection are inhibited
Activation of PI3-AKT pathway
Neurosurvival and Neuroprotection are activated

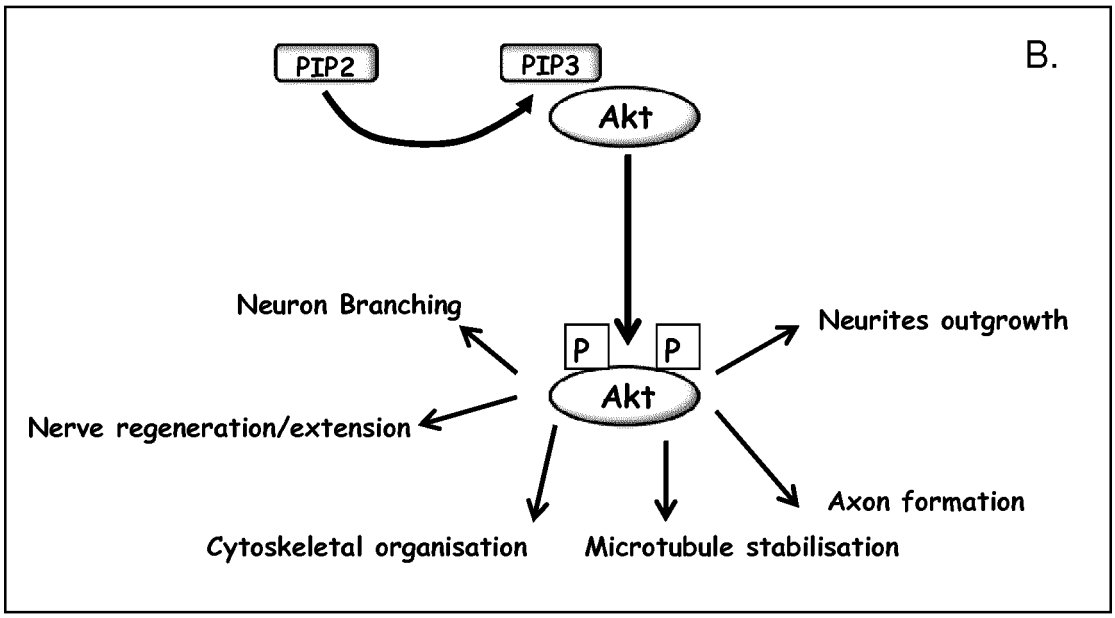
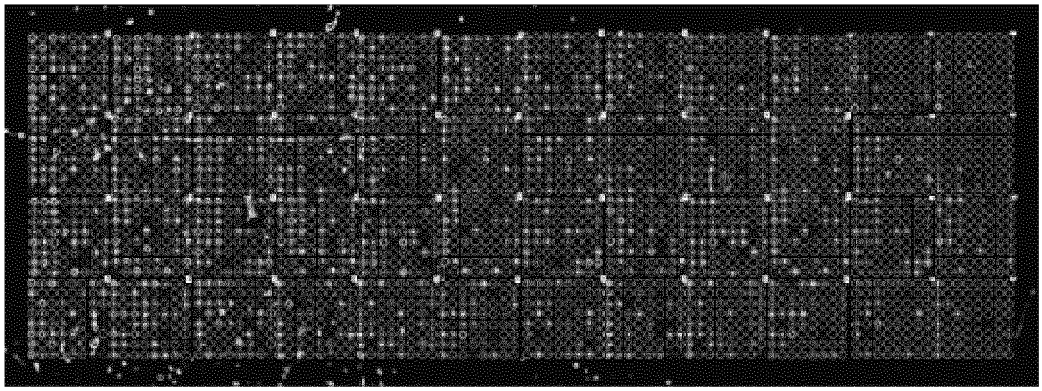

B.
PIP2
PIP3
Akt
Neuron Branching
Neurites outgrowth
P
P
Akt
Nerve regeneration/extension
Axon formation
Cytoskeletal organisation
Microtubule stabilisation

FIG. 2

A.



B.

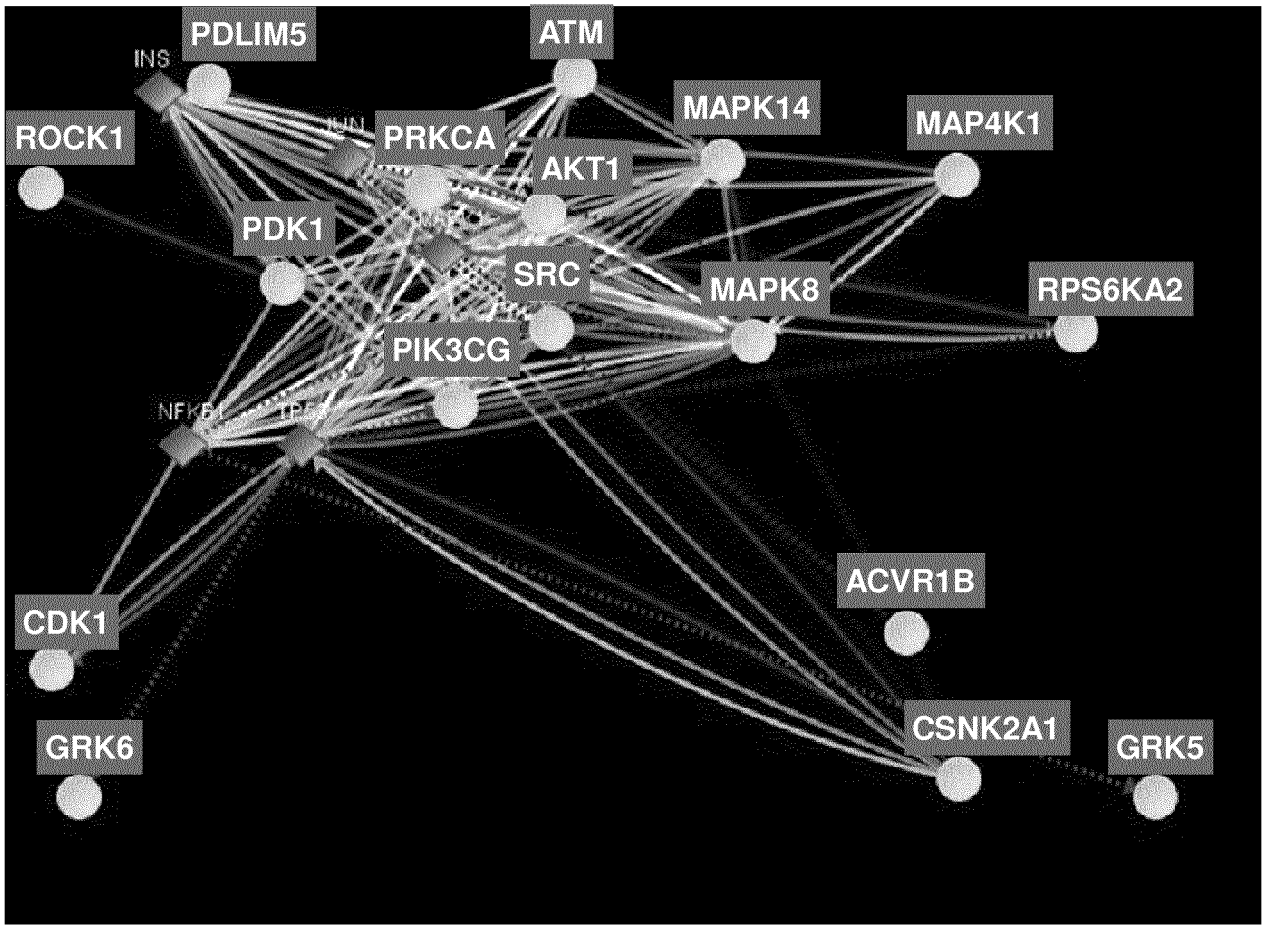
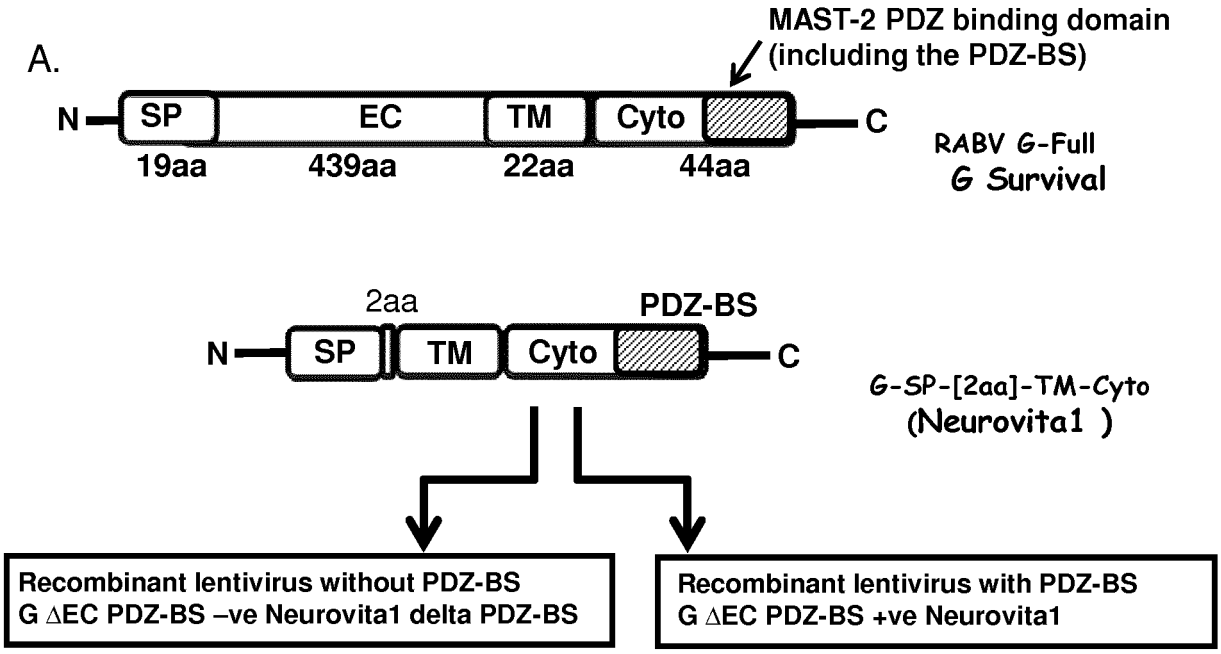
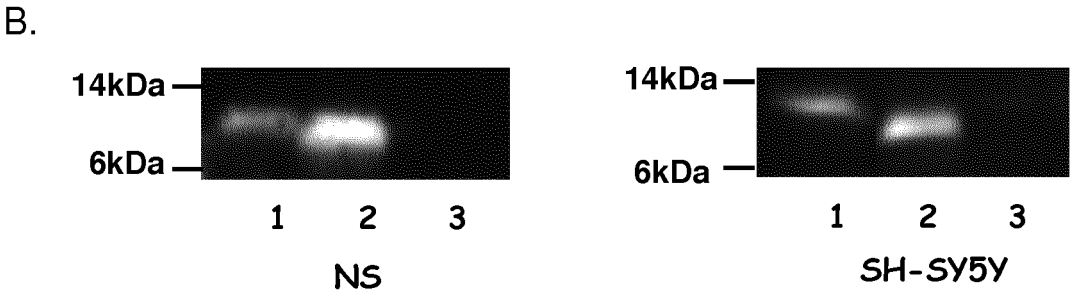

PDLIM5
ATM
INS
MAPK14
MAP4K1
ROCK1
JUN
PRKCA
AKT1
PDK1
SRC
MAPK8
RPS6KA2
PIK3CG
NFKB
ACVR1B
CDK1
CSNK2A1
GRK6
GRK5

FIG. 3


A.
MAST-2 PDZ binding domain
(including the PDZ-BS)
N
SP
EC
TM
Cyto
C
19aa
439aa
22aa
44aa
RABV G-Full
G Survival
2aa
PDZ-BS
N
SP
TM
Cyto
C
G-SP-[2aa]-TM-Cyto
(Neurovita1)
Recombinant lentivirus without PDZ-BS
G ΔEC PDZ-BS –ve Neurovita1 delta PDZ-BS
Recombinant lentivirus with PDZ-BS
G ΔEC PDZ-BS +ve Neurovita1


B.
14kDa
6kDa
1 2 3
NS
14kDa
6kDa
1 2 3
SH-SY5Y

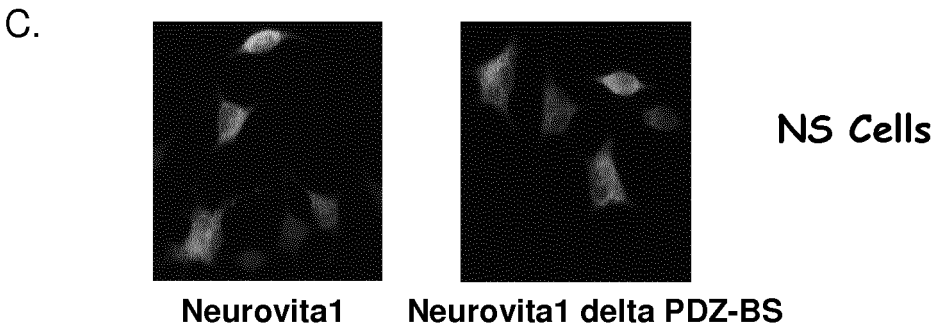
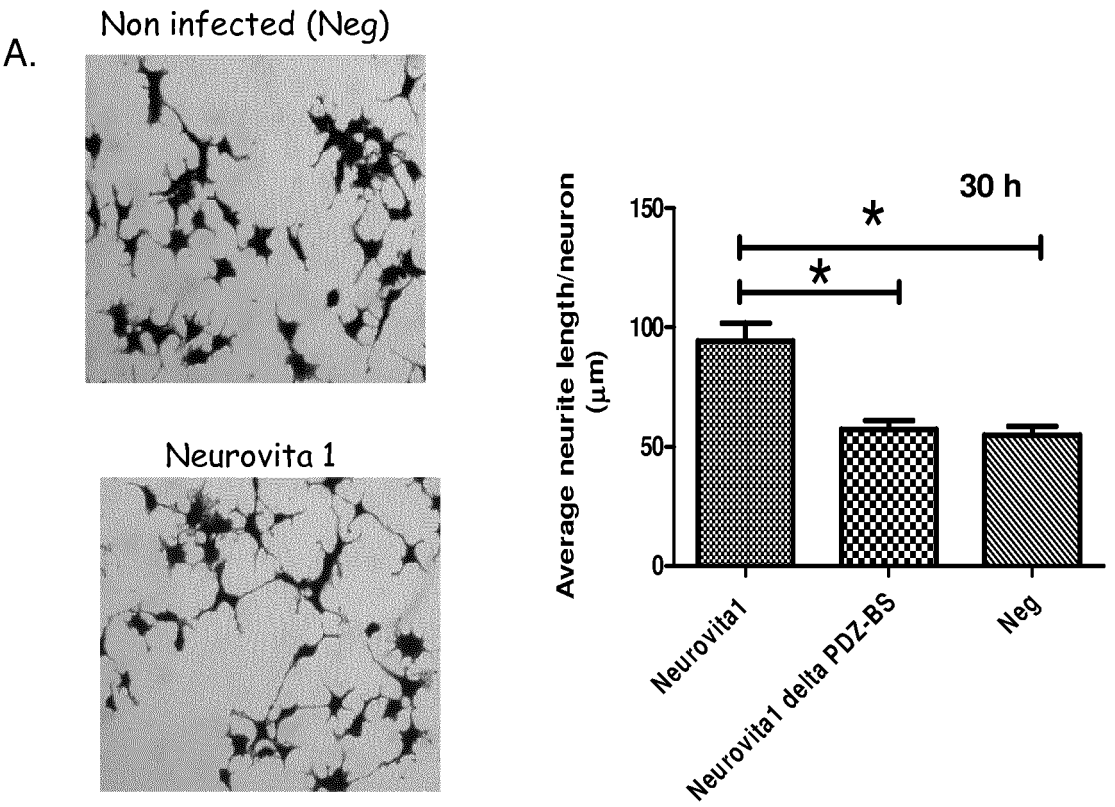

C.
NS Cells
Neurovita1
Neurovita1 delta PDZ-BS

FIG. 4

A.


Non infected (Neg)
Neurovita 1
30 h
*
*
Average neurite length/neuron (µm)
150
100
50
0
Neurovita1
Neurovita1 delta PDZ-BS
Neg

B.

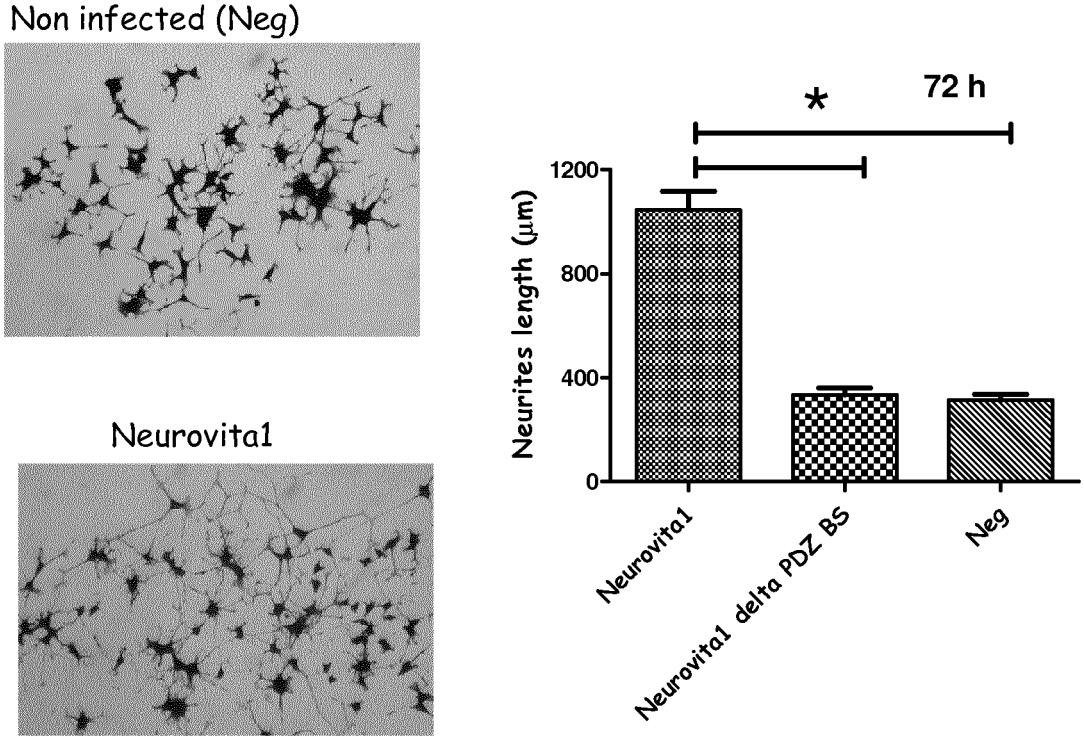
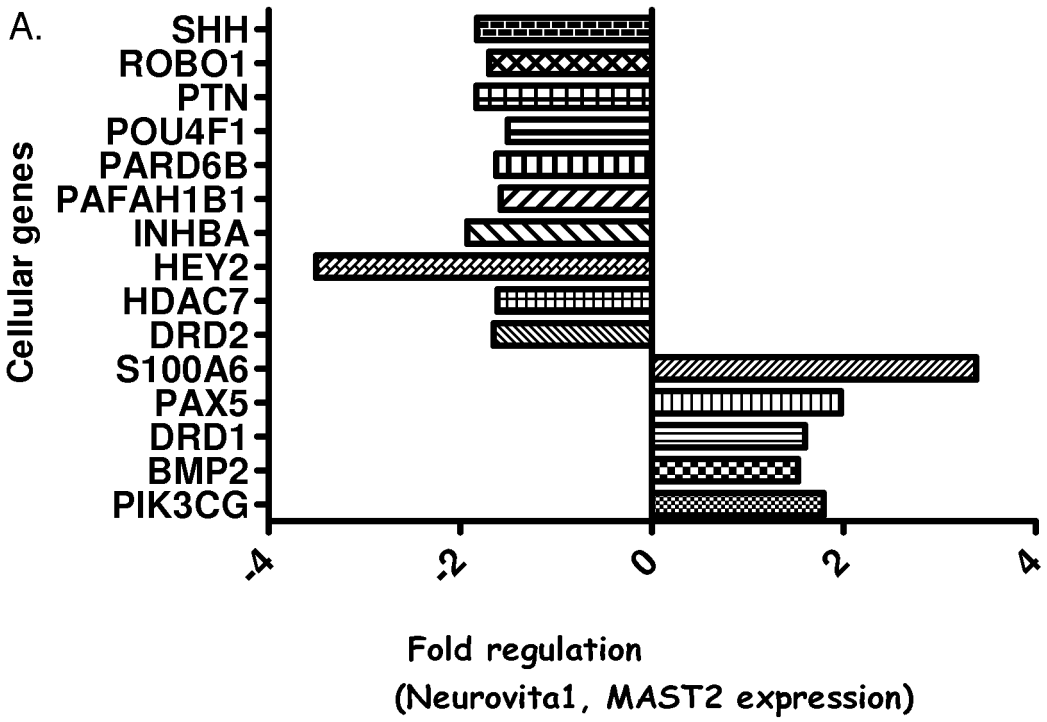

Non infected (Neg)
Neurovita1
72 h
*
Neurites length (µm)
1200
800
400
0
Neurovita1
Neurovita1 delta PDZ BS
Neg

FIG. 5

A.


SHH
ROBO1
PTN
POU4F1
PARD6B
PAFAH1B1
INHBA
HEY2
HDAC7
DRD2
S100A6
PAX5
DRD1
BMP2
PIK3CG
Cellular genes
-4
-2
0
2
4
Fold regulation
(Neurovita1, MAST2 expression)

B.

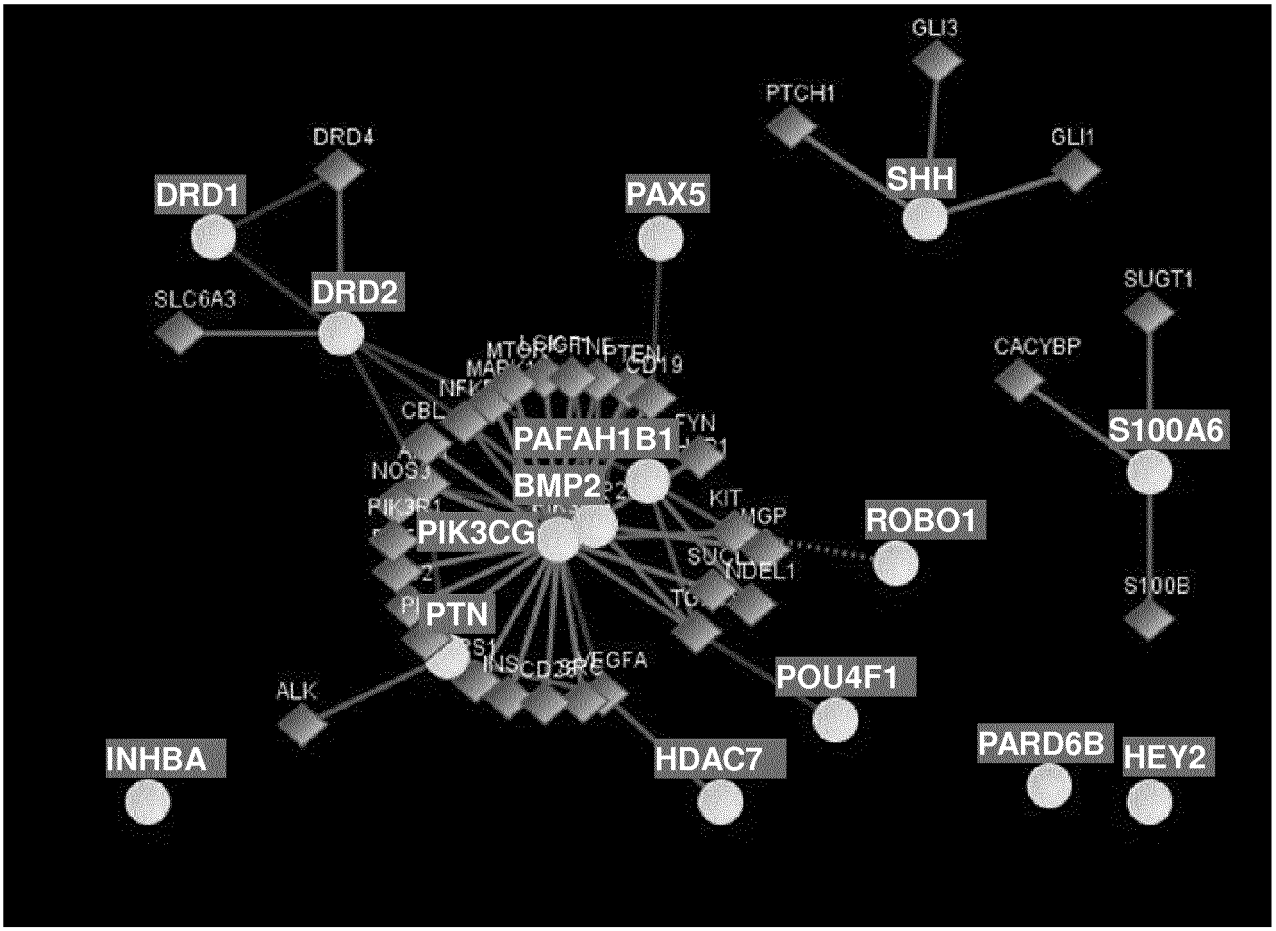

GLI3
PTCH1
GLI1
SHH
DRD4
DRD1
PAX5
SLC6A3
DRD2
SUGT1
CACYBP
S100A6
PAFAH1B1
BMP2
PIK3CG
ROBO1
S100B
PTN
POU4F1
ALK
INHBA
HDAC7
PARD6B
HEY2

FIG. 6

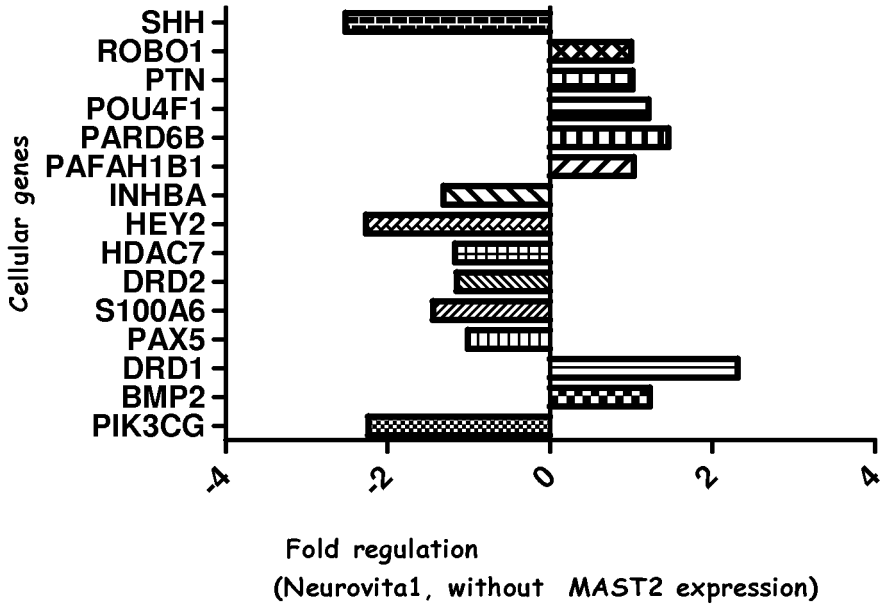

SHH
ROBO1
PTN
POU4F1
PARD6B
PAFAH1B1
INHBA
HEY2
HDAC7
DRD2
S100A6
PAX5
DRD1
BMP2
PIK3CG
Cellular genes
-4
-2
0
2
4
Fold regulation
(Neurovita1, without MAST2 expression)

FIG. 7

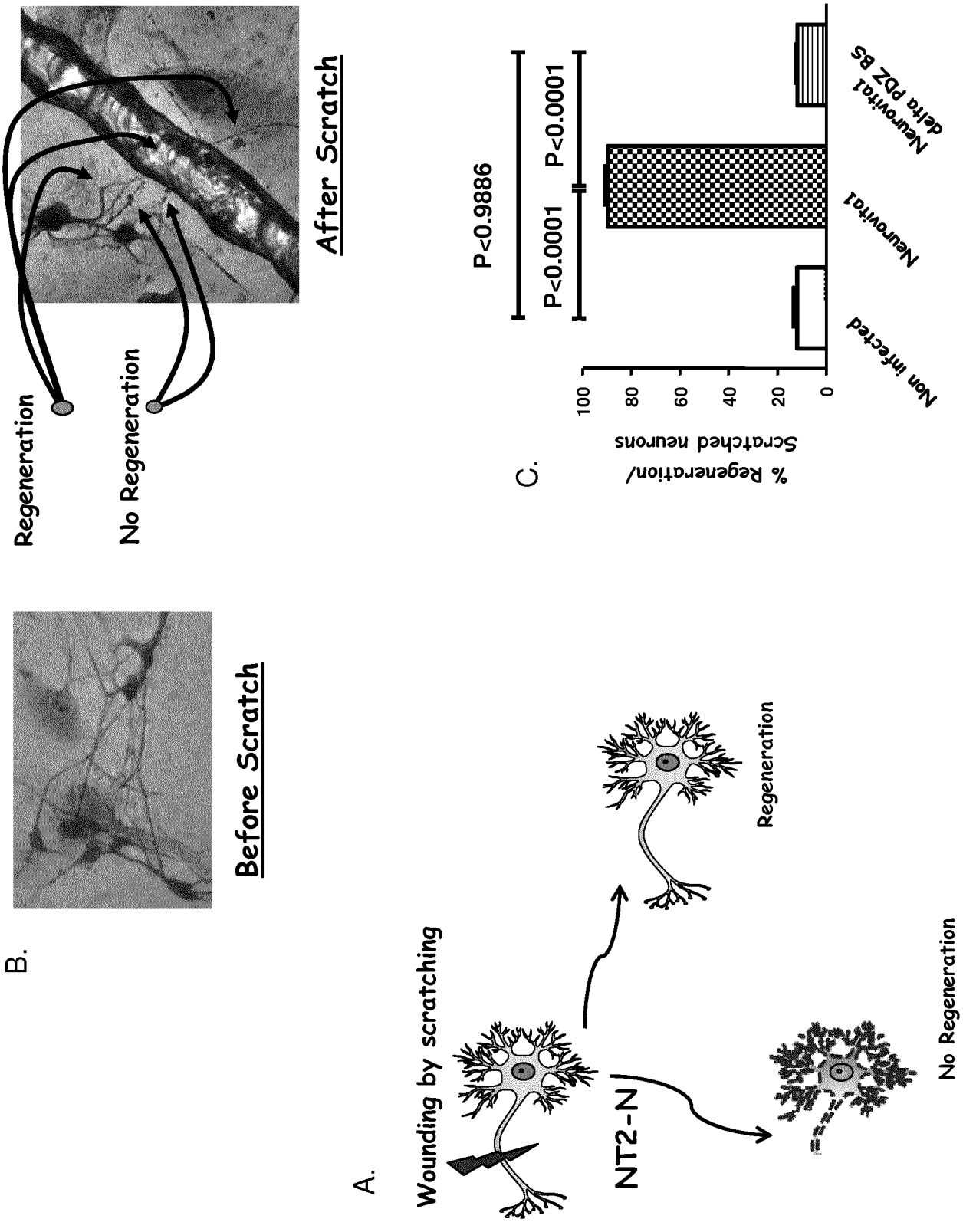
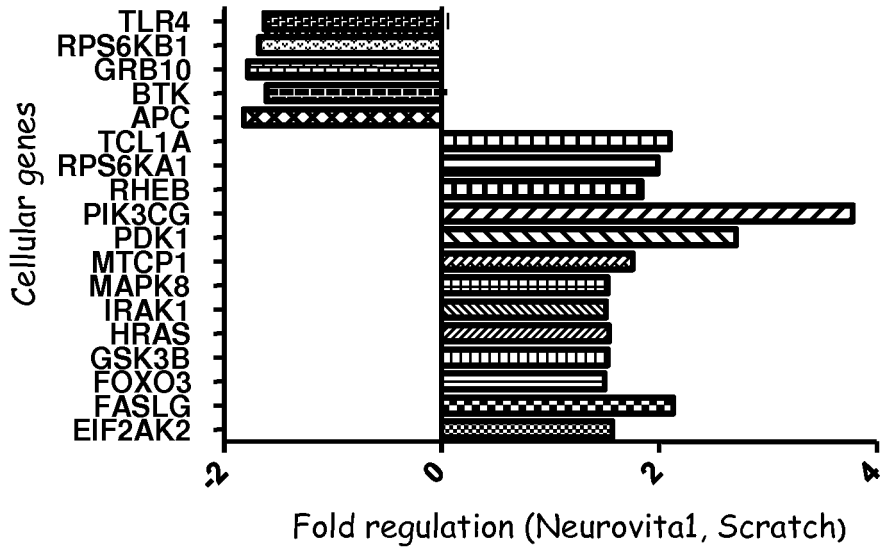
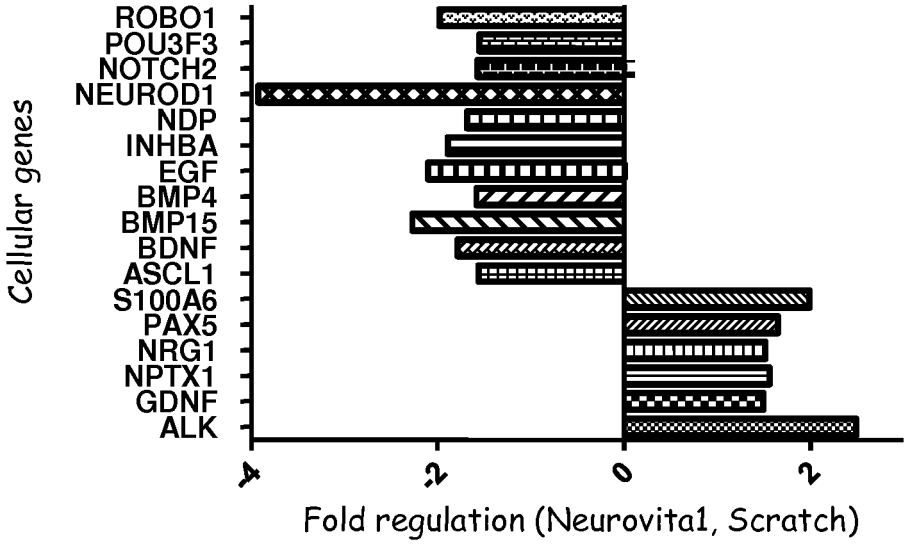

A.
Wounding by scratching
NT2-N
Regeneration
No Regeneration
B.
Before Scratch
After Scratch
Regeneration
No Regeneration
C.
% Regeneration/ Scratched neurons
100
80
60
40
20
0
P<0.9886
P<0.0001
P<0.0001
Non infected
Neurovital
Neurovital delta PDZ BS

FIG. 8

A.


TLR4
RPS6KB1
GRB10
BTK
APC
TCL1A
RPS6KA1
RHEB
PIK3CG
PDK1
MTCP1
MAPK8
IRAK1
HRAS
GSK3B
FOXO3
FASLG
EIF2AK2
Cellular genes
-2
0
2
4
Fold regulation (Neurovita1, Scratch)

B.


ROBO1
POU3F3
NOTCH2
NEUROD1
NDP
INHBA
EGF
BMP4
BMP15
BDNF
ASCL1
S100A6
PAX5
NRG1
NPTX1
GDNF
ALK
Cellular genes
-4
-2
0
2
Fold regulation (Neurovita1, Scratch)

C.

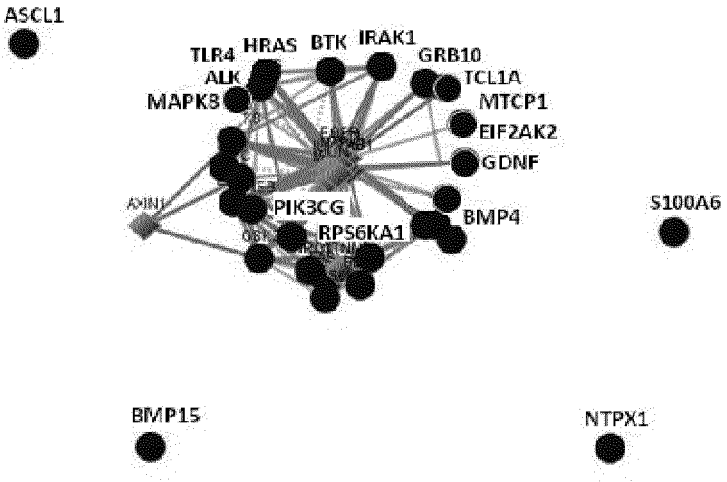
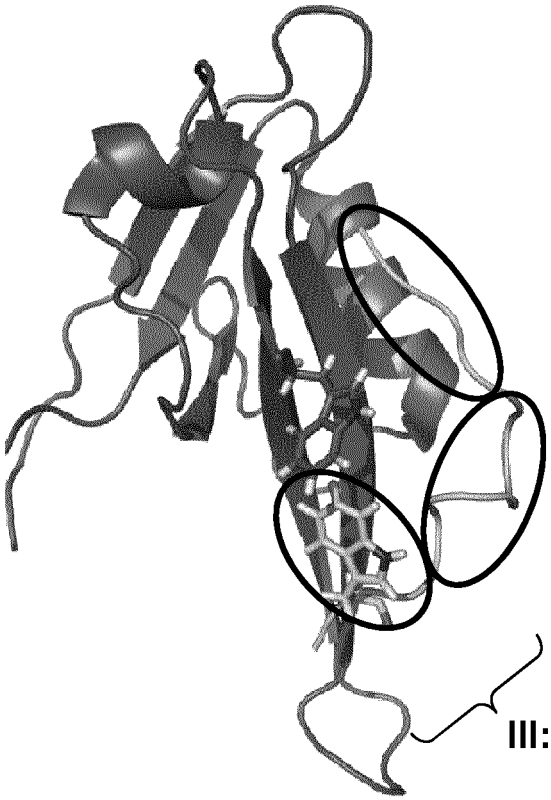

ASCL1
TLR4
HRAS
BTK
IRAK1
GRB10
ALK
TCL1A
MAPK8
MTCP1
EIF2AK2
GDNF
PIK3CG
BMP4
RPS6KA1
S100A6
BMP15
NTPX1

FIG. 9

A.

Neurovita1 sequence: $^{NH3+}$SWESHKSGGQTRL$_{COOH-}$

III II I



I: C-terminal anchoring (PDZ-BS)

II: Flexible linker

III: N-terminal Anchoring

B.

Dissociation constant (K_D) of the MAST2-PDZ/polypeptide complexes

Neuronal survival

Gain in affinity

Correlation

FIG. 10

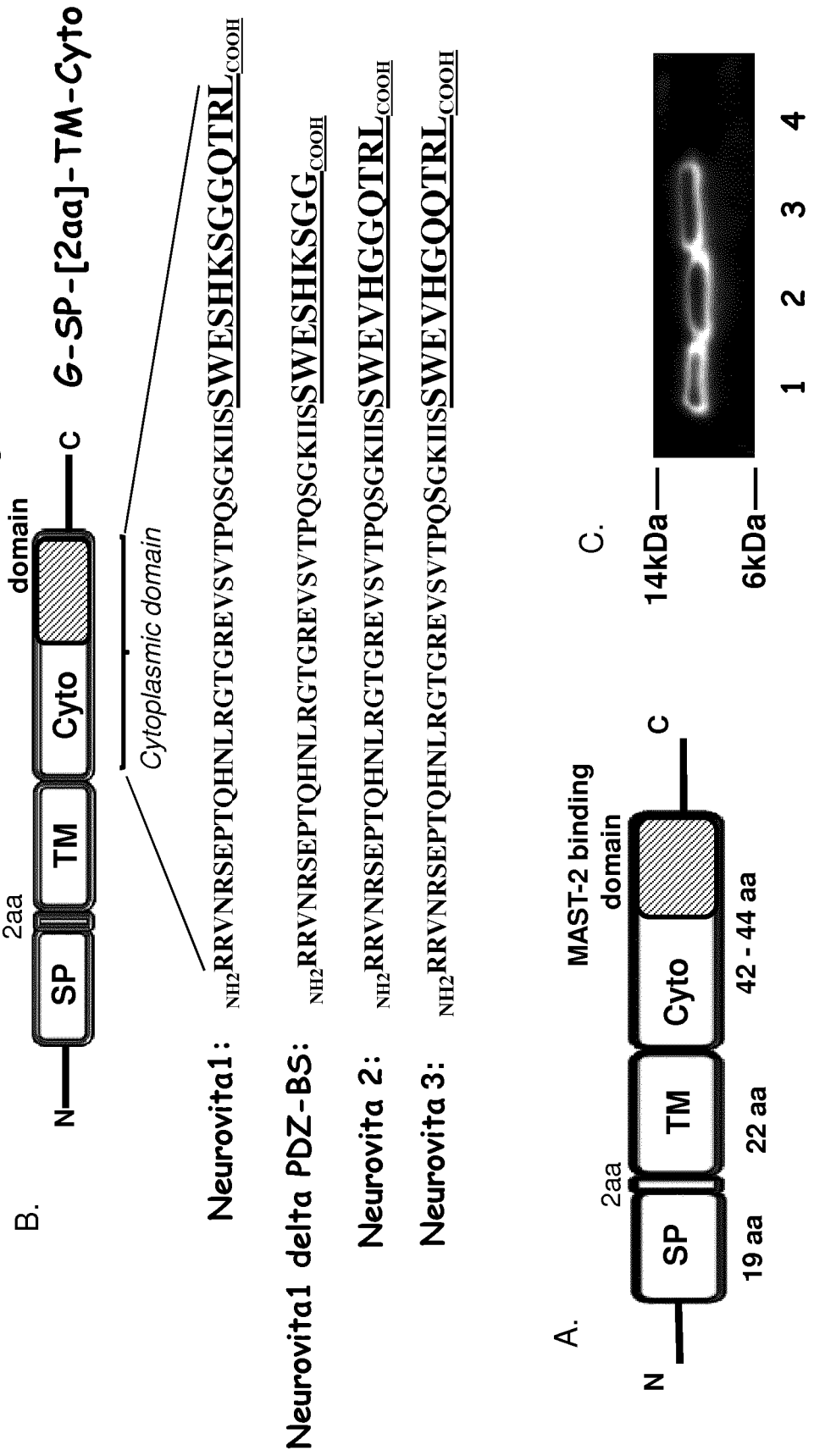
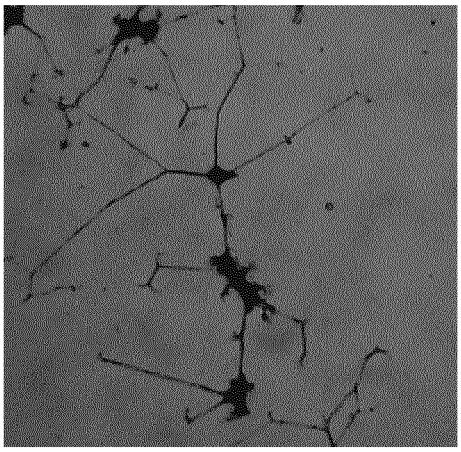
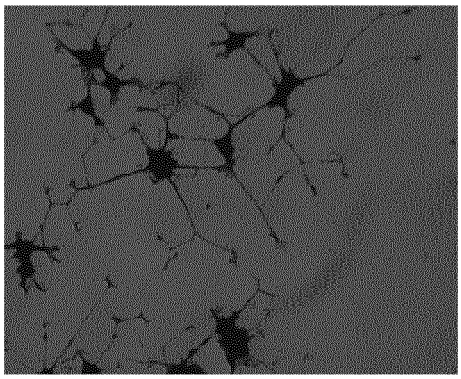

B.
MAST-2 binding domain
2aa
SP
TM
Cyto
N
C
G-SP-[2aa]-TM-Cyto
Cytoplasmic domain
Neurovita1: NH2RRVNRSEPTQHNLRGTGREVSVTPQSGKIISSWESHKSGGQTRLCOOH
Neurovita1 delta PDZ-BS: NH2RRVNRSEPTQHNLRGTGREVSVTPQSGKIISSWESHKSGGCOOH
Neurovita 2: NH2RRVNRSEPTQHNLRGTGREVSVTPQSGKIISSWEVHGGQTRLCOOH
Neurovita 3: NH2RRVNRSEPTQHNLRGTGREVSVTPQSGKIISSWEVHGQQTRLCOOH
A.
MAST-2 binding domain
2aa
SP
TM
Cyto
N
C
19 aa
22 aa
42 - 44 aa
C.
14kDa
6kDa
1 2 3 4

FIG. 11

A.



Neurovita1



Neurovita2

B.

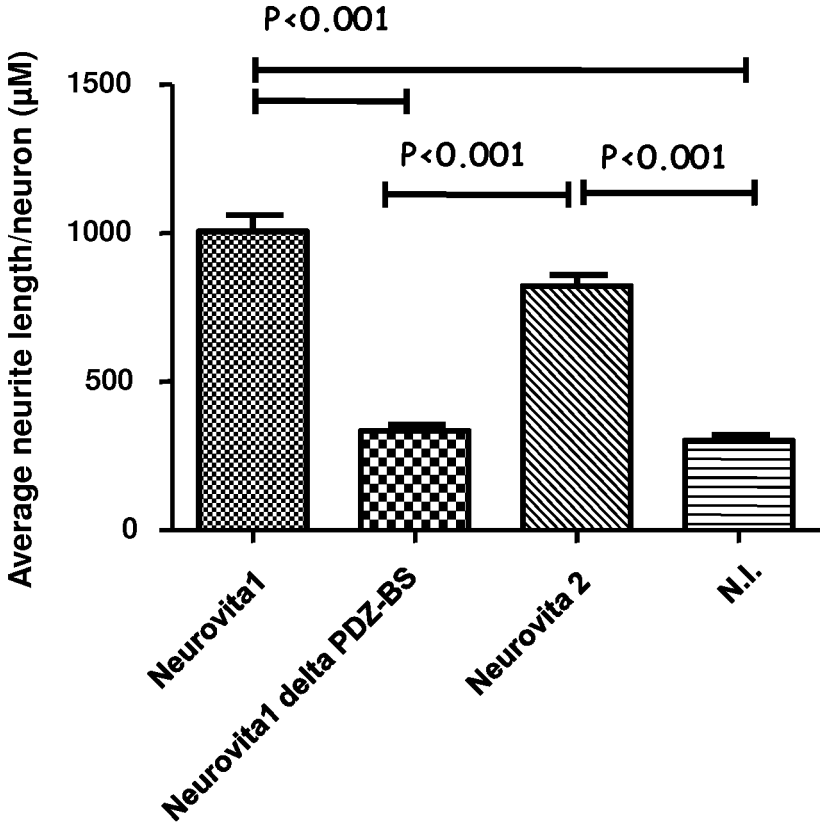


FIG. 12

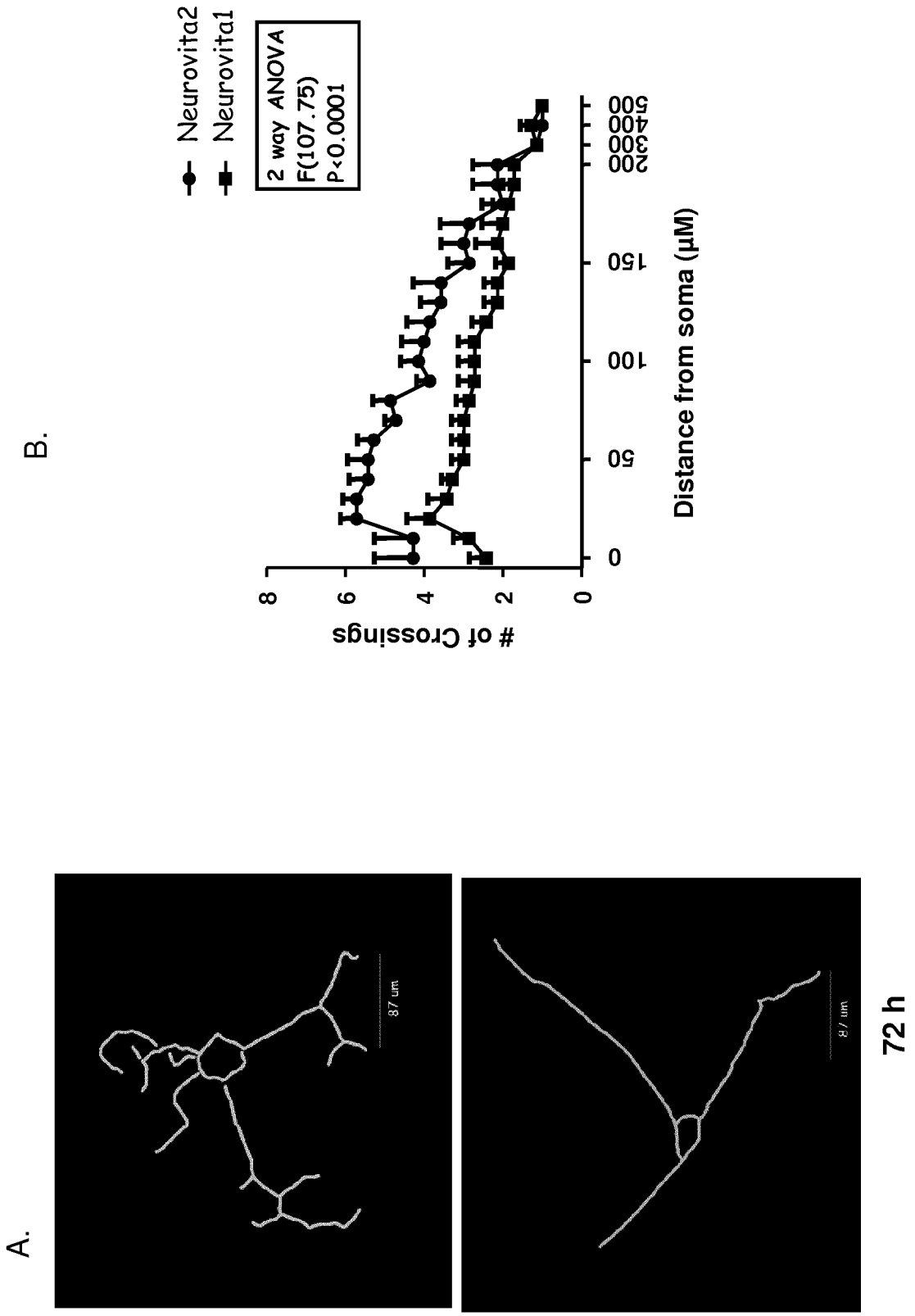
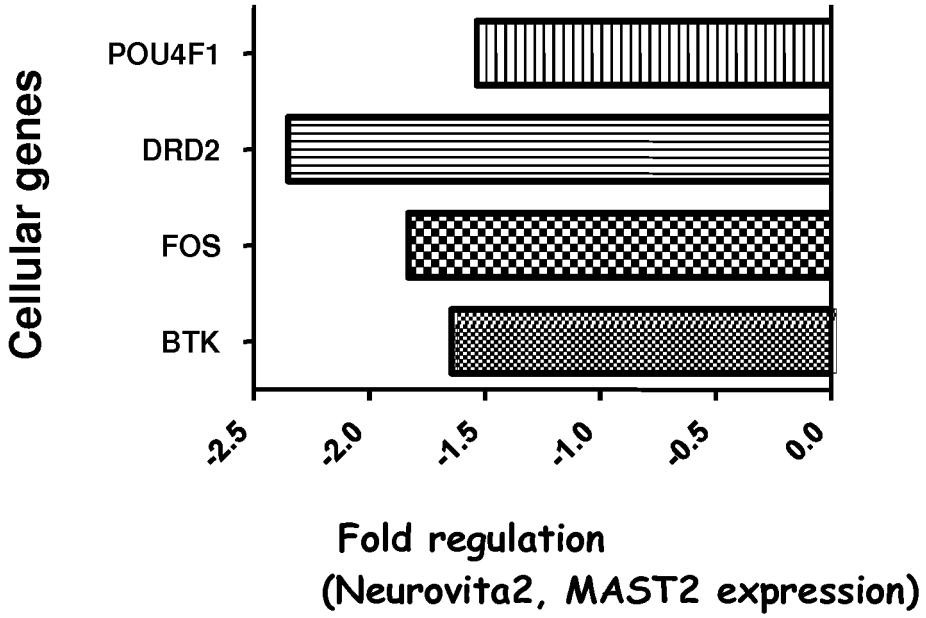

A.
87 um
87 um
72 h
B.
Neurovita2
Neurovita1
2 way ANOVA
F(107.75)
P<0.0001
# of Crossings
0
2
4
6
8
0
50
100
150
200
300
400
500
Distance from soma (µM)

FIG. 13

A.


Cellular genes
POU4F1
DRD2
FOS
BTK
-2.5
-2.0
-1.5
-1.0
-0.5
0.0
Fold regulation
(Neurovita2, MAST2 expression)

B.

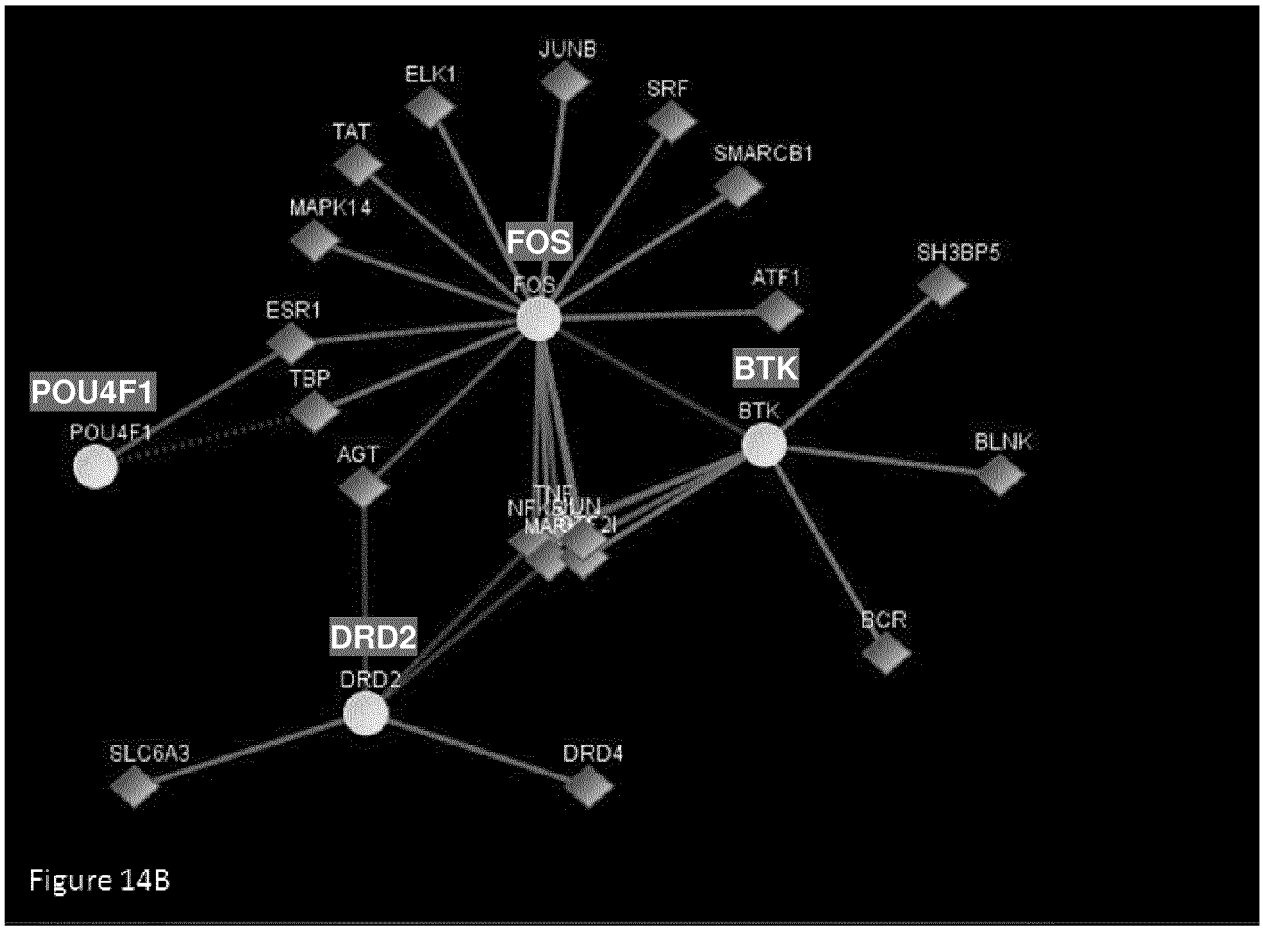
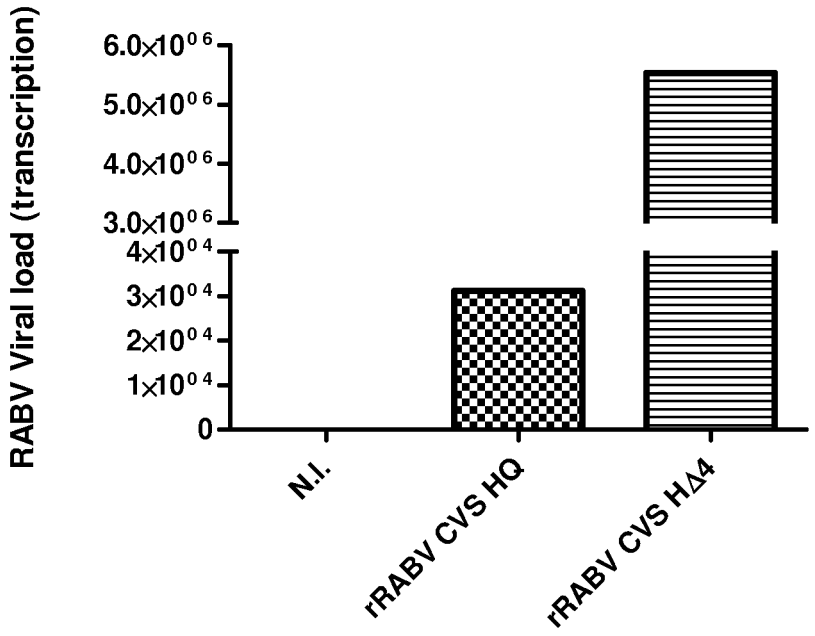

JUNB
ELK1
SRF
TAT
SMARCB1
MAPK14
FOS
FOS
SH3BP5
ATF1
ESR1
BTK
POU4F1
TBP
BTK
POU4F1
BLNK
AGT
BCR
DRD2
DRD2
SLC6A3
DRD4
Figure 14B

FIG. 14

A.


RABV Viral load (transcription)
6.0x10^06
5.0x10^06
4.0x10^06
3.0x10^06
4x10^04
3x10^04
2x10^04
1x10^04
0
N.I.
rRABV CVS HQ
rRABV CVS HΔ4

B.

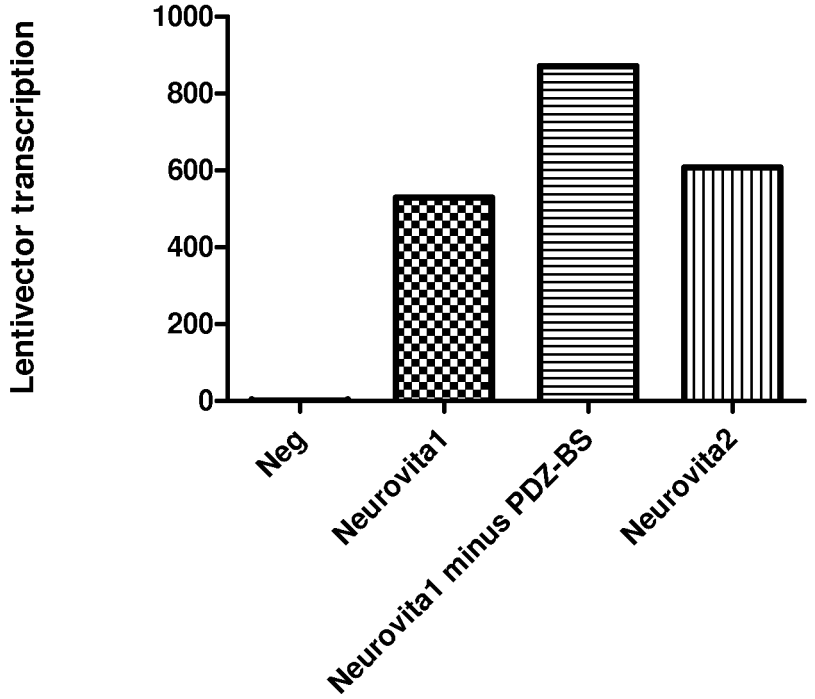
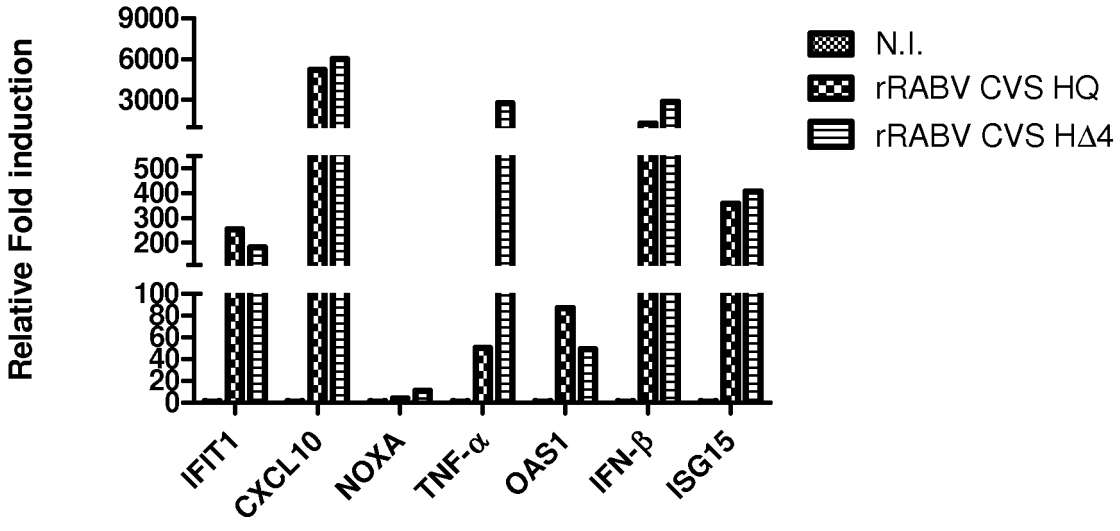

Lentivector transcription
1000
800
600
400
200
0
Neg
Neurovita1
Neurovita1 minus PDZ-BS
Neurovita2

FIG. 15

A.


Relative Fold induction
9000
6000
3000
500
400
300
200
100
80
60
40
20
0
IFIT1
CXCL10
NOXA
TNF-α
OAS1
IFN-β
ISG15
N.I.
rRABV CVS HQ
rRABV CVS HΔ4

B.

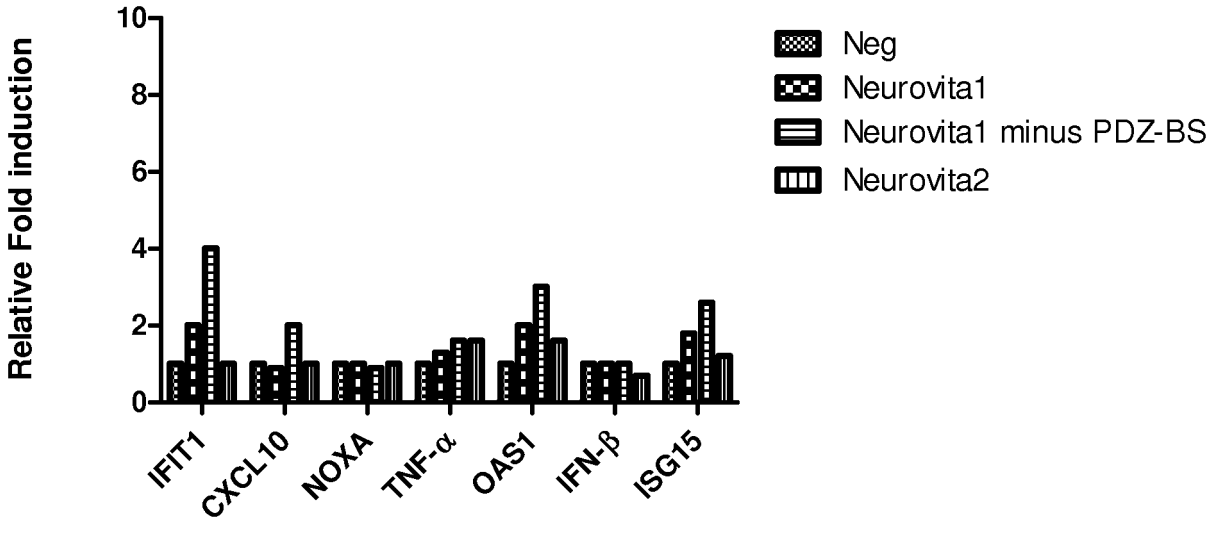

Relative Fold induction
10
8
6
4
2
0
IFIT1
CXCL10
NOXA
TNF-α
OAS1
IFN-β
ISG15
Neg
Neurovita1
Neurovita1 minus PDZ-BS
Neurovita2

FIG. 16

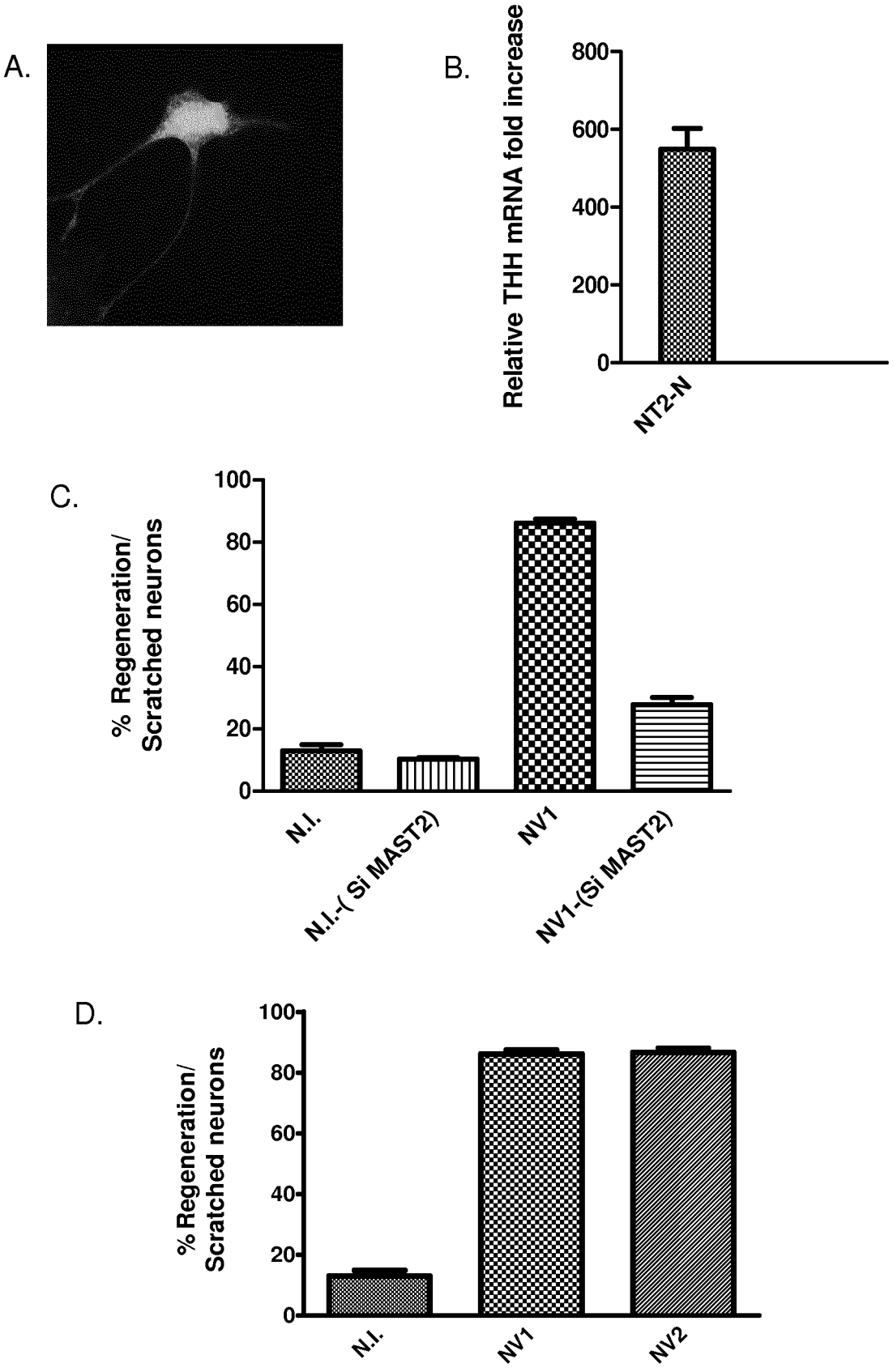
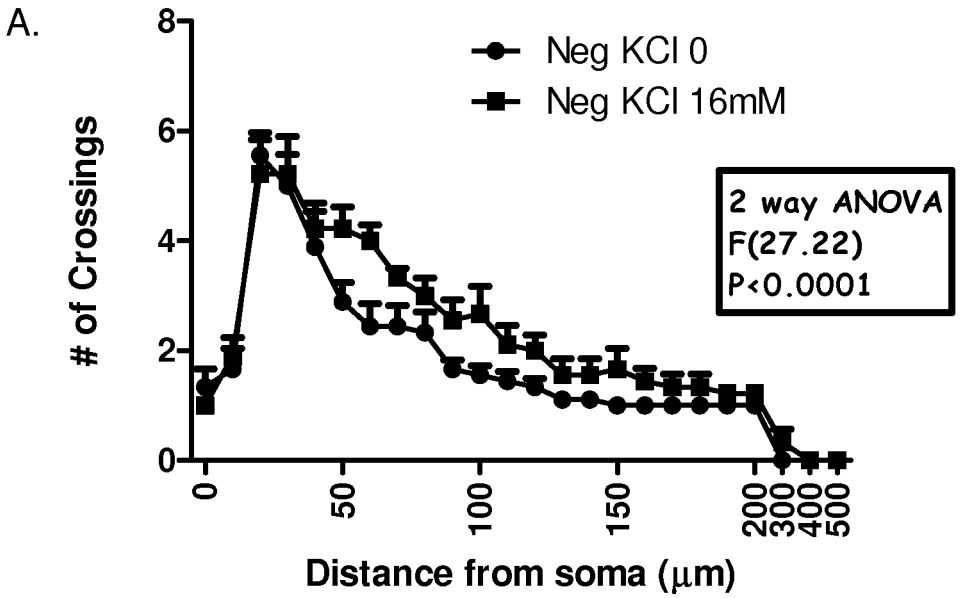

A.
B.
Relative THH mRNA fold increase
800
600
400
200
0
NT2-N
C.
% Regeneration/ Scratched neurons
100
80
60
40
20
0
N.I.
N.I.-(Si MAST2)
NV1
NV1-(Si MAST2)
D.
% Regeneration/ Scratched neurons
100
80
60
40
20
0
N.I.
NV1
NV2

FIG. 17


A.
Neg KCl 0
Neg KCl 16mM
2 way ANOVA
F(27.22)
P<0.0001
# of Crossings
Distance from soma (μm)

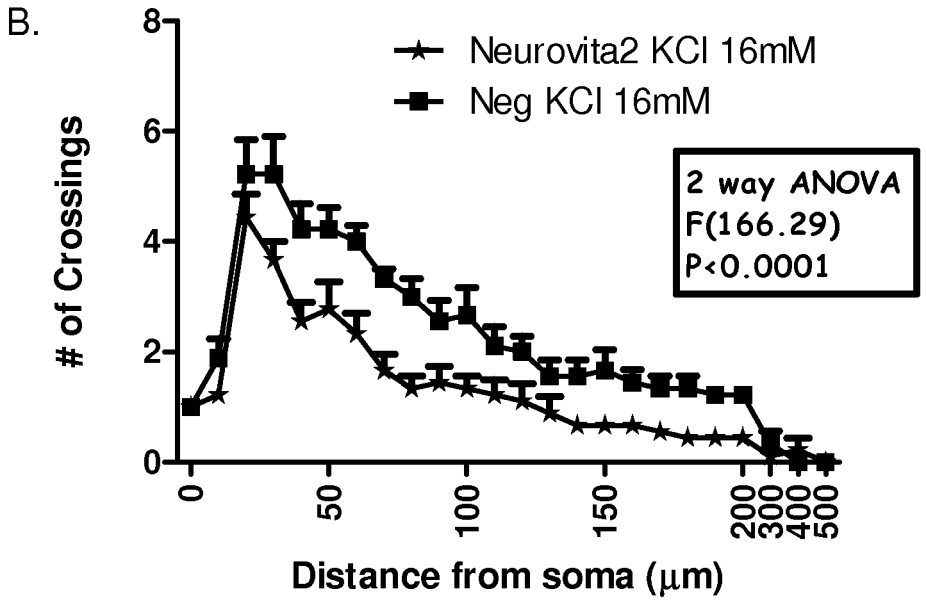
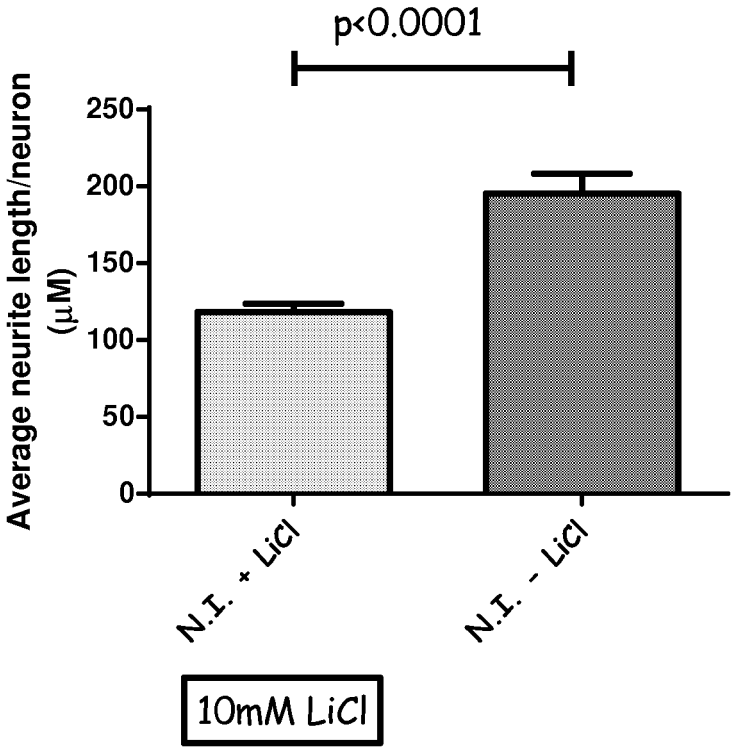

B.
Neurovita2 KCl 16mM
Neg KCl 16mM
2 way ANOVA
F(166.29)
P<0.0001
# of Crossings
Distance from soma (μm)

FIG. 18

A.


p<0.0001
Average neurite length/neuron (µM)
250
200
150
100
50
0
N.I. + LiCl
N.I. - LiCl
10mM LiCl

B.

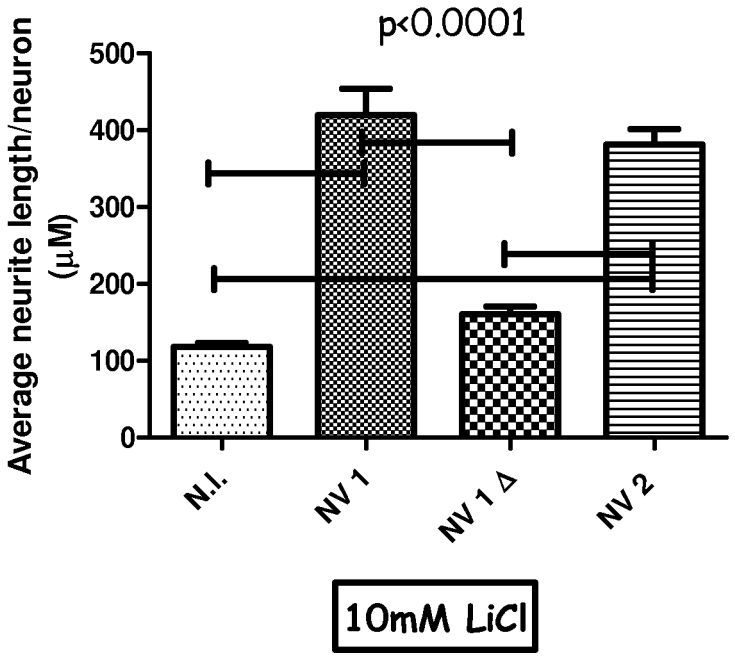

p<0.0001
Average neurite length/neuron (µM)
500
400
300
200
100
0
N.I.
NV 1
NV 1 Δ
NV 2
10mM LiCl

FIG. 19

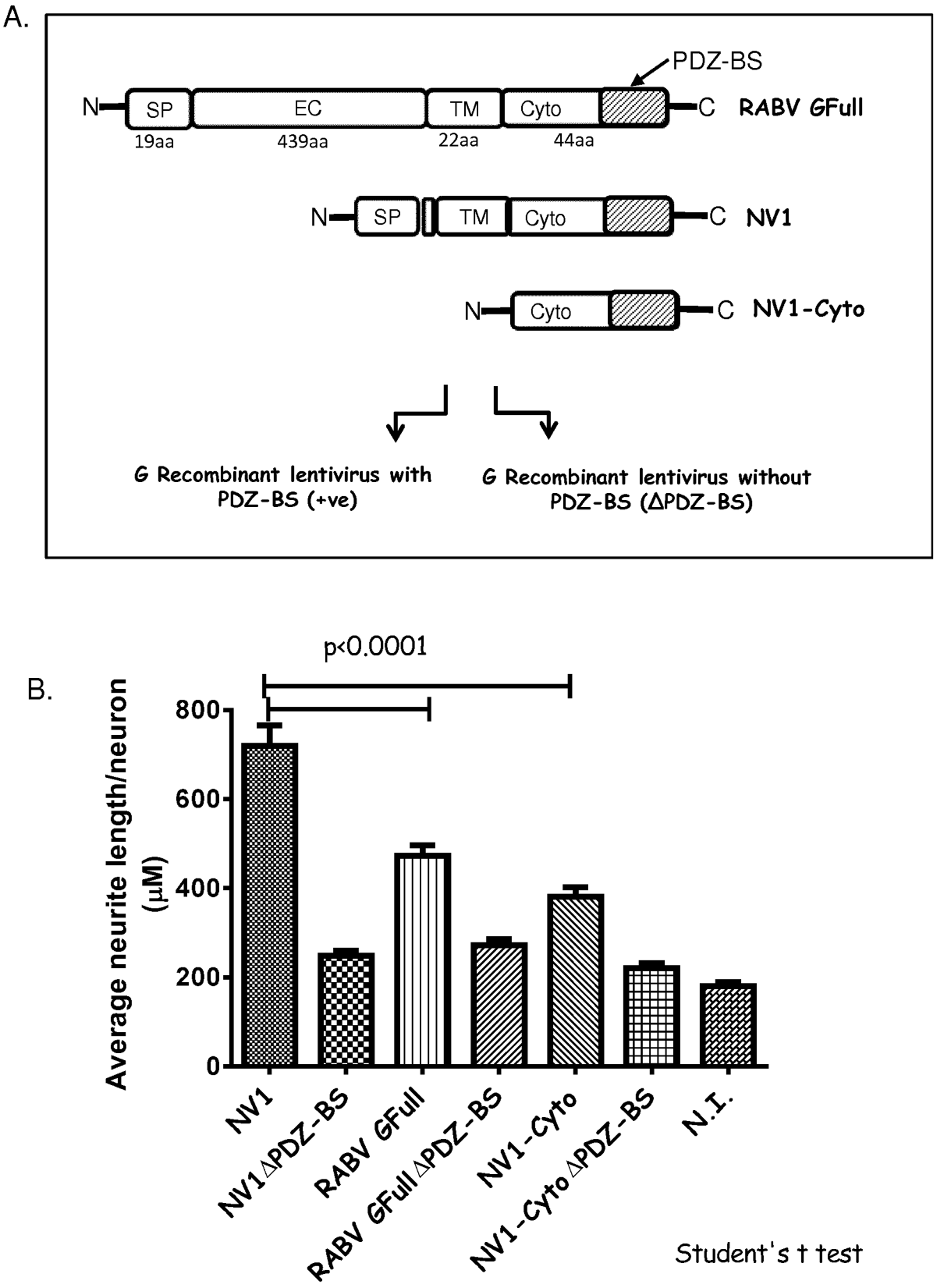
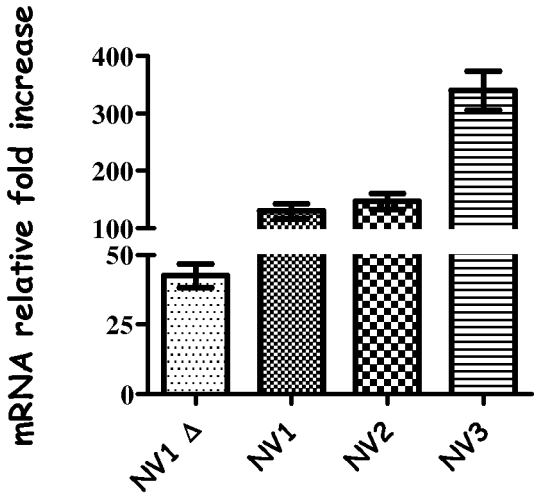

A.
PDZ-BS
N
SP
EC
TM
Cyto
C
RABV GFull
19aa
439aa
22aa
44aa
N
SP
TM
Cyto
C
NV1
N
Cyto
C
NV1-Cyto
G Recombinant lentivirus with PDZ-BS (+ve)
G Recombinant lentivirus without PDZ-BS (ΔPDZ-BS)
B.
p<0.0001
Average neurite length/neuron (μM)
800
600
400
200
0
NV1
NV1ΔPDZ-BS
RABV GFull
RABV GFullΔPDZ-BS
NV1-Cyto
NV1-CytoΔPDZ-BS
N.I.
Student's t test

FIG. 20

A.



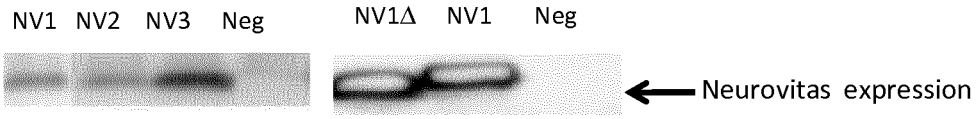
B.



C.

	% of GFP expression
Neg	0
NV1Δ	15,56
NV1	48,98
NV2	33,66
NV3	59,7

D.



E.

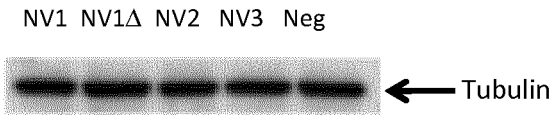


FIG. 21

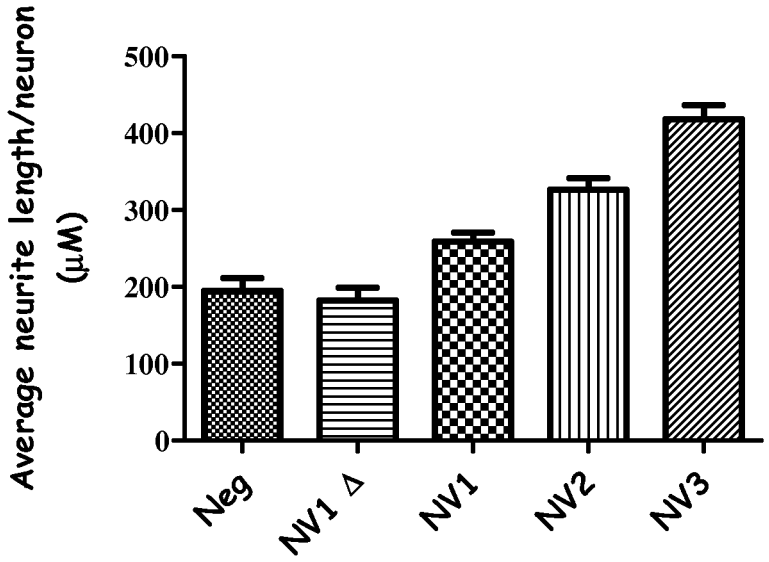
A.



Non infected NS cells (Neg)

NV3 infected NS cells

B.

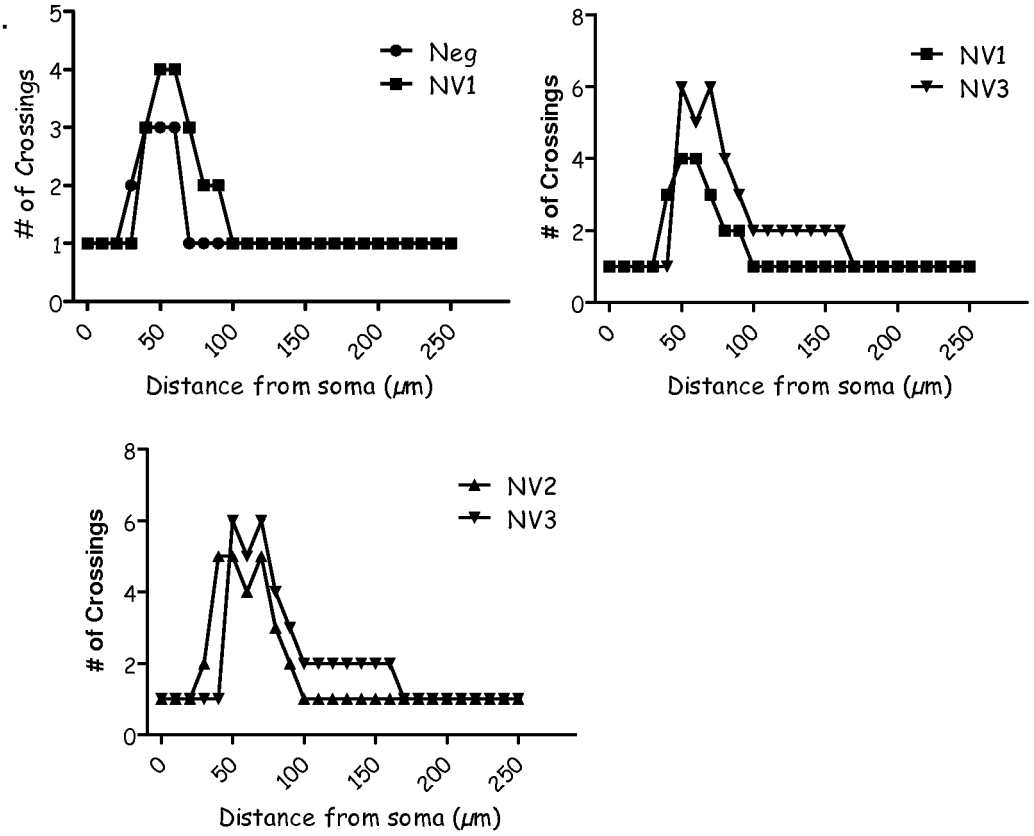


C.

Neg					
NV1Δ	0,6076				
NV1	0,047	0,0010			
NV2	< 0,0001	< 0,0001	0,0010		
NV3	< 0,0001	< 0,0001	< 0,0001	0,0003	
	Neg	NV1Δ	NV1	NV2	NV3

FIG. 22

A.

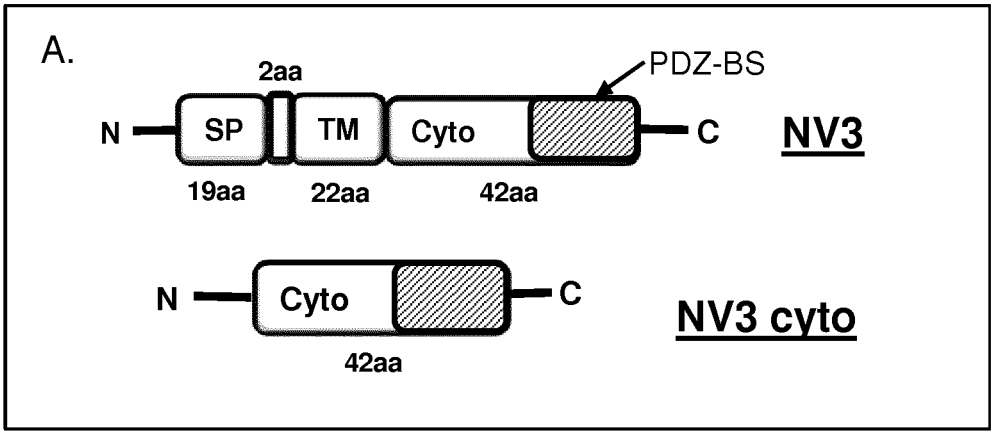


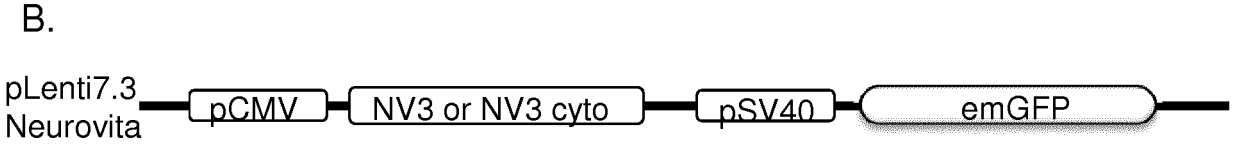
B.

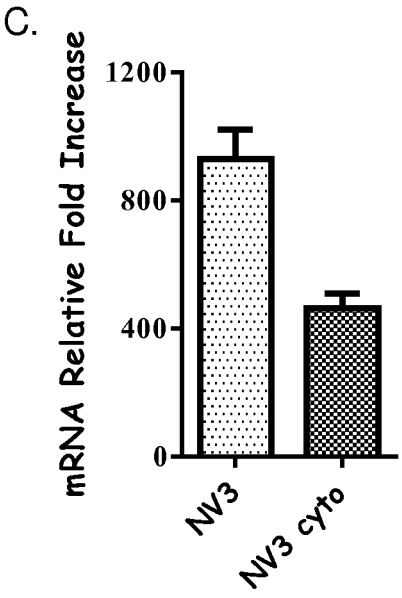
	Neg	NV1
NV2	0,0178	0,0053

	Neg	NV1	NV2
NV3	< 0,0001	< 0,0001	0,0007

FIG. 23





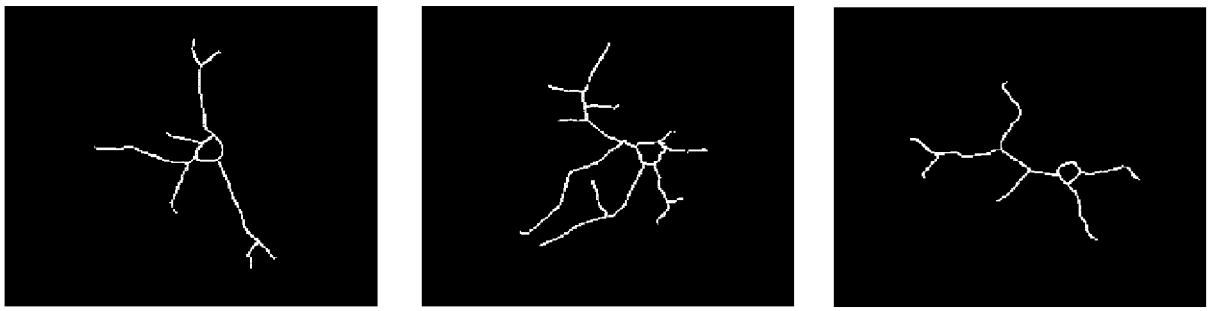


D.

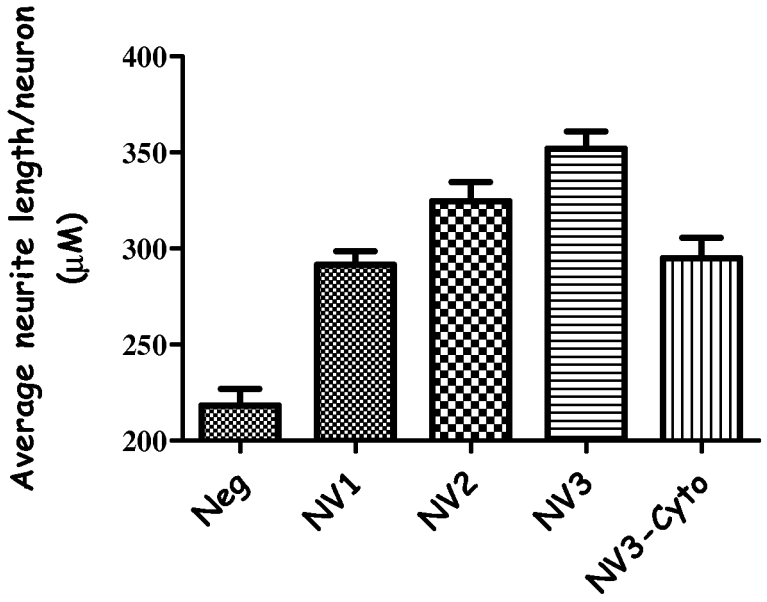
	Neg	NV3	NV3 cyto
% of GFP expression	0	60.41	36.71

FIG. 24

A.



B.

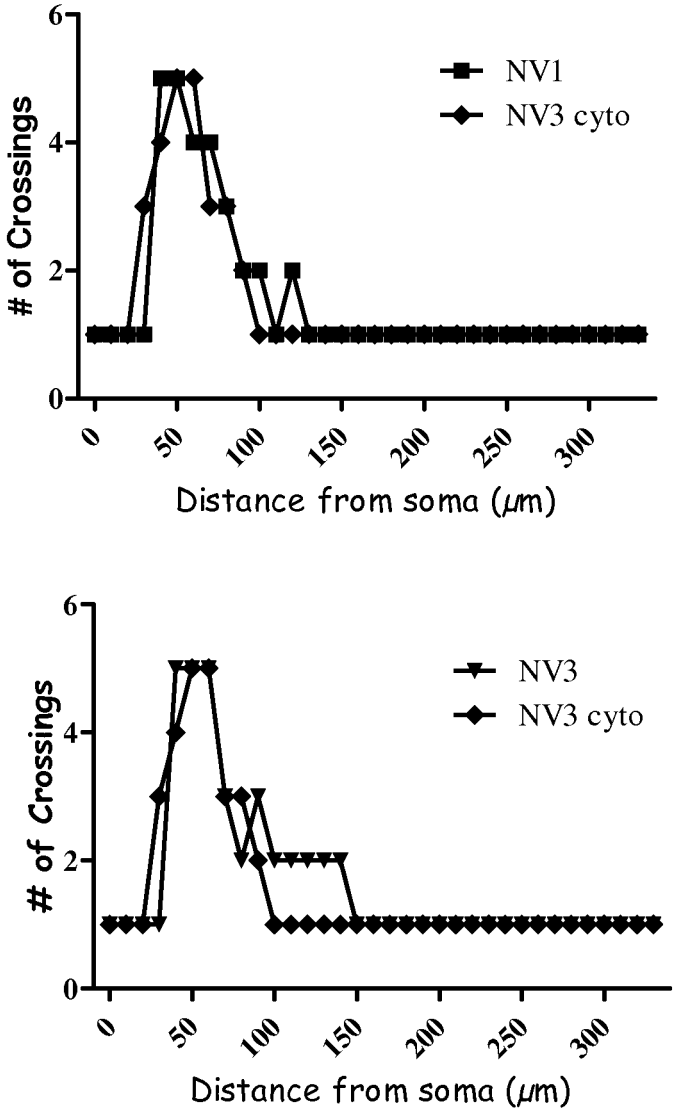


C.

	Neg	NV1	NV2	NV3
NV3 cyto	< 0,0001	0,7784	0,0457	< 0,0001

FIG. 25

A.



B.

	Neg	NV1	NV2	NV3
NV3 cyto	< 0,0001	0,088	0,006	< 0,0001

FIG. 26

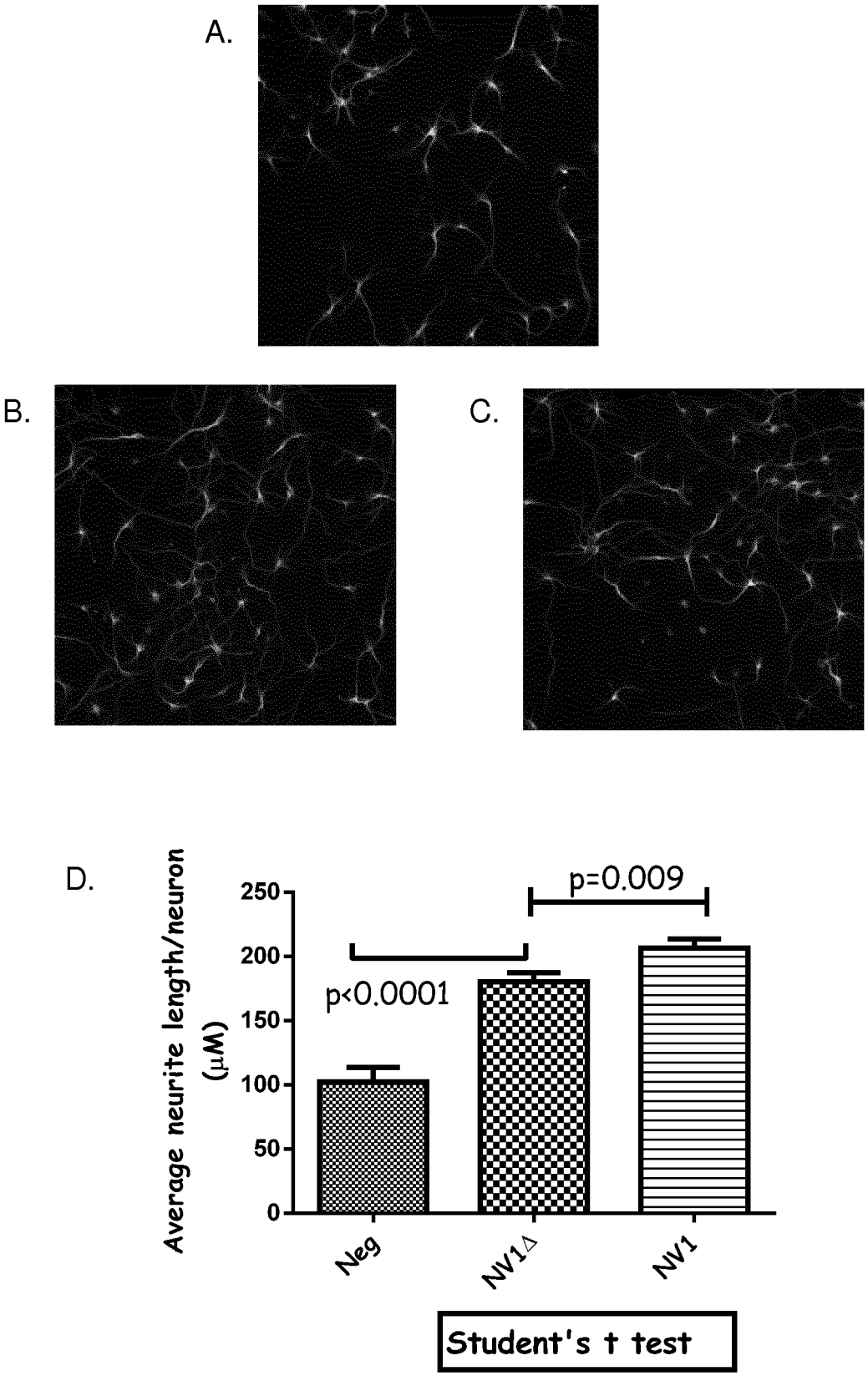
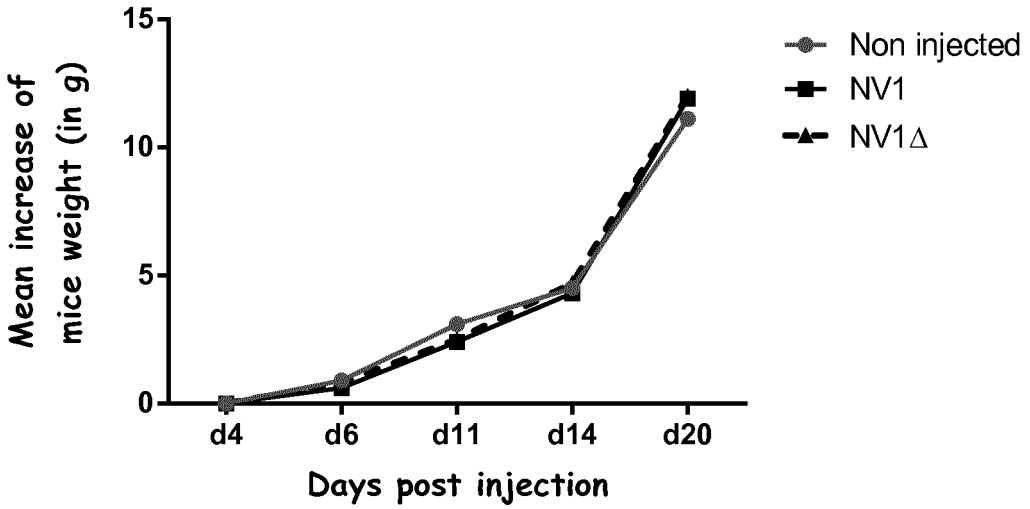

A.
B.
C.
D.
Average neurite length/neuron (µM)
250
200
150
100
50
0
p=0.009
p<0.0001
Neg
NV1Δ
NV1
Student's t test

FIG. 27

A.


Mean increase of mice weight (in g)
15
10
5
0
d4
d6
d11
d14
d20
Days post injection
Non injected
NV1
NV1Δ

B.

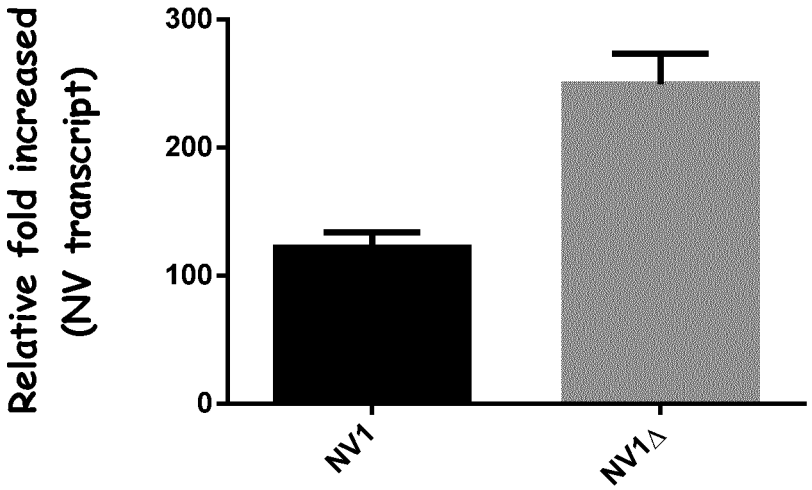

Relative fold increased (NV transcript)
300
200
100
0
NV1
NV1Δ

FIG. 28

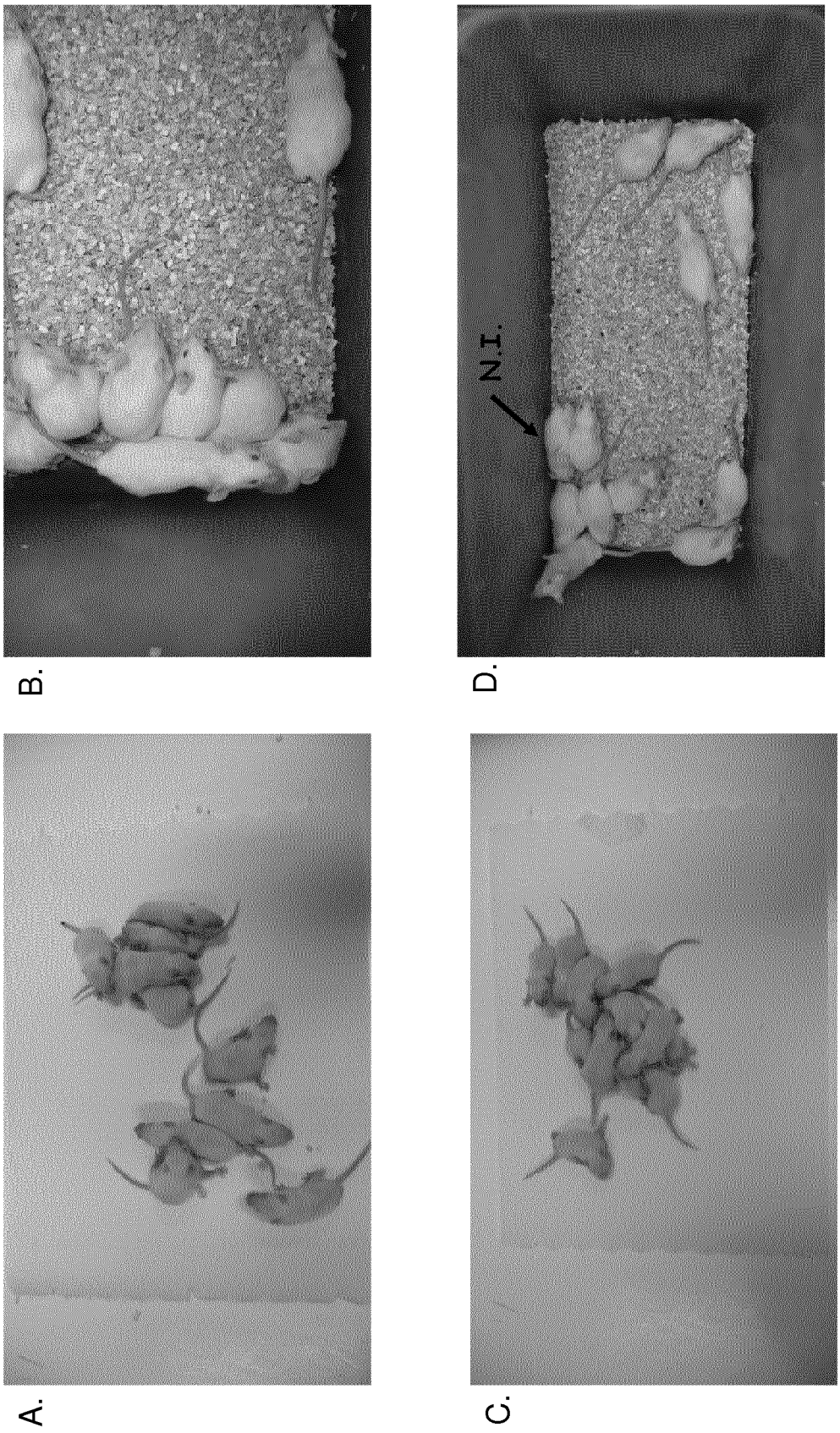


FIG. 29

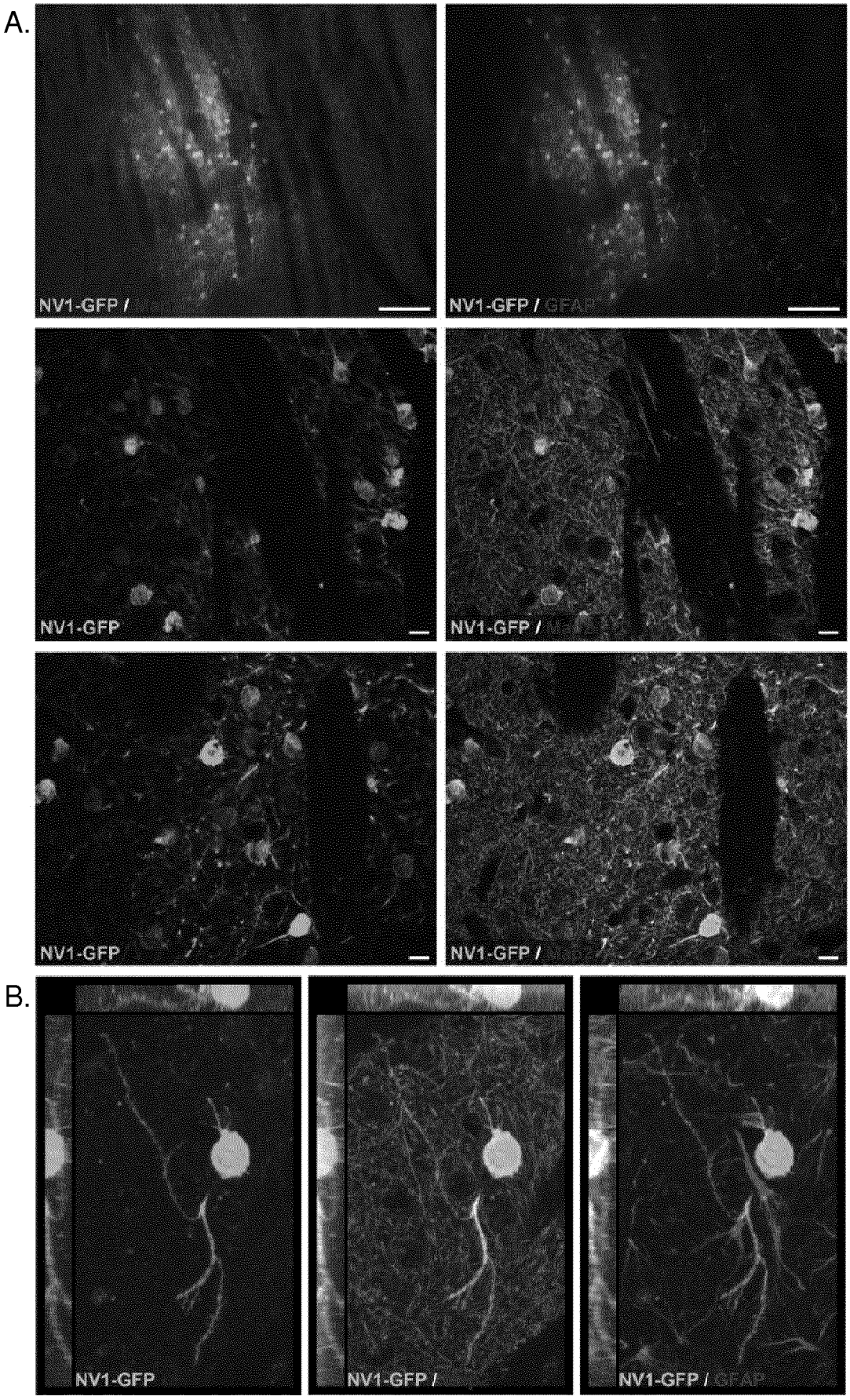

A.
NV1-GFP /
NV1-GFP / GFAP
NV1-GFP
NV1-GFP /
NV1-GFP
NV1-GFP /
B.
NV1-GFP
NV1-GFP /
NV1-GFP / GFAP

FIG. 30

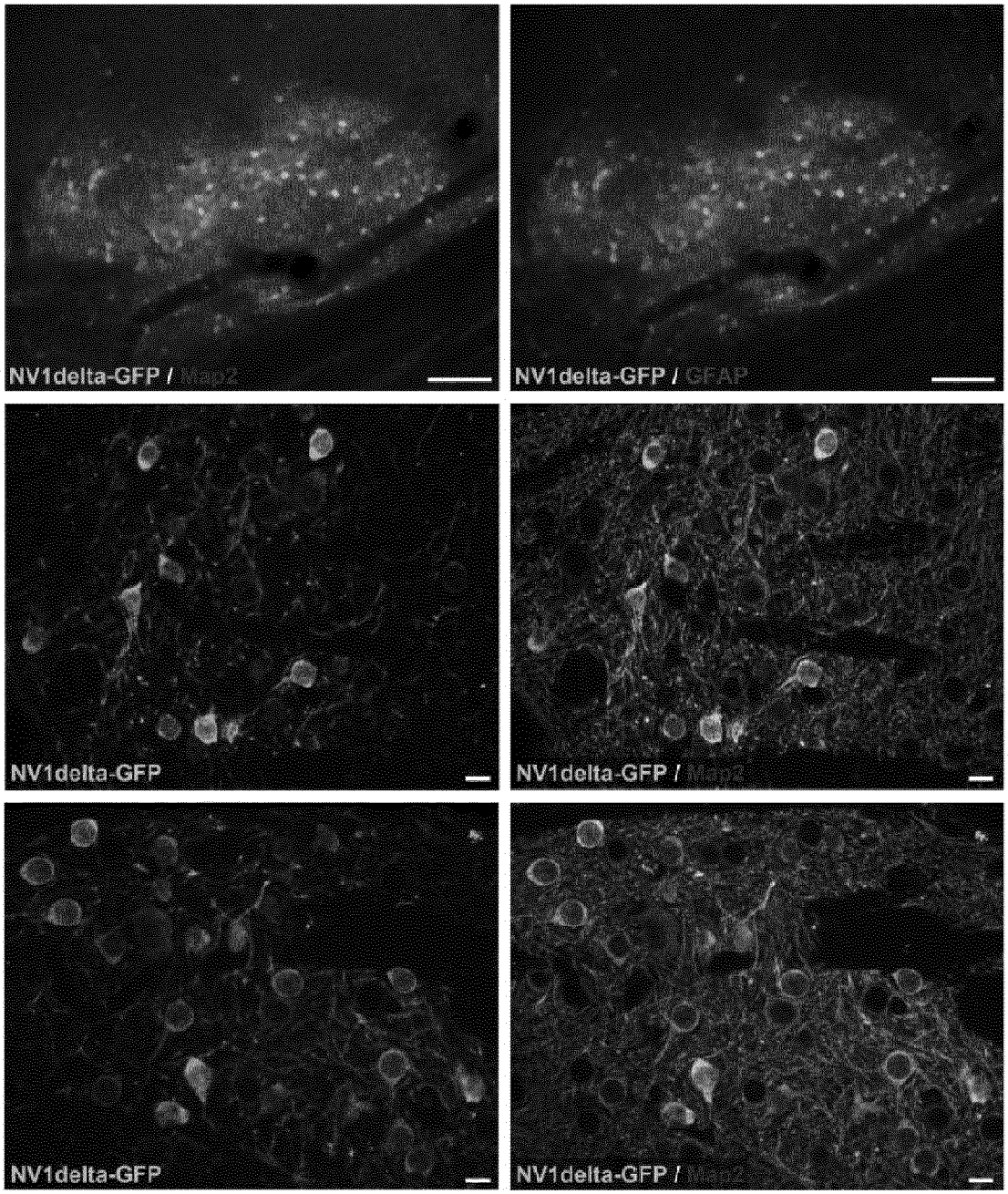

NV1delta-GFP / Map2
NV1delta-GFP / GFAP
NV1delta-GFP
NV1delta-GFP / Map2
NV1delta-GFP
NV1delta-GFP / Map2

FIG. 31