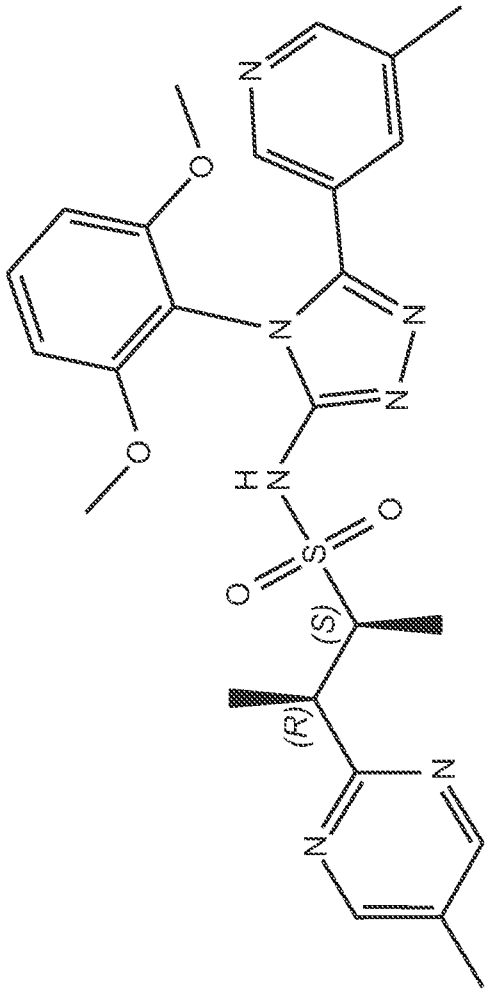


FIG. 1

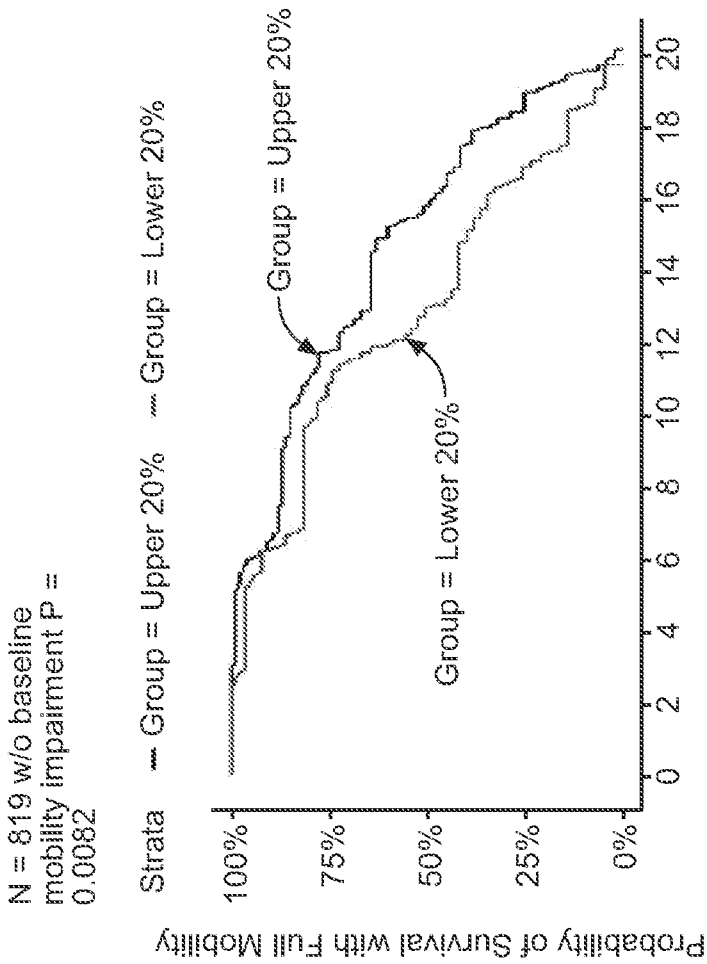

N = 819 w/o baseline
mobility impairment P =
0.0082
Strata — Group = Upper 20% — Group = Lower 20%
Probability of Survival with Full Mobility
100%
75%
50%
25%
0%
0 2 4 6 8 10 12 14 16 18 20
Follow-up Time (Years)
Group = Upper 20%
Group = Lower 20%

FIG. 2B

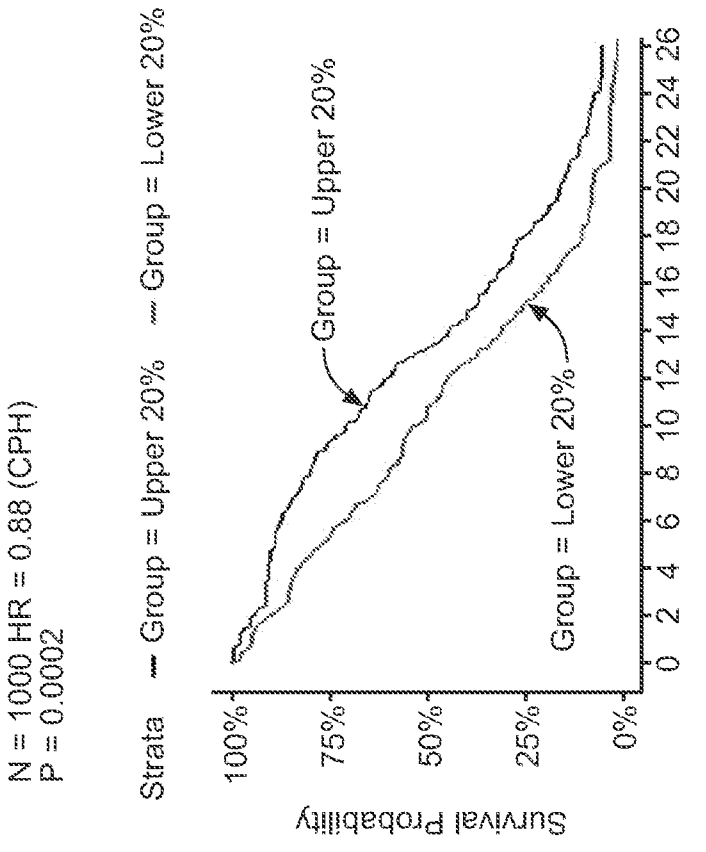

N = 1000 HR = 0.88 (CPH)
P = 0.0002
Strata — Group = Upper 20% — Group = Lower 20%
Survival Probability
100%
75%
50%
25%
0%
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Follow-up Time (Years)
Group = Upper 20%
Group = Lower 20%

FIG. 2A

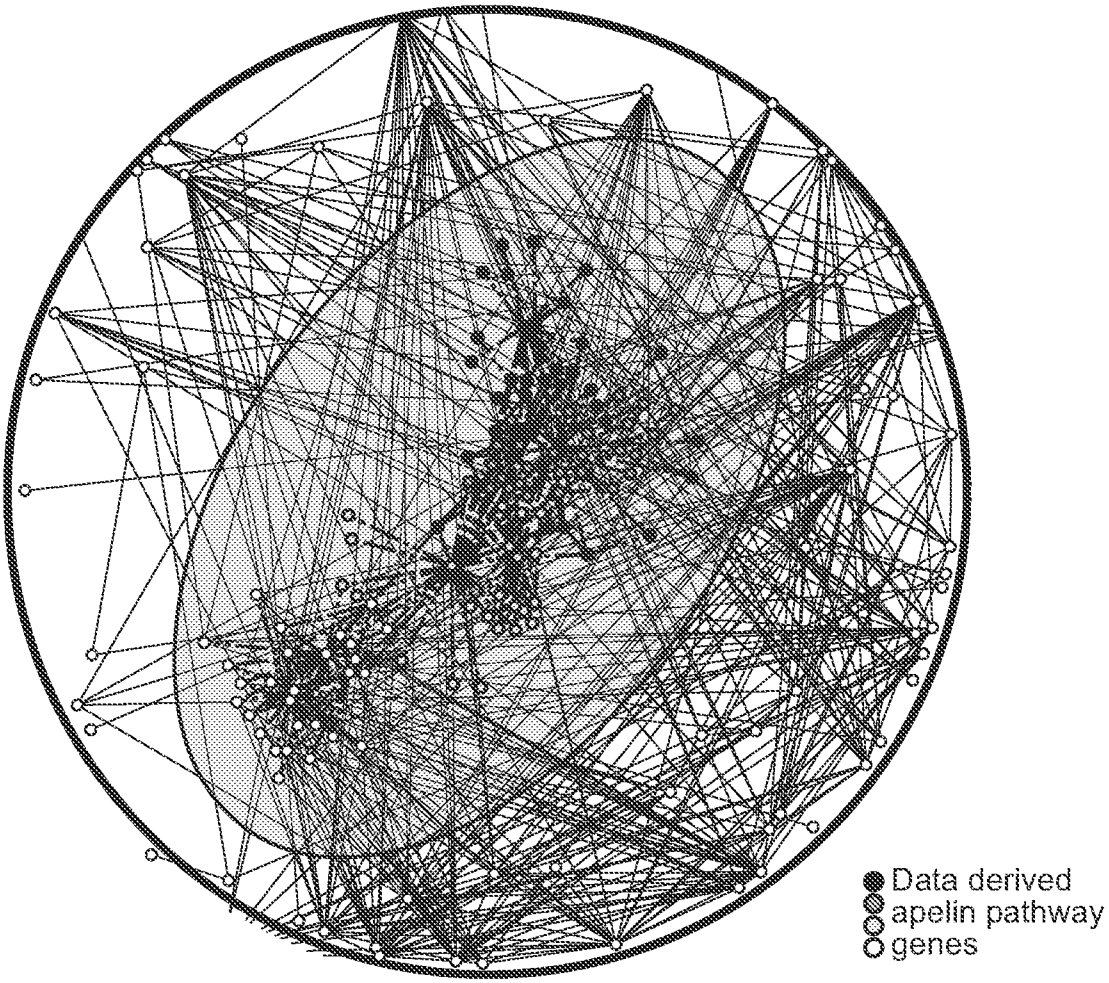

Data derived
apelin pathway
genes

FIG. 2C

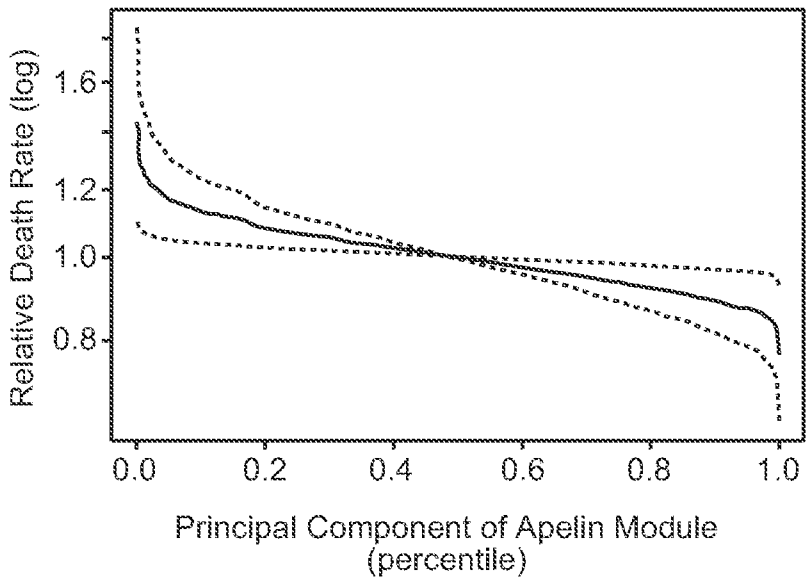

Relative Death Rate (log)
1.6
1.2
1.0
0.8
0.0
0.2
0.4
0.6
0.8
1.0
Principal Component of Apelin Module
(percentile)

FIG. 2D

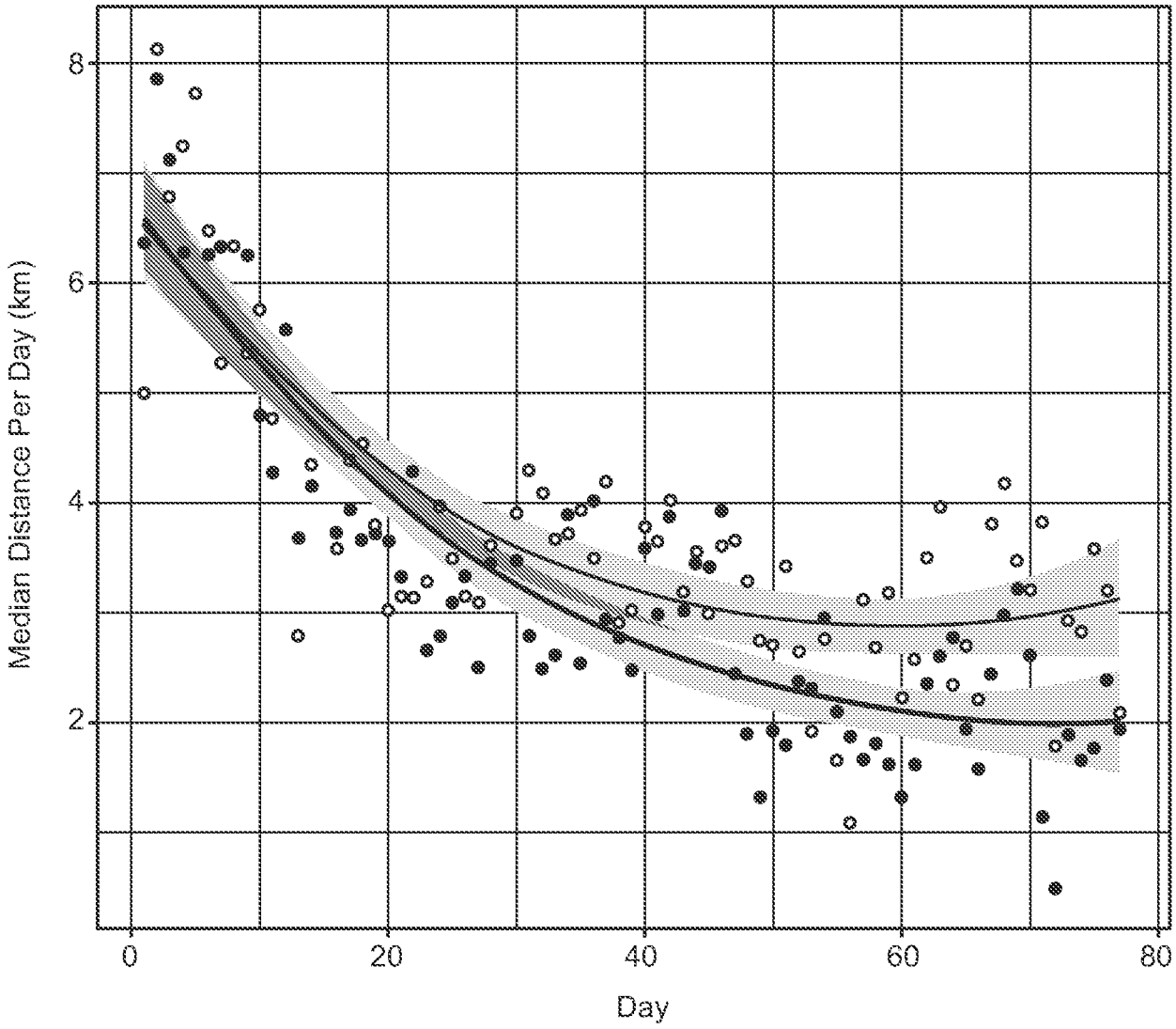

Median Distance Per Day (km)
8
6
4
2
0
20
40
60
80
Day
Kendall's Rank Correlation Tau P-Value = 0.00228

FIG. 3A

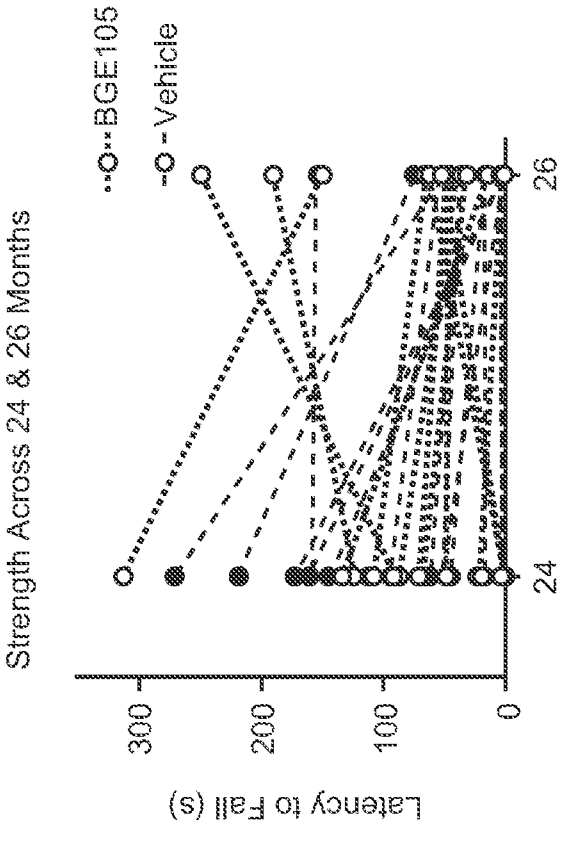

Strength Across 24 & 26 Months
BGE105
Vehicle
Latency to Fall (s)
300
200
100
0
24
26
Age (months)

FIG. 3B

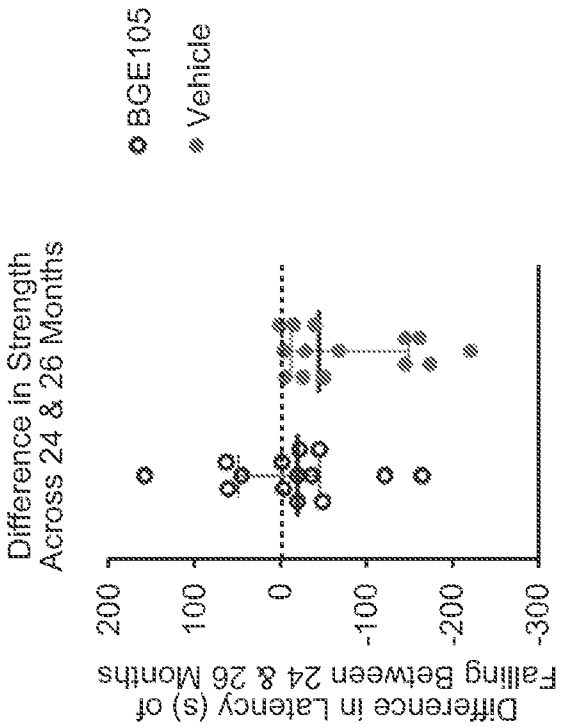

Difference in Strength
Across 24 & 26 Months
BGE105
Vehicle
Difference in Latency (s) of
Falling Between 24 & 26 Months
200
100
0
-100
-200
-300

FIG. 3C

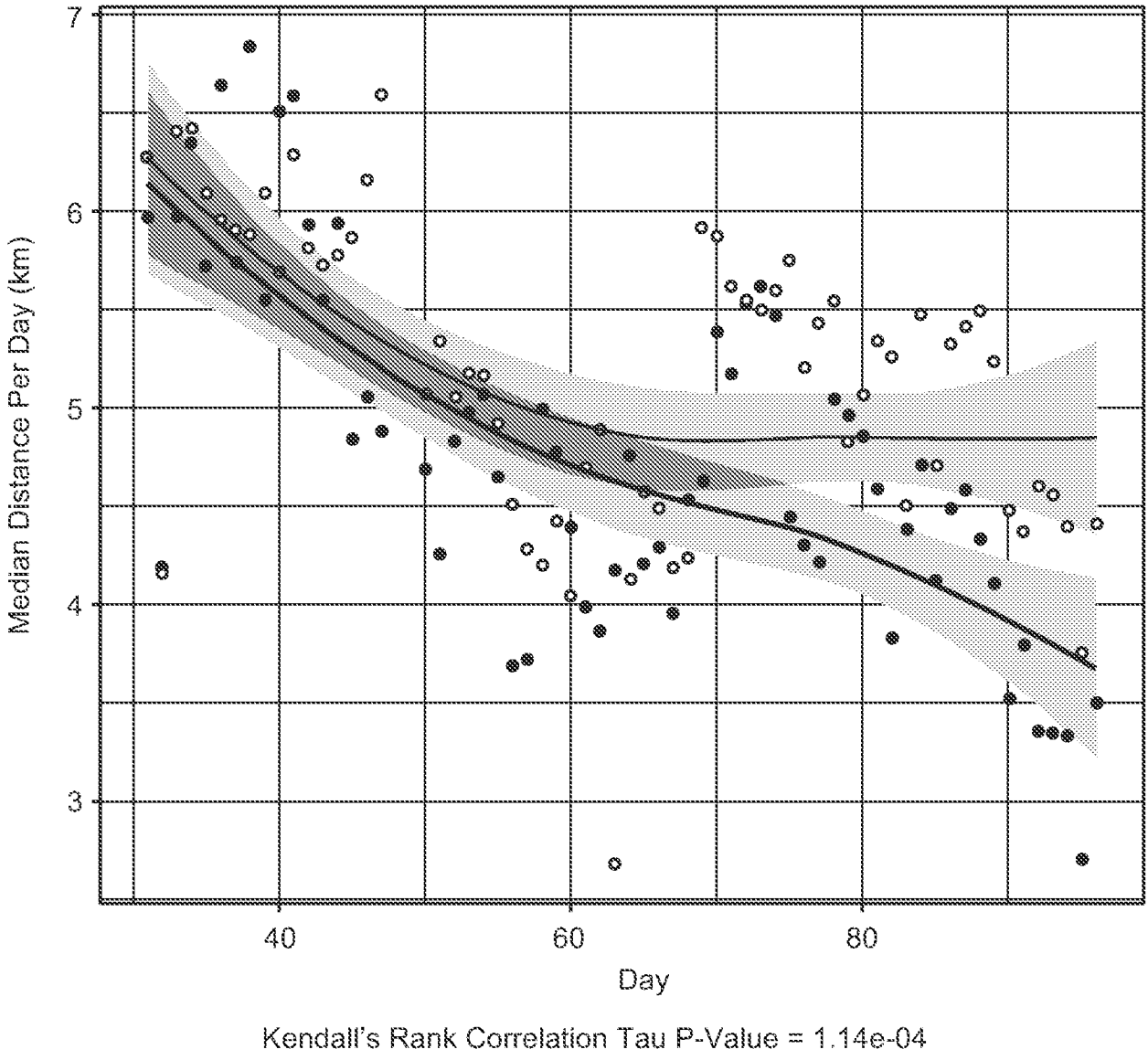

Median Distance Per Day (km)
7
6
5
4
3
40
60
80
Day
Kendall's Rank Correlation Tau P-Value = 1.14e-04

FIG. 3D

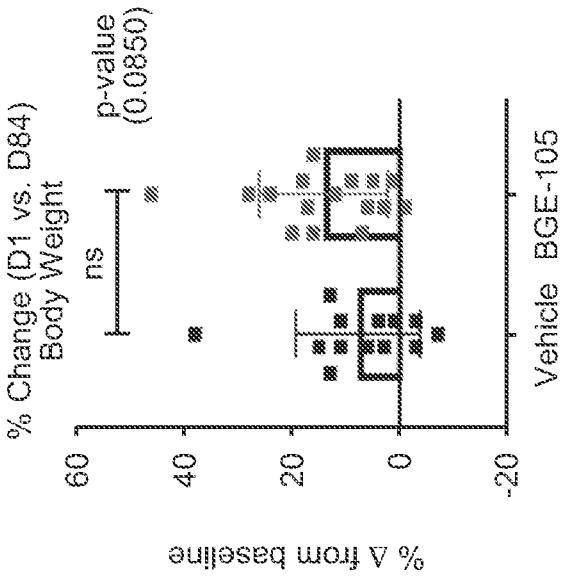

% Change (D1 vs. D84)
Body Weight
ns
p-value
(0.0850)
% Δ from baseline
60
40
20
0
-20
Vehicle
BGE-105

FIG. 3E

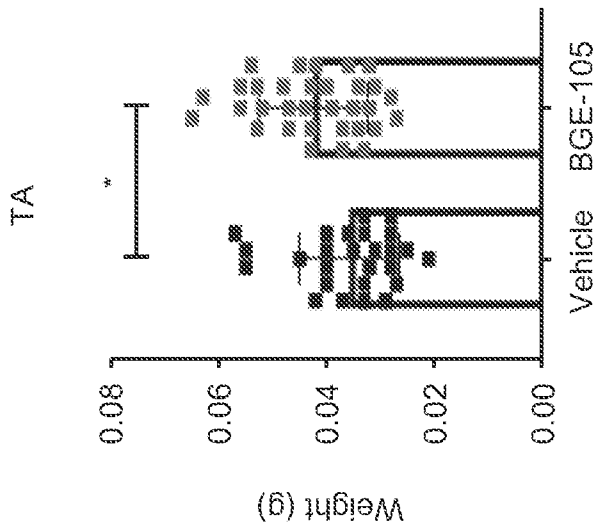

TA
*
Weight (g)
0.08
0.06
0.04
0.02
0.00
Vehicle
BGE-105

FIG. 3F

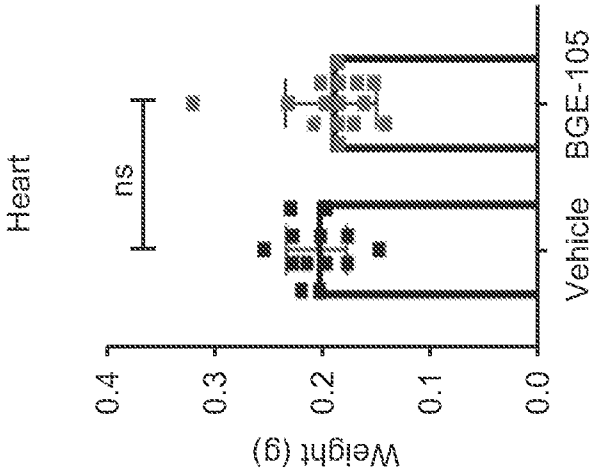


FIG. 3I

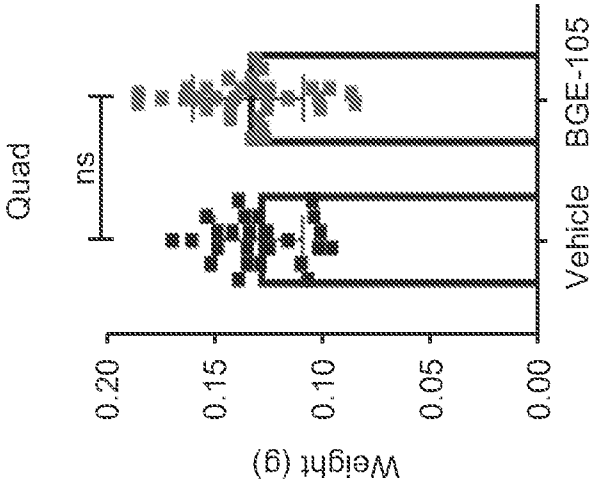


FIG. 3H

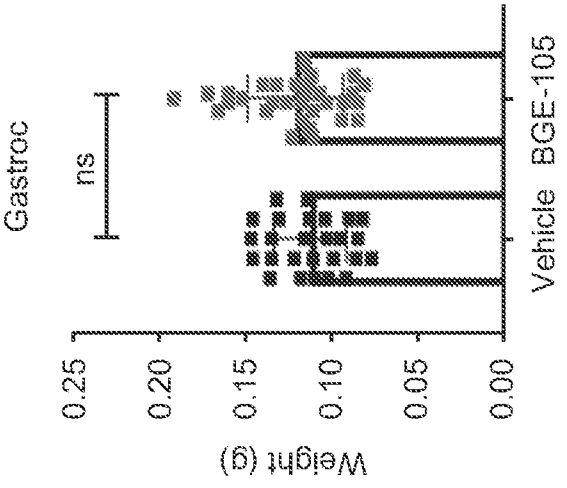


FIG. 3G

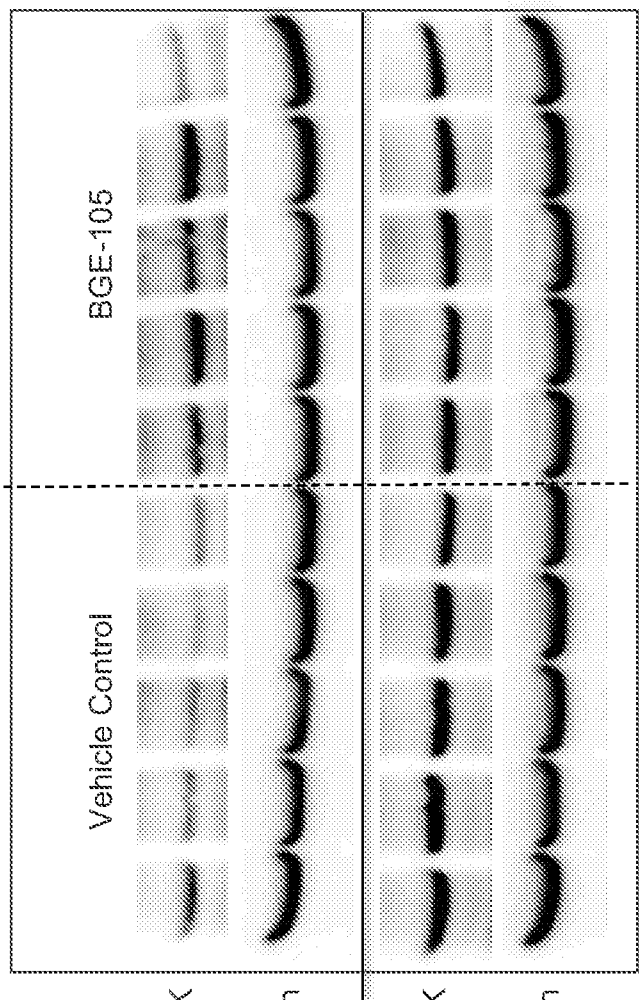

Vehicle Control
BGE-105
pAMPK
β-Actin
AMPK
β-Actin
Mouse Tissue (70 µg)

FIG. 4B

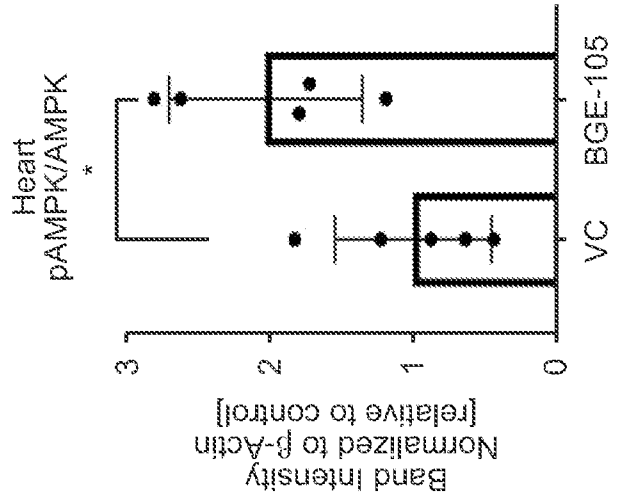

Heart
pAMPK/AMPK
*
Band Intensity
Normalized to β-Actin
[relative to control]
3
2
1
0
VC
BGE-105

FIG. 4A

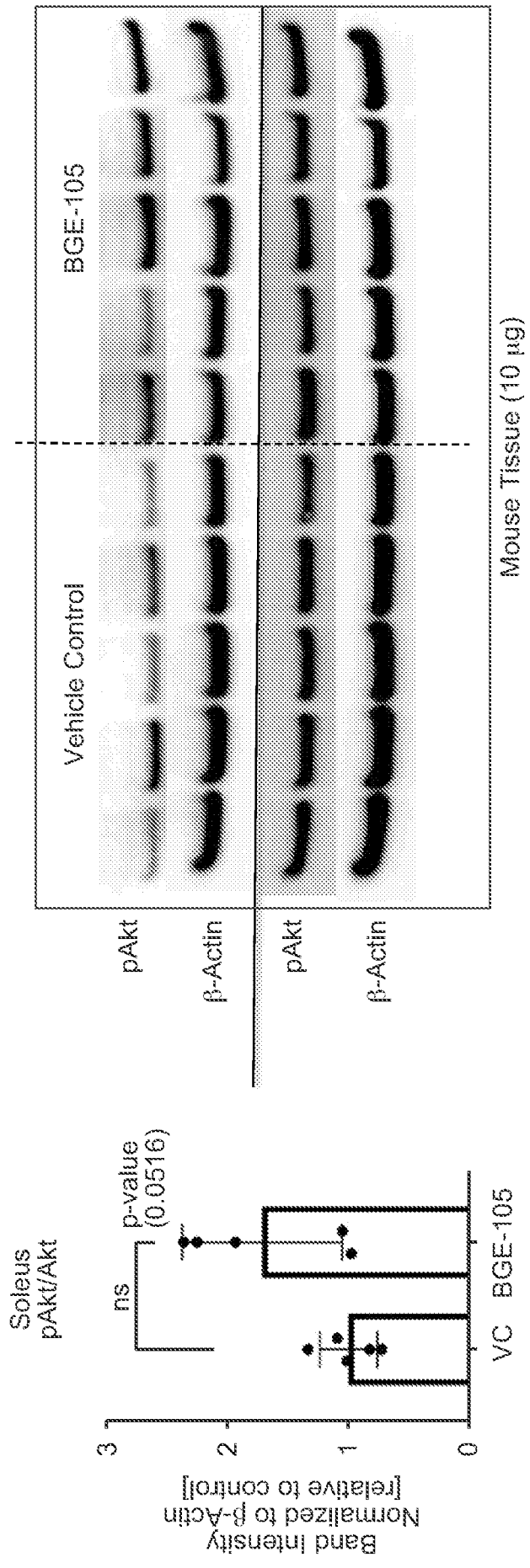

Soleus
pAkt/Akt
ns
p-value
(0.0516)
VC
BGE-105
Band Intensity
Normalized to β-Actin
[relative to control]
0
1
2
3
Vehicle Control
BGE-105
pAkt
β-Actin
pAkt
β-Actin
Mouse Tissue (10 µg)

FIG. 4C

FIG. 4D

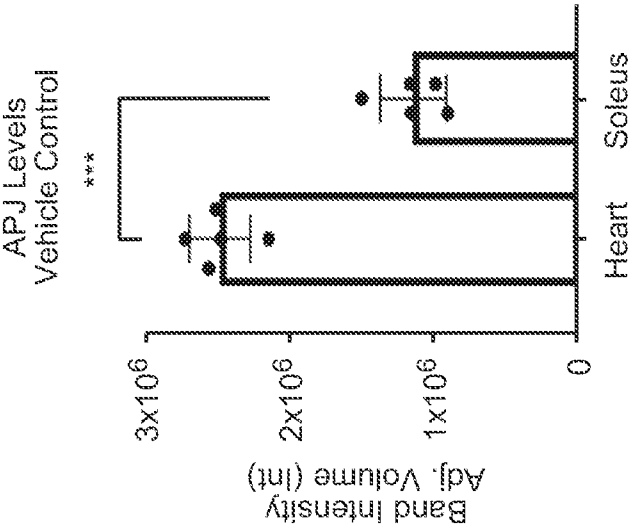

APJ Levels
Vehicle Control
***
Band Intensity
Adj. Volume (Int)
3x10^6
2x10^6
1x10^6
0
Heart
Soleus

FIG. 4E


APJ Levels
Vehicle Control Group
Heart
Soleus
Heart
Soleus
APJ
Mouse Tissue
(10 µg)

FIG. 4F

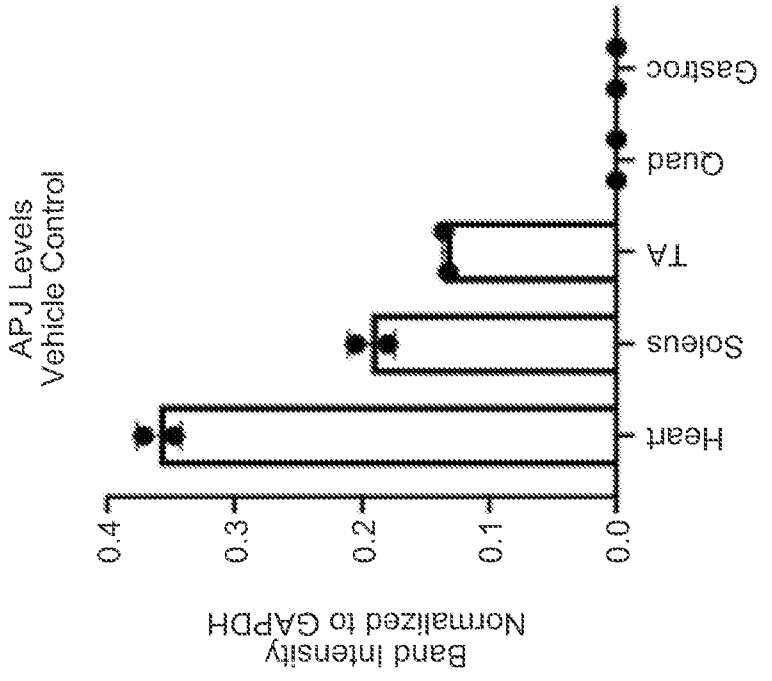

APJ Levels
Vehicle Control
Band Intensity
Normalized to GAPDH
0.4
0.3
0.2
0.1
0.0
Heart
Soleus
TA
Quad
Gastroc

FIG. 5A

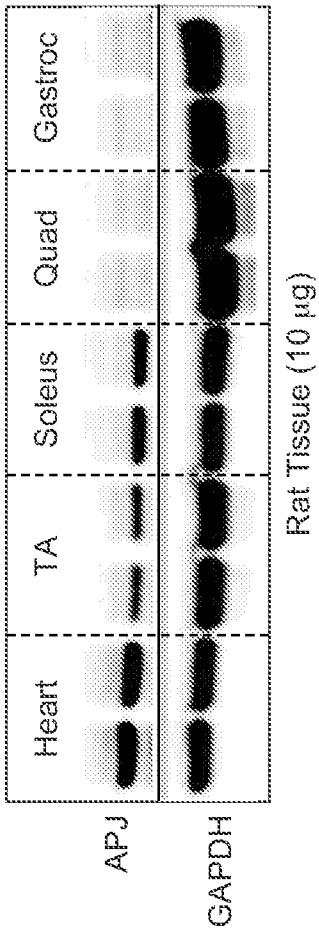

APJ
GAPDH
Heart
TA
Soleus
Quad
Gastroc
Rat Tissue (10 µg)

FIG. 5B

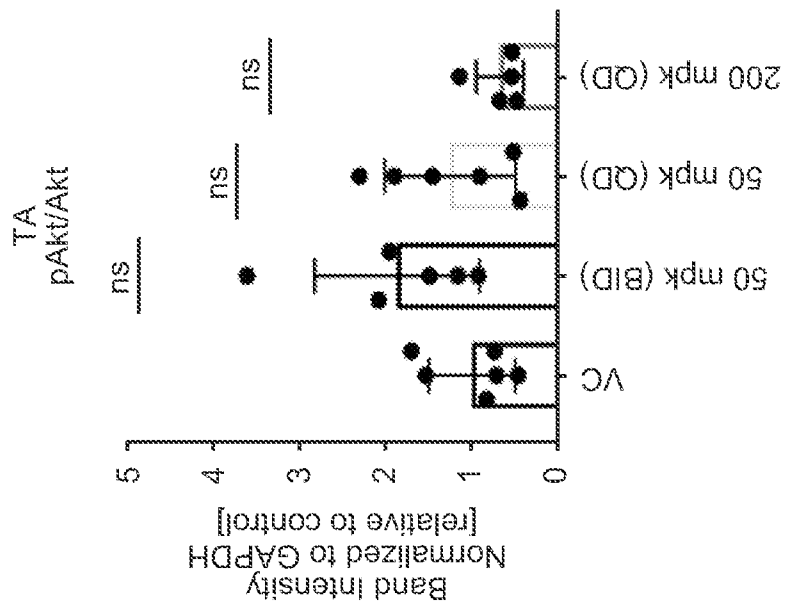

TA
pAkt/Akt
ns
ns
ns
Band Intensity
Normalized to GAPDH
[relative to control]
0
1
2
3
4
5
VC
50 mpk (BID)
50 mpk (QD)
200 mpk (QD)
Rat Tissue (69 μg)

FIG. 5C

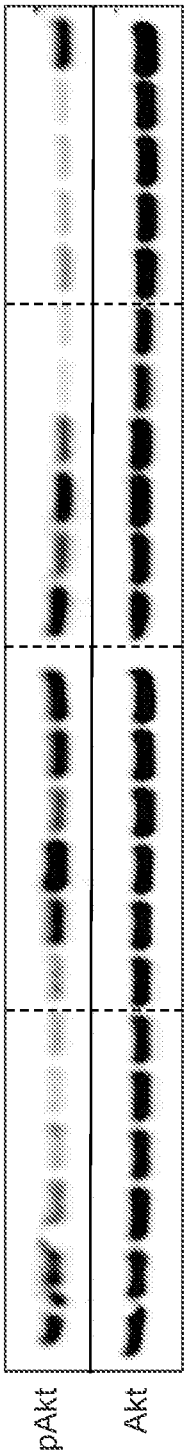

Vehicle Control
BGE-105
50 mg/kg BID
BGE-105
50 mg/kg QD
BGE-105
200 mg/kg QD
pAkt
Akt

FIG. 5D

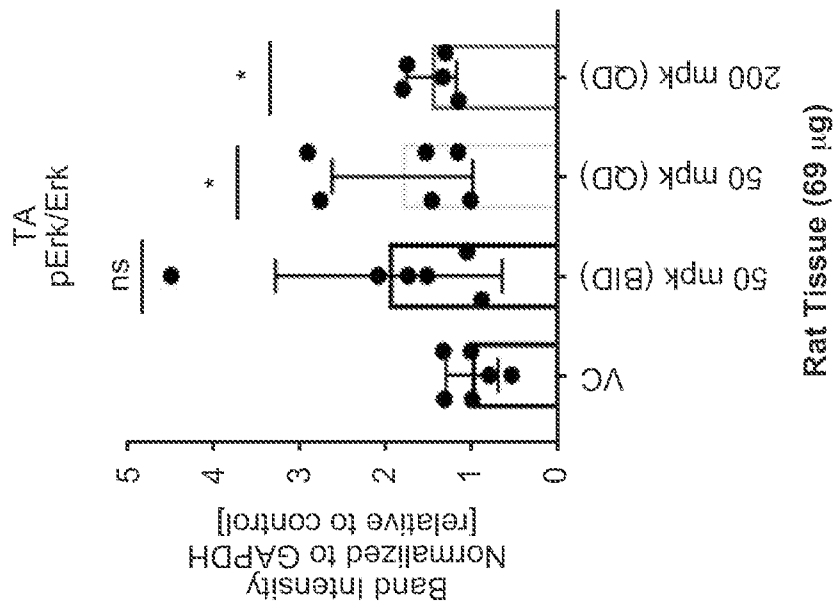

TA
pErk/Erk
ns
*
*
Band Intensity
Normalized to GAPDH
[relative to control]
0
1
2
3
4
5
VC
50 mpk (BID)
50 mpk (QD)
200 mpk (QD)
Rat Tissue (69 μg)

FIG. 5E


Vehicle Control
BGE-105
50 mg/kg BID
BGE-105
50 mg/kg QD
BGE-105
200 mg/kg QD
pErk
Erk

FIG. 5F

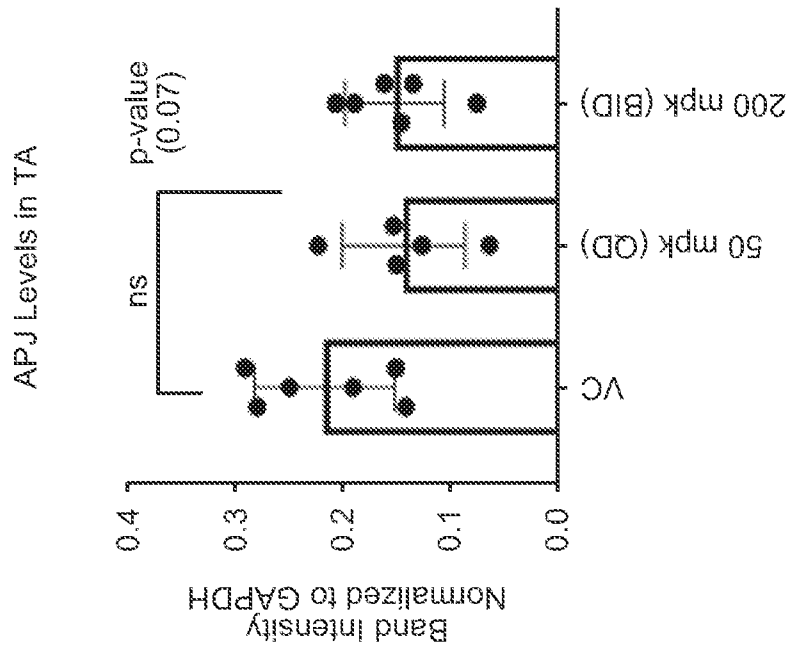

APJ Levels in TA
ns
p-value
(0.07)
0.4
0.3
0.2
0.1
0.0
Band Intensity
Normalized to GAPDH
VC
50 mpk (QD)
200 mpk (BIID)
Rat Tissue (20 µg)

FIG. 5G

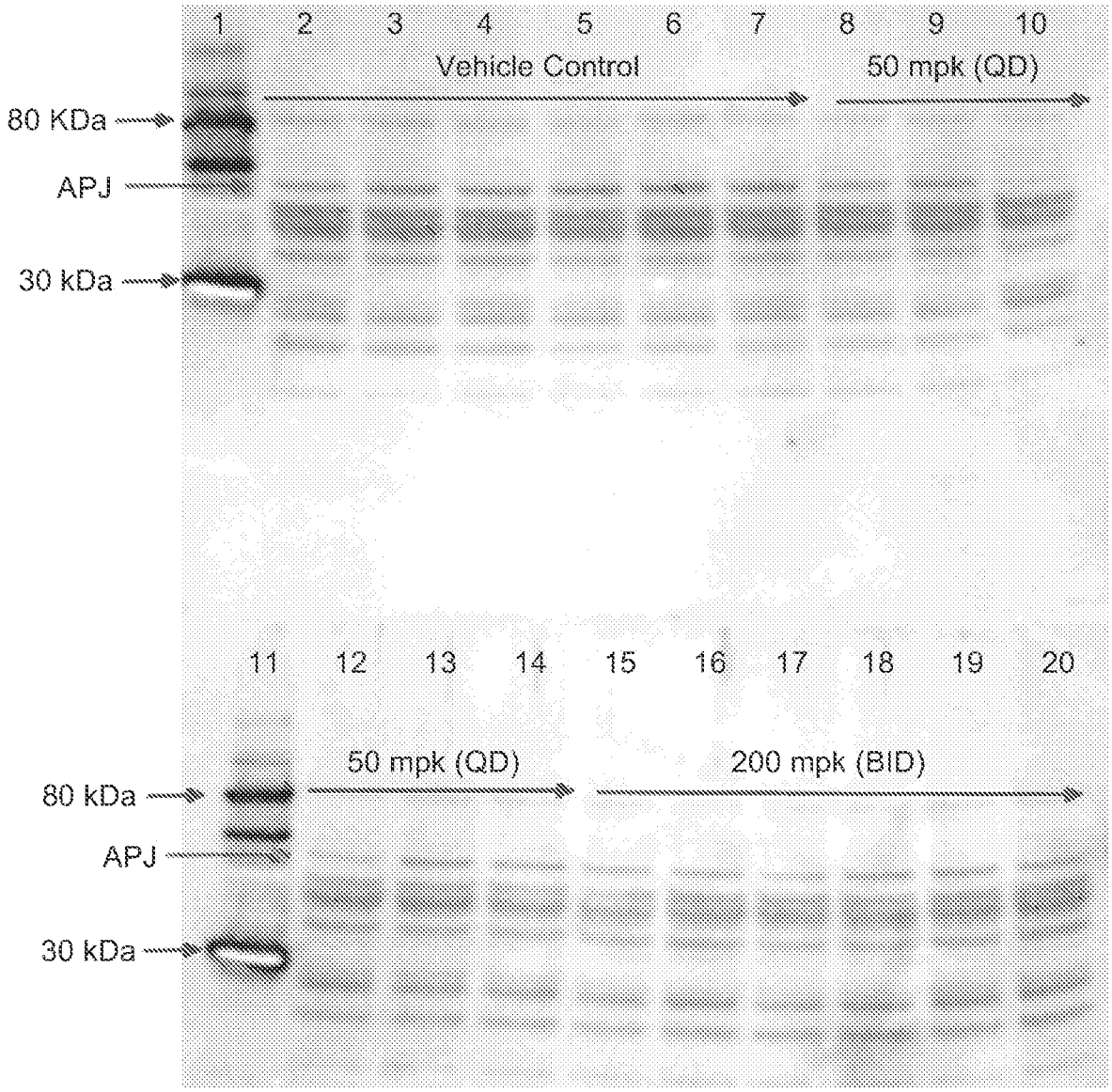

1
2
3
4
5
6
7
8
9
10
Vehicle Control
50 mpk (QD)
80 KDa
APJ
30 kDa
11
12
13
14
15
16
17
18
19
20
50 mpk (QD)
200 mpk (BID)
80 kDa
APJ
30 kDa

FIG. 5H

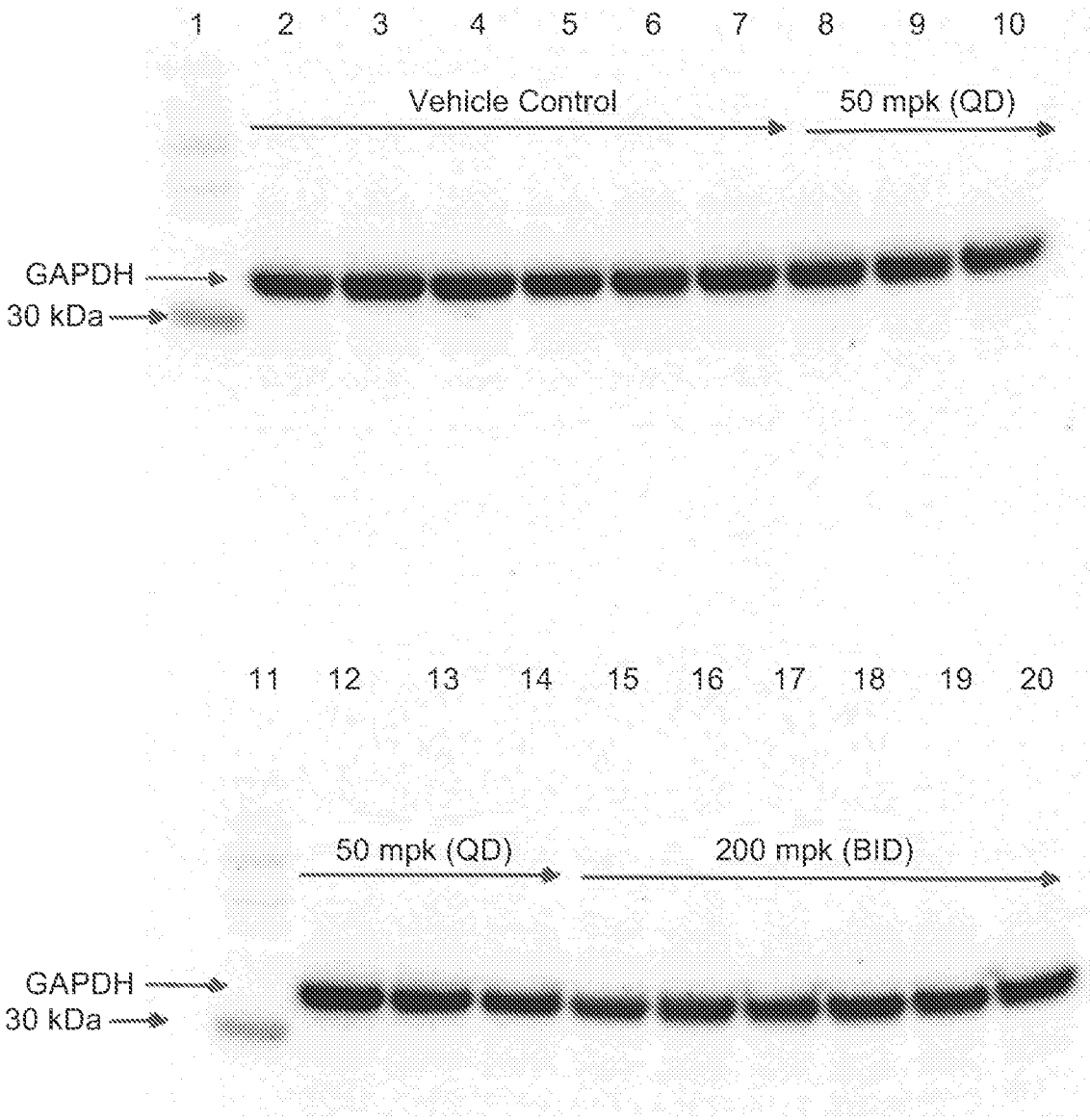

1 2 3 4 5 6 7 8 9 10
Vehicle Control
50 mpk (QD)
GAPDH
30 kDa
11 12 13 14 15 16 17 18 19 20
50 mpk (QD)
200 mpk (BID)
GAPDH
30 kDa

FIG. 5I

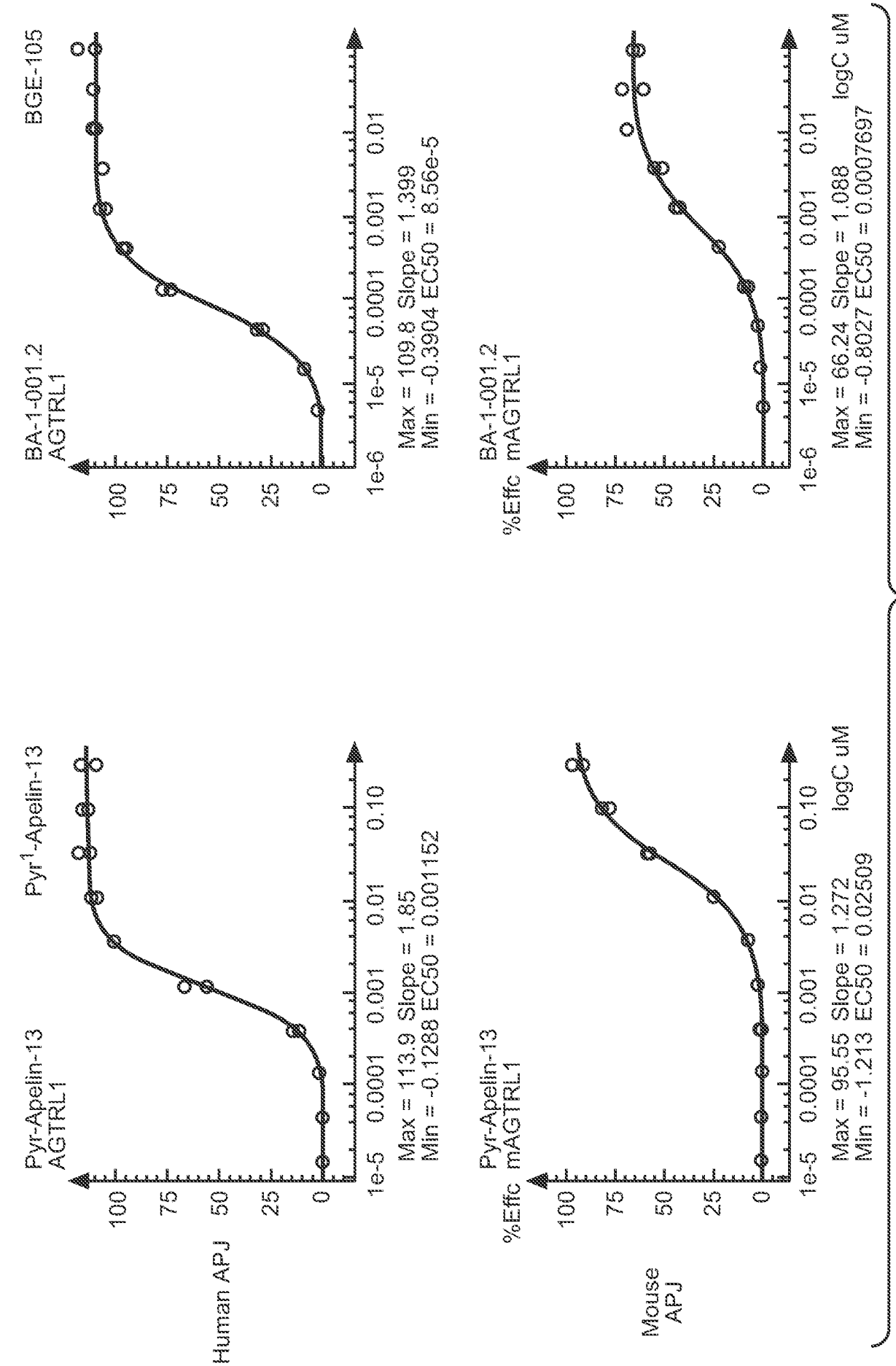

Pyr-Apelin-13
AGTRL1
Pyr[1]-Apelin-13
Human APJ
100
75
50
25
0
1e-5 0.0001 0.001 0.01 0.10
Max = 113.9 Slope = 1.85
Min = -0.1288 EC50 = 0.001152
BA-1-001.2
AGTRL1
BGE-105
1e-6 1e-5 0.0001 0.001 0.01
Max = 109.8 Slope = 1.399
Min = -0.3904 EC50 = 8.56e-5
Pyr-Apelin-13
%Effc mAGTRL1
Mouse APJ
1e-5 0.0001 0.001 0.01 0.10
Max = 95.55 Slope = 1.272
Min = -1.213 EC50 = 0.02509
logC uM
BA-1-001.2
%Effc mAGTRL1
1e-6 1e-5 0.0001 0.001 0.01
Max = 66.24 Slope = 1.088
Min = -0.8027 EC50 = 0.0007697
logC uM

FIG. 6A

Compound	Human APJ		Mouse APJ	
	EC50 (nM)	Emax (%)	EC50 (nM)	Emax (%)
Pyr[1]-Apelin-13	1.2	115%	25	93%
BGE-105	0.1	114%	0.8	65%
			0.4	60%

FIG. 6B

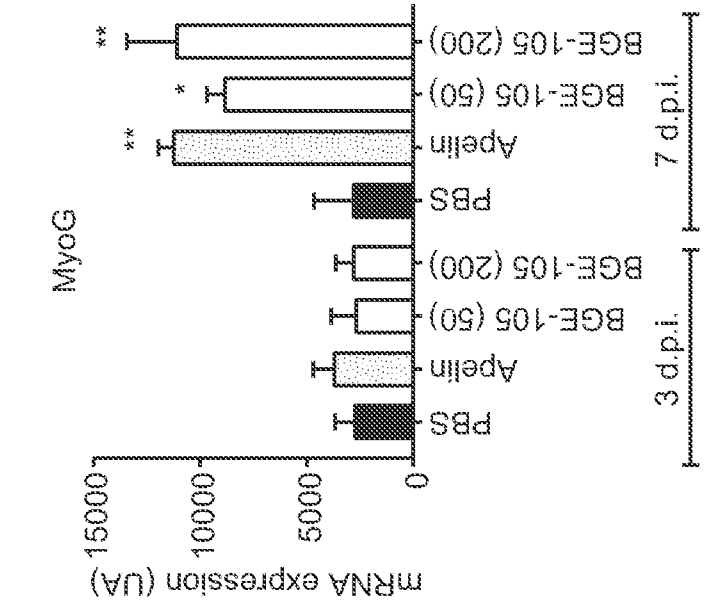


FIG. 7C

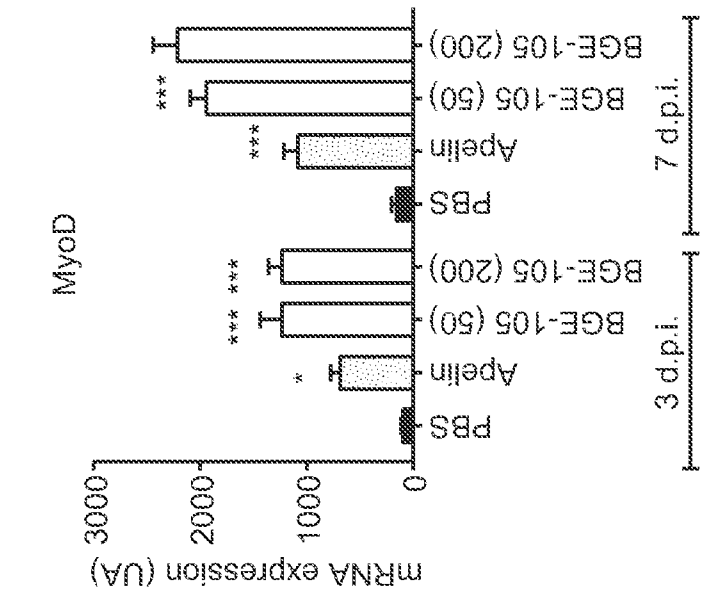


FIG. 7B

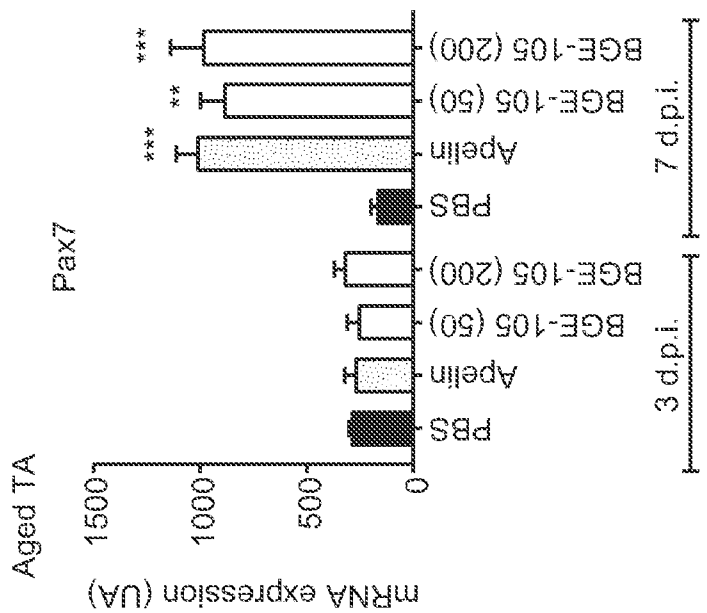


FIG. 7A

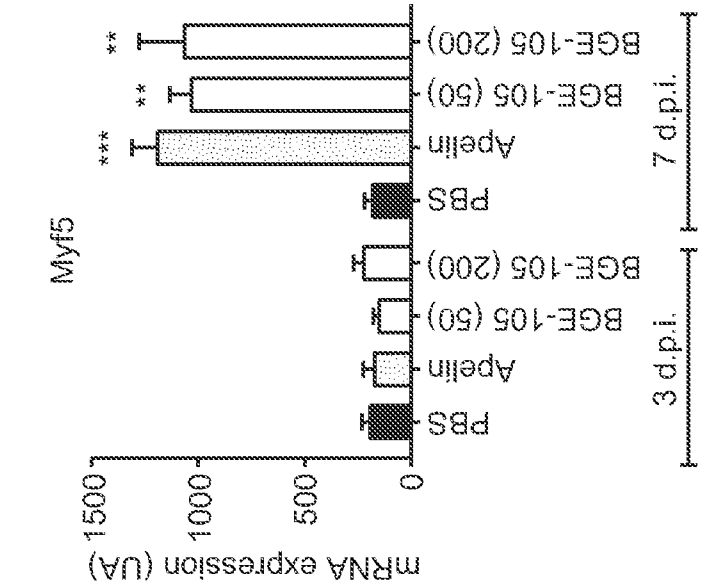


FIG. 7F

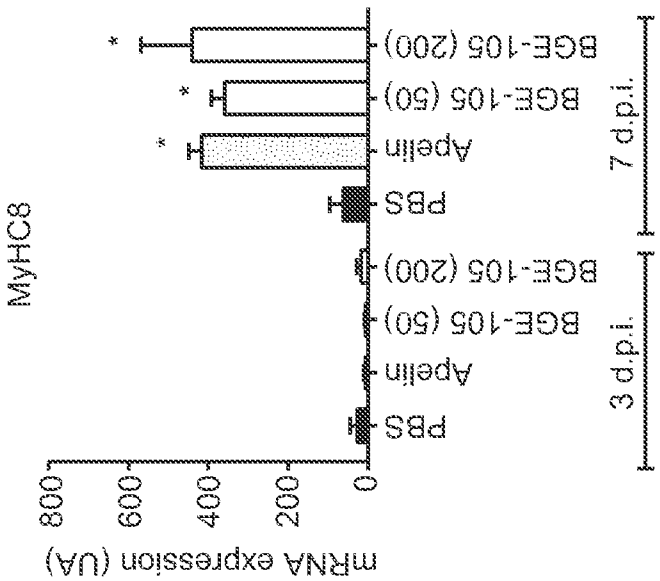


FIG. 7E

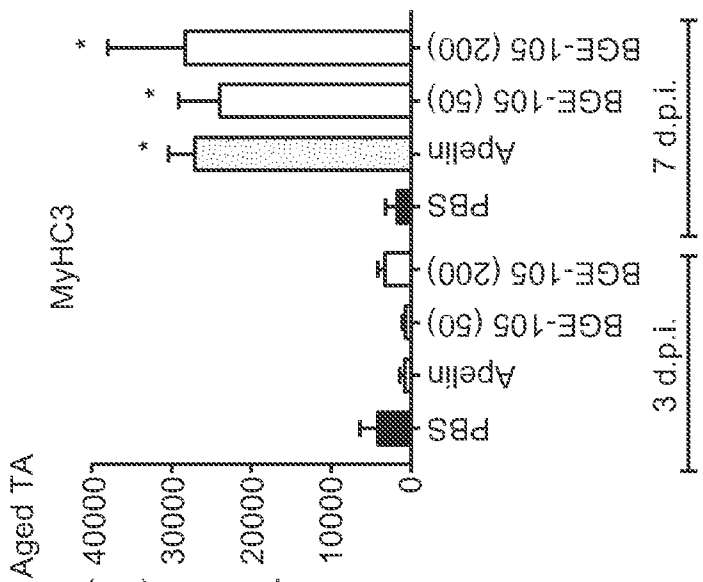


FIG. 7D

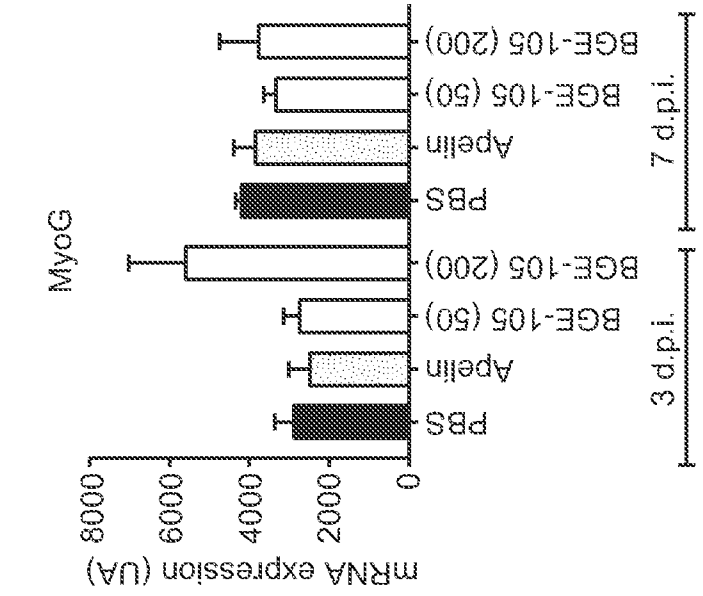


FIG. 7I

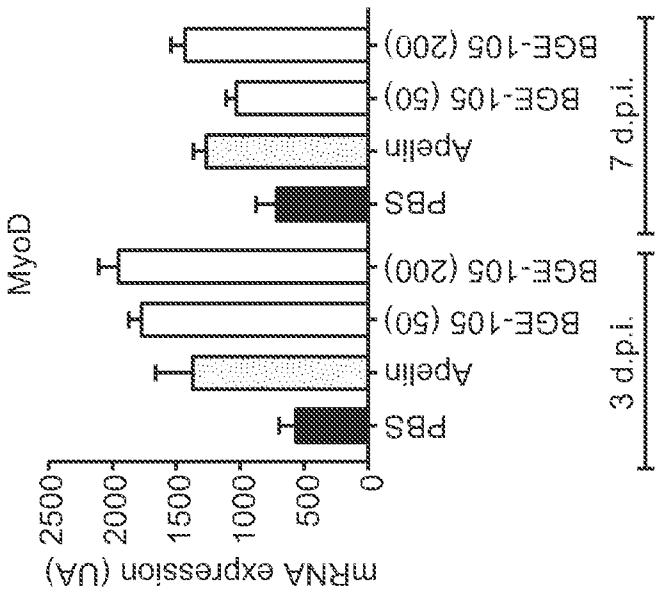


FIG. 7H

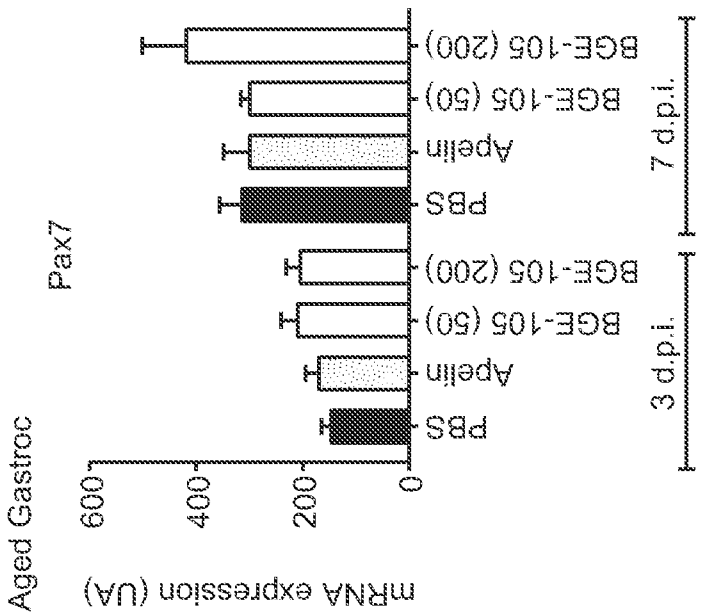


FIG. 7G

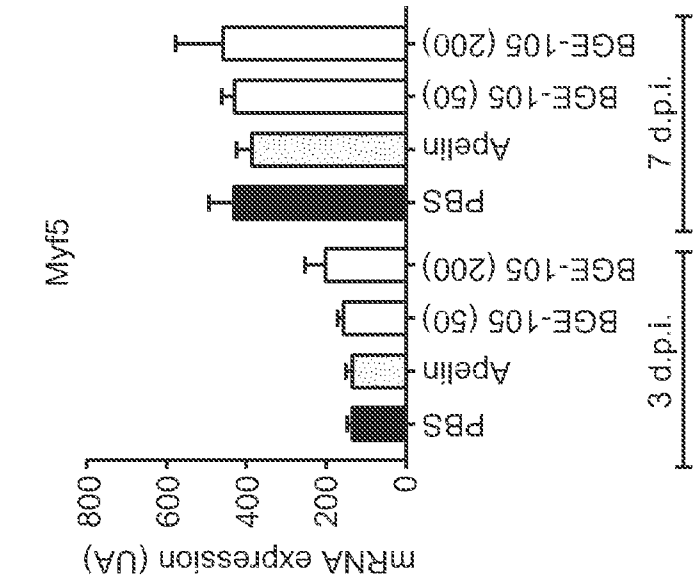


FIG. 7L

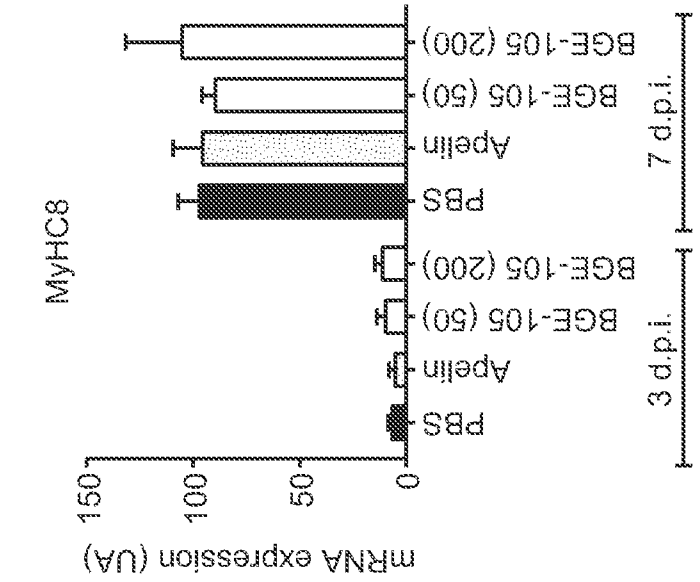


FIG. 7K

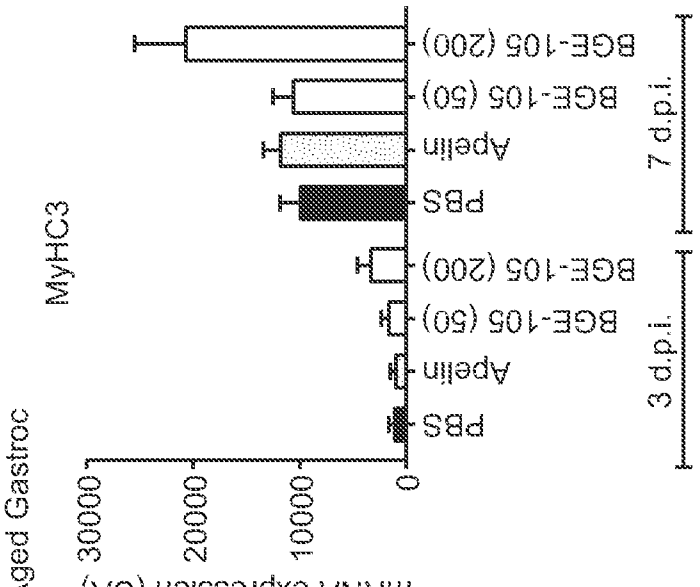


FIG. 7J

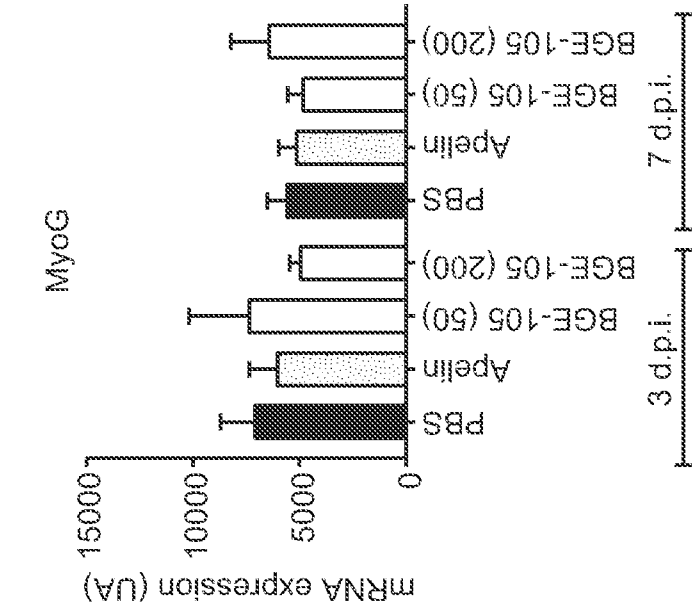


FIG. 7O

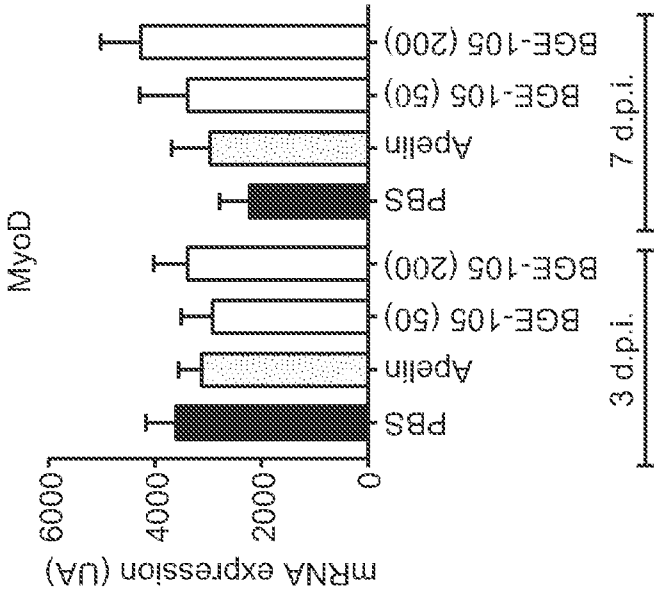


FIG. 7N

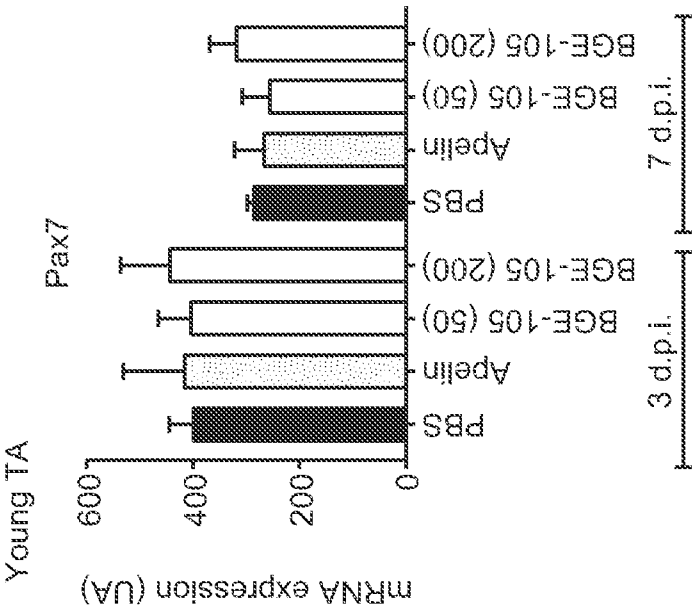


FIG. 7M

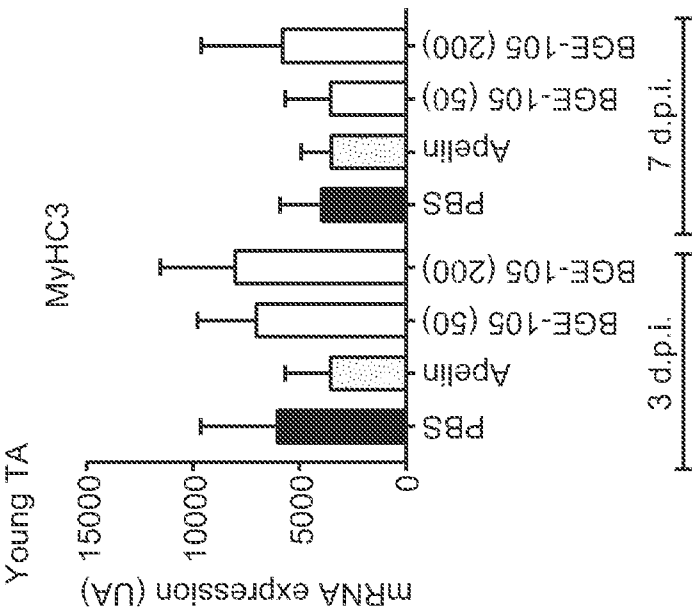


FIG. 7P

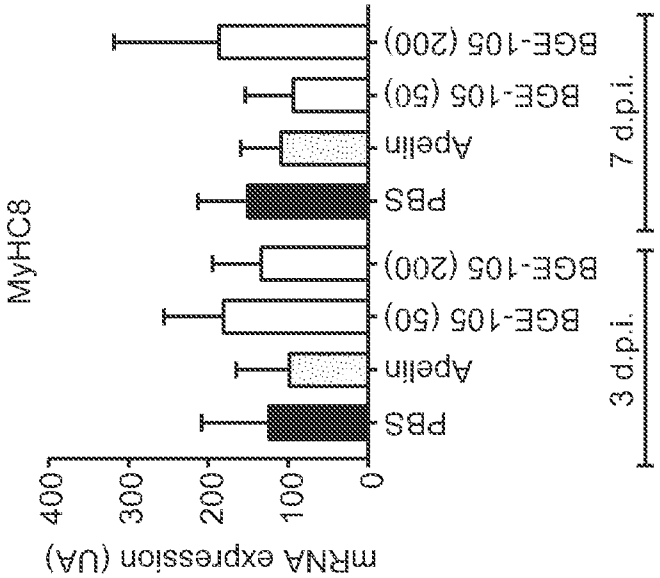


FIG. 7Q

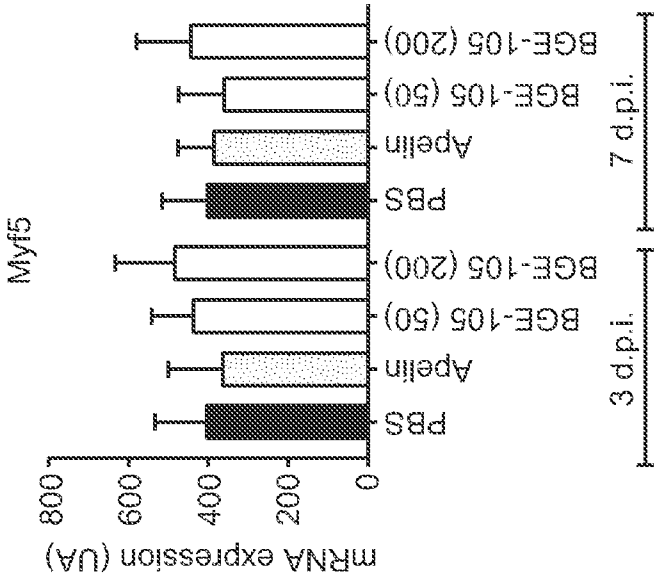


FIG. 7R

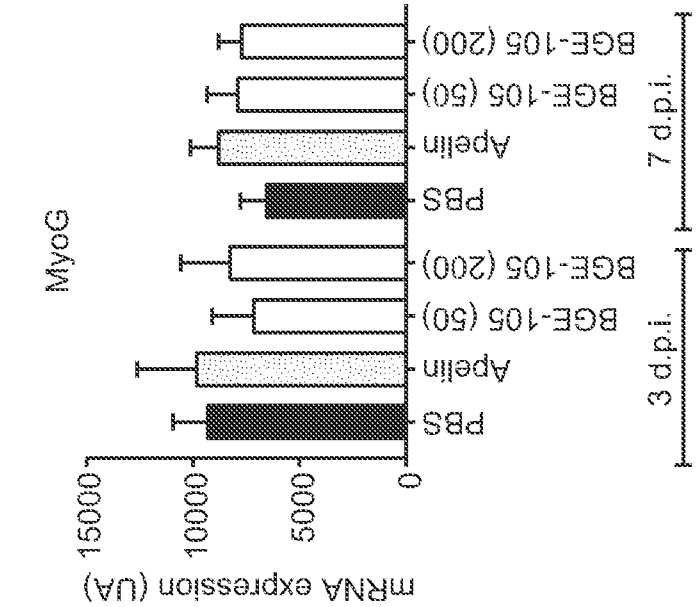


FIG. 7U

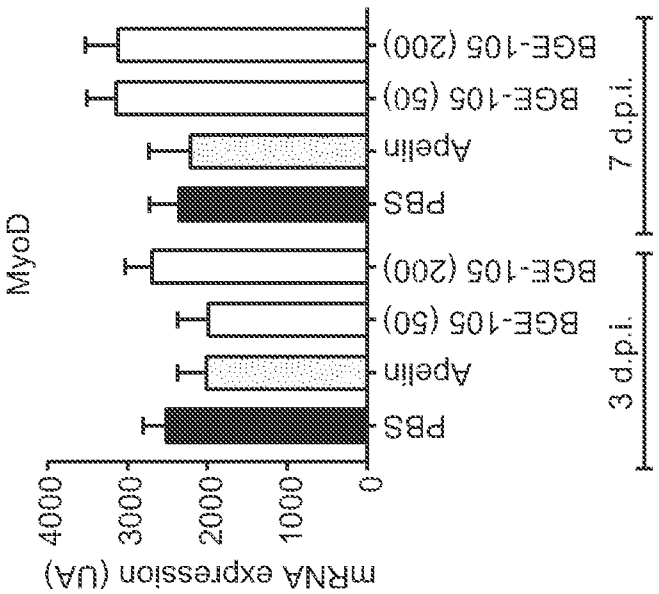


FIG. 7T

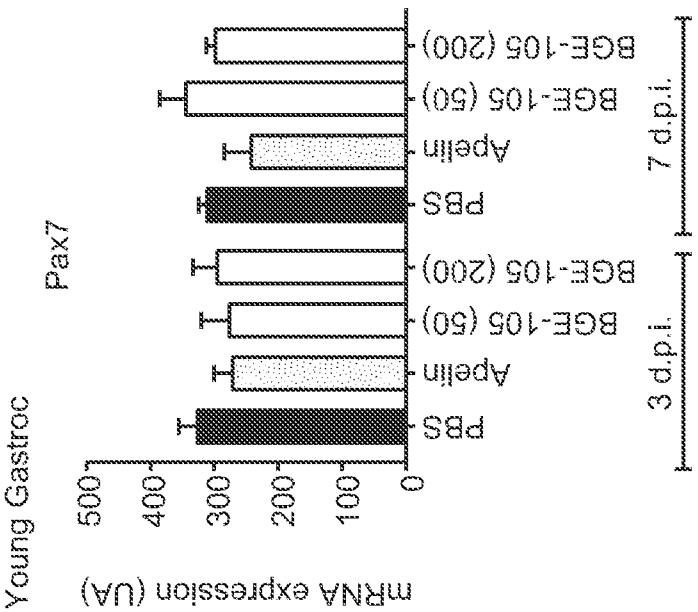


FIG. 7S

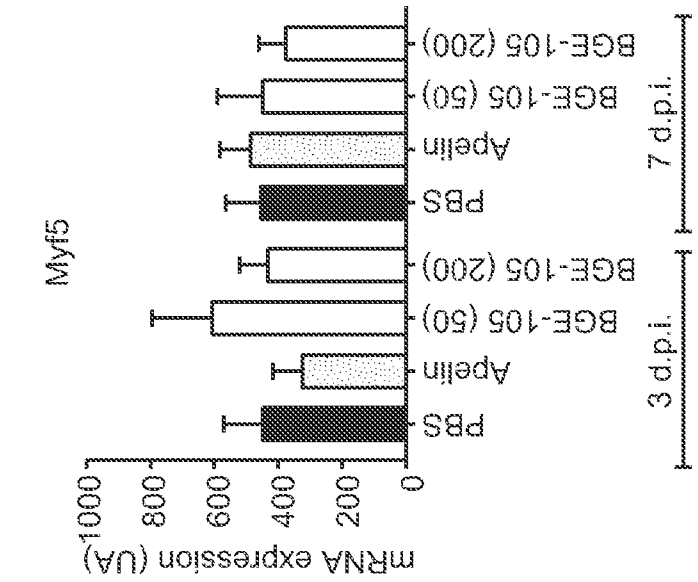


FIG. 7X

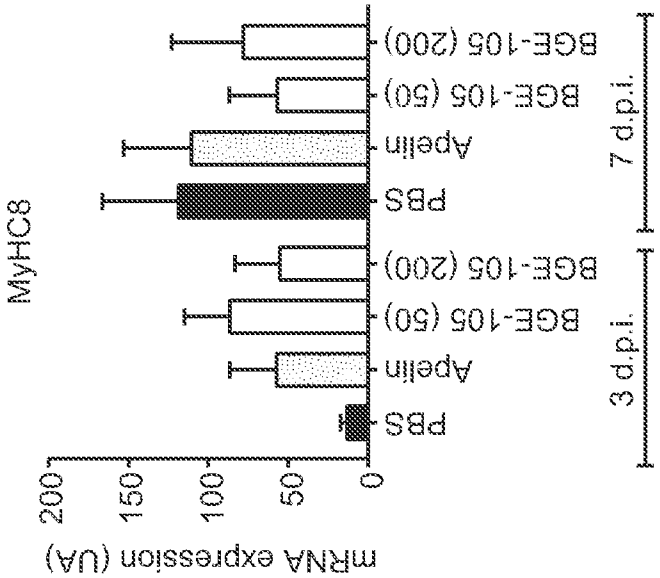


FIG. 7W

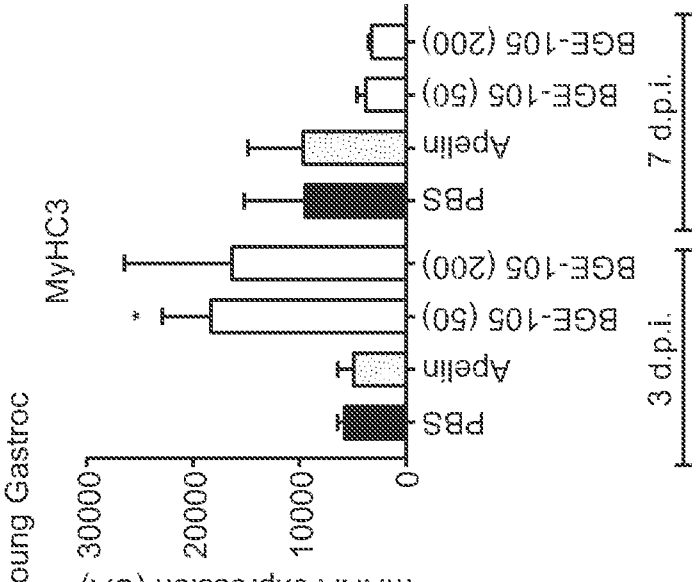


FIG. 7V

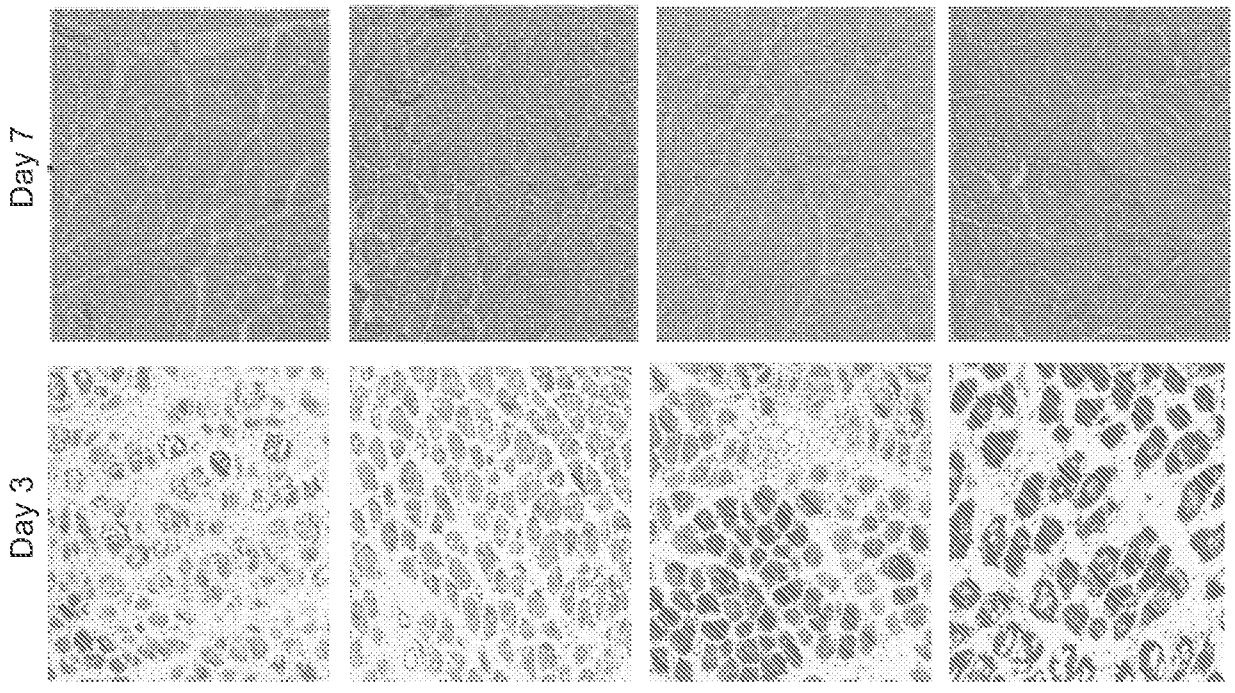

Day 3
Day 7
PBS
Apelin
BA1
BA2

FIG. 7Y

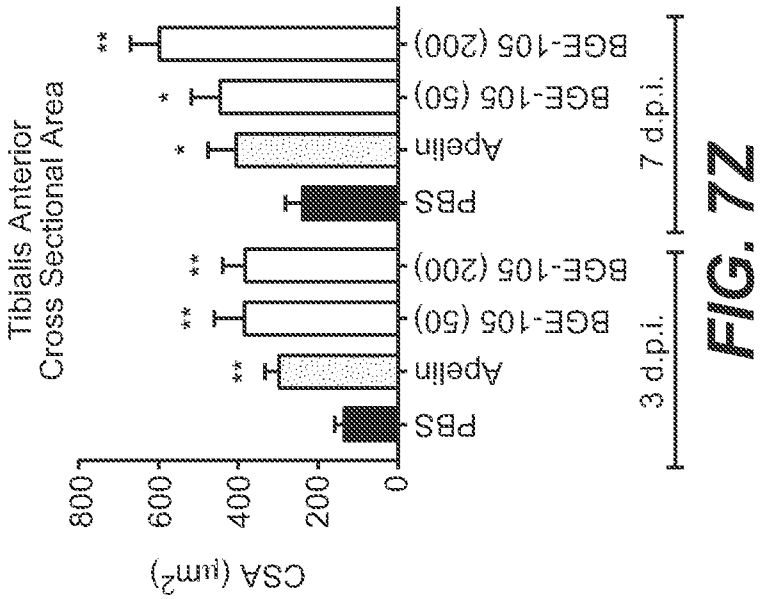

Tibialis Anterior
Cross Sectional Area
CSA (μm²)
800
600
400
200
0
PBS
Apelin
BGE-105 (50)
BGE-105 (200)
PBS
Apelin
BGE-105 (50)
BGE-105 (200)
3 d.p.i.
7 d.p.i.

FIG. 7Z

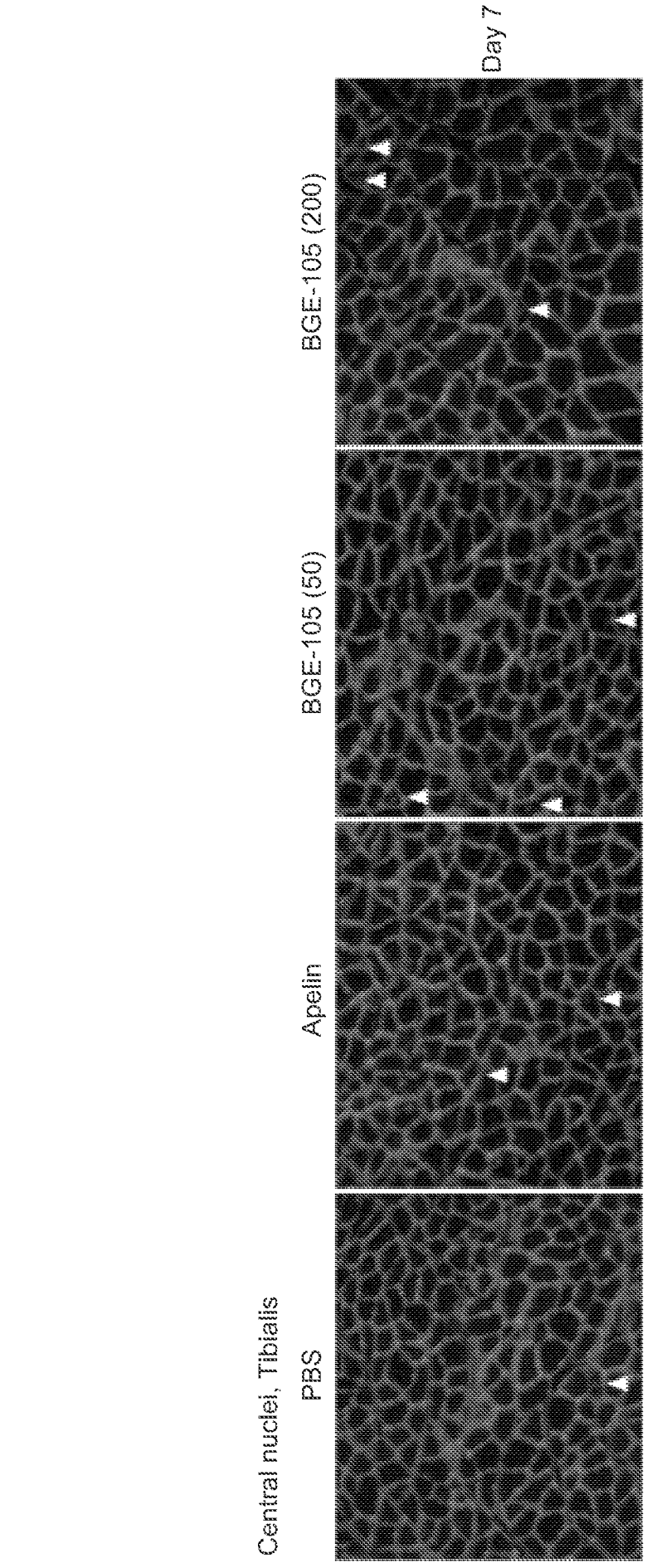

Central nuclei, Tibialis
PBS
Apelin
BGE-105 (50)
BGE-105 (200)
Day 7

FIG. 7AA


Tibialis Anterior
Central Nuclei
% of fibers
with central nuclei
8
6
4
2
0
*
*
*
PBS
Apelin
BGE-105 (50)
BGE-105 (200)
7 d.p.i.

FIG. 7BB

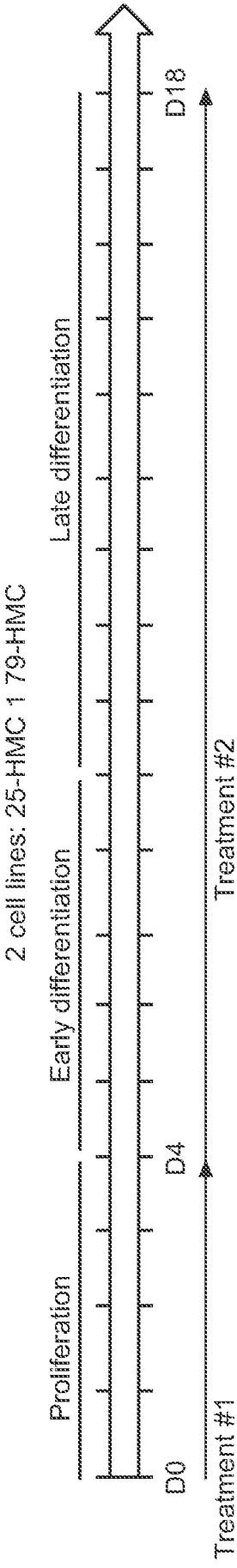


FIG. 8A

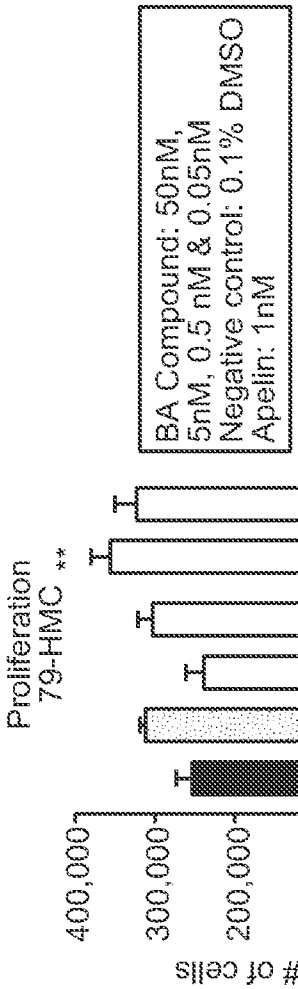


FIG. 8C

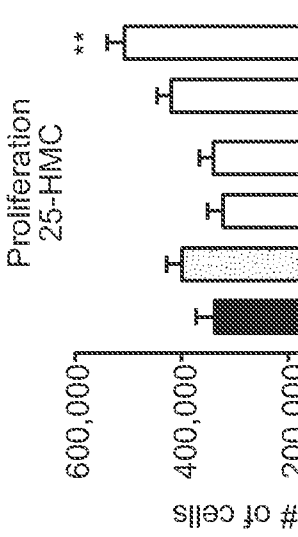


FIG. 8B

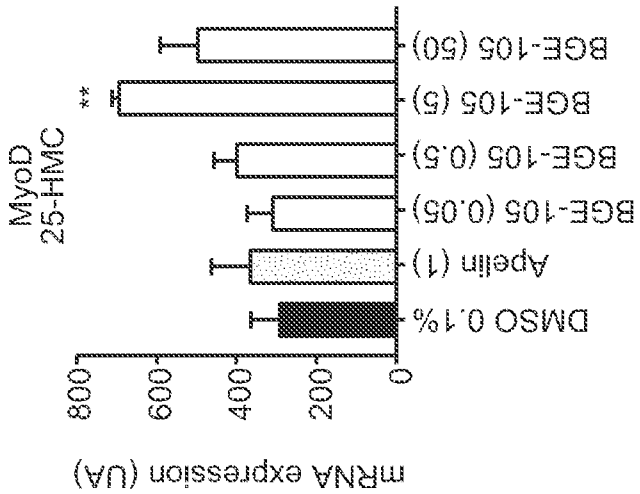

MyoD
25-HMC
mRNA expression (UA)
800
600
400
200
0
**
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)

FIG. 8E

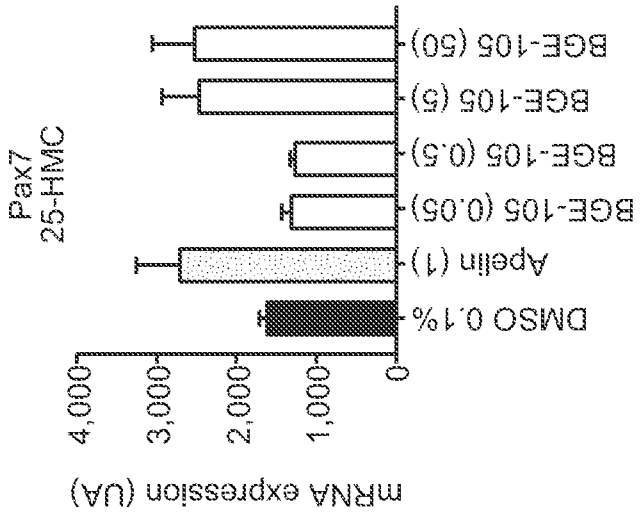

Pax7
25-HMC
mRNA expression (UA)
4,000
3,000
2,000
1,000
0
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)

FIG. 8D

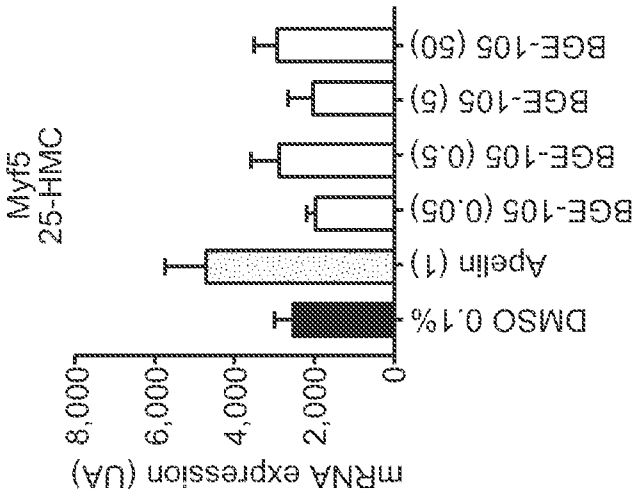

Myf5
25-HMC
mRNA expression (UA)
8,000
6,000
4,000
2,000
0
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)

FIG. 8G

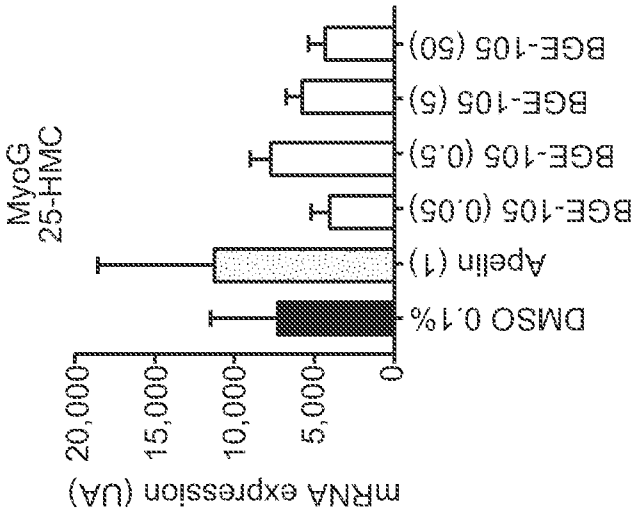

MyoG
25-HMC
mRNA expression (UA)
20,000
15,000
10,000
5,000
0
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)

FIG. 8F

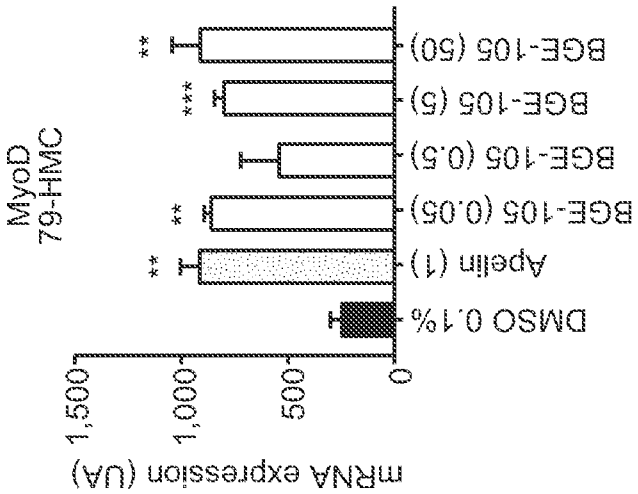

MyoD
79-HMC
mRNA expression (UA)
1,500
1,000
500
0
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)
**
**
**
***
**

FIG. 8I

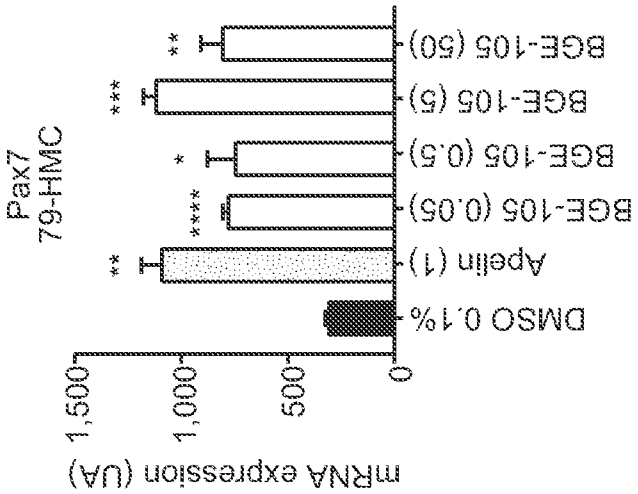

Pax7
79-HMC
mRNA expression (UA)
1,500
1,000
500
0
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)
**
****
*
***
**

FIG. 8H

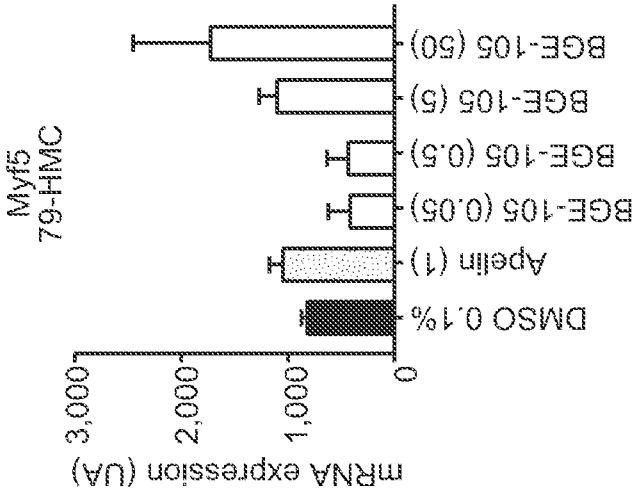

Myf5
79-HMC
mRNA expression (UA)
3,000
2,000
1,000
0
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)

FIG. 8K

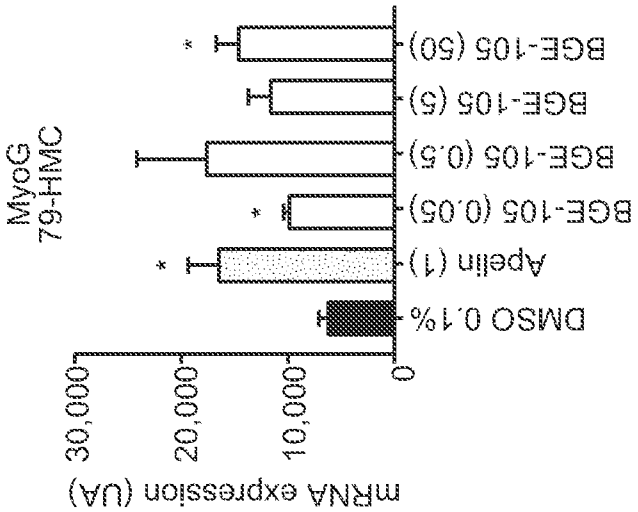

MyoG
79-HMC
mRNA expression (UA)
30,000
20,000
10,000
0
DMSO 0.1%
Apelin (1)
BGE-105 (0.05)
BGE-105 (0.5)
BGE-105 (5)
BGE-105 (50)
*
*

FIG. 8J

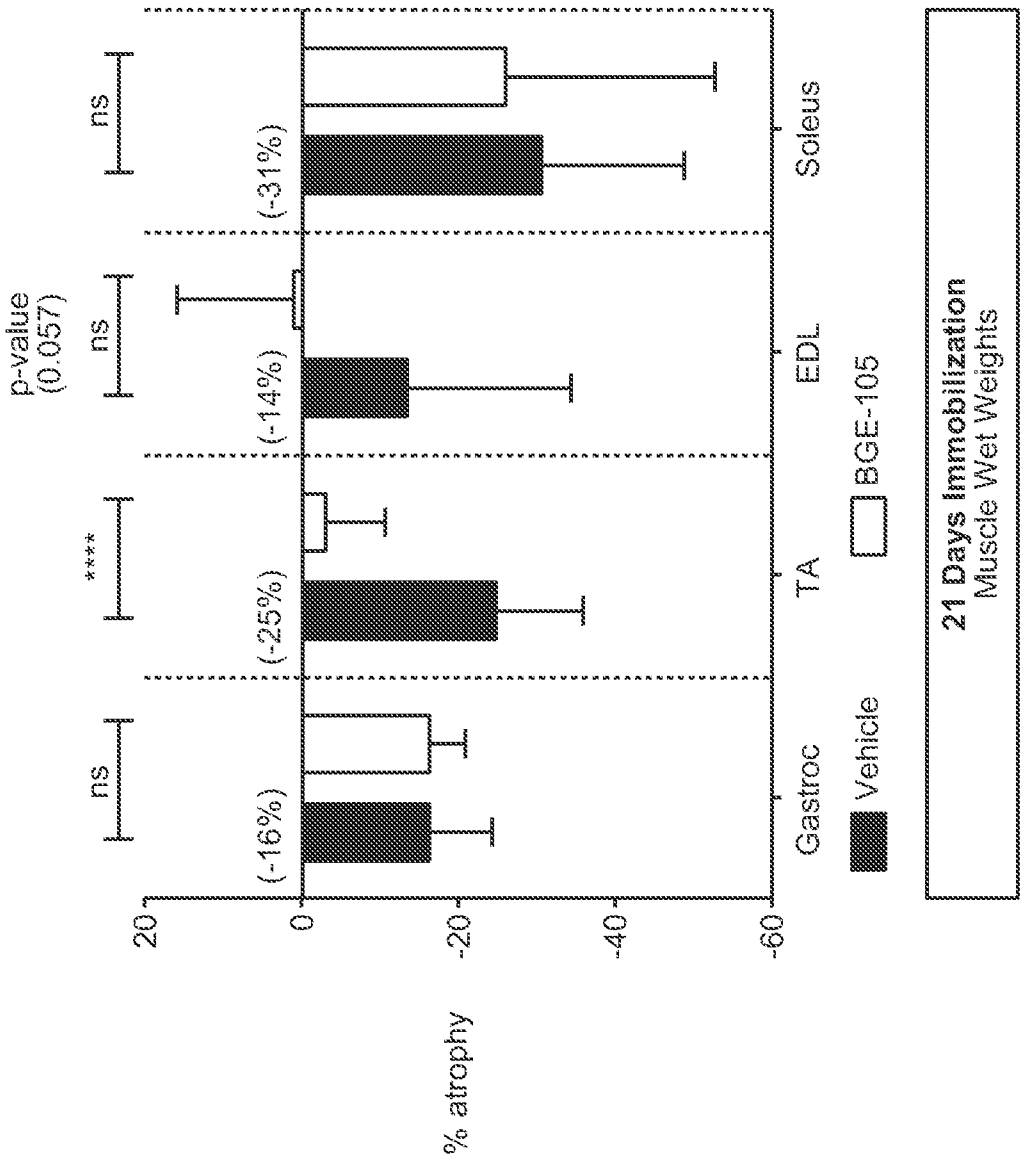

21 Days Immobilization
Muscle Wet Weights
Vehicle
BGE-105
% atrophy
20
0
-20
-40
-60
Gastroc
TA
EDL
Soleus
(-16%)
ns
(-25%)
****
(-14%)
ns
(-31%)
ns
p-value
(0.057)

FIG. 9A

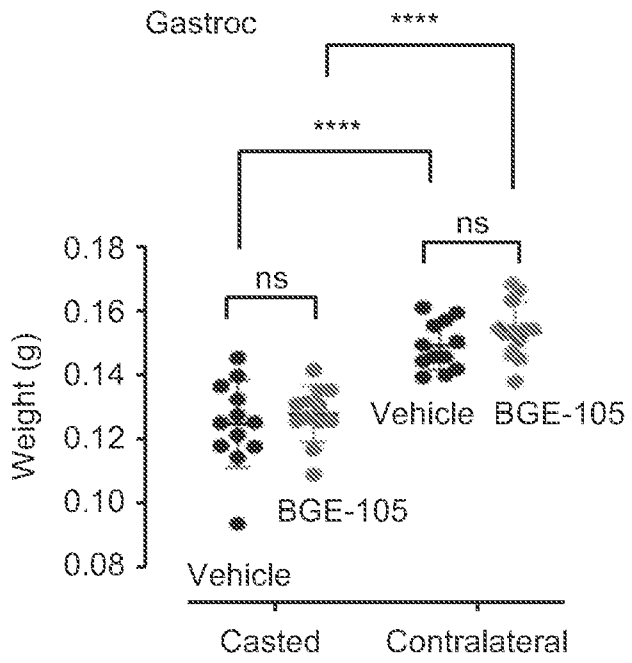


FIG. 9B

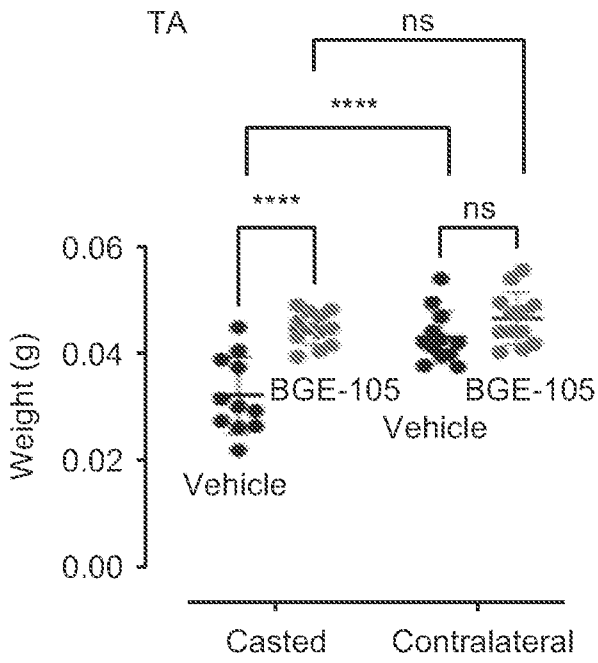


FIG. 9D

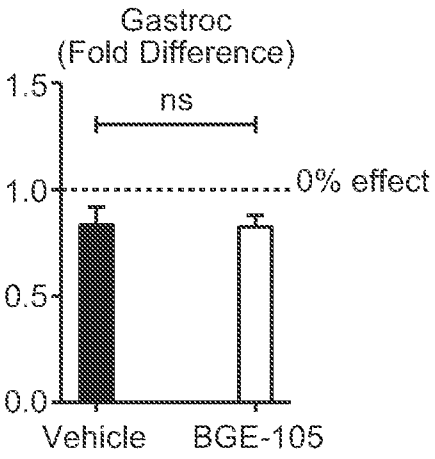


FIG. 9C

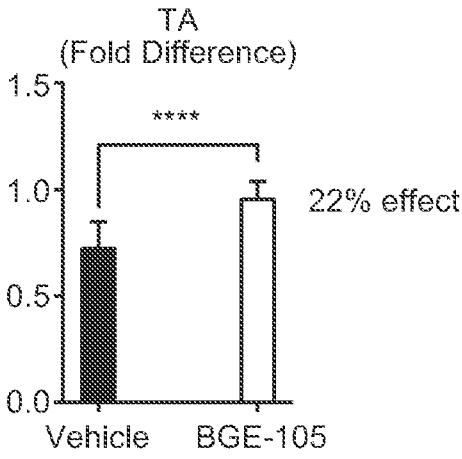


FIG. 9E

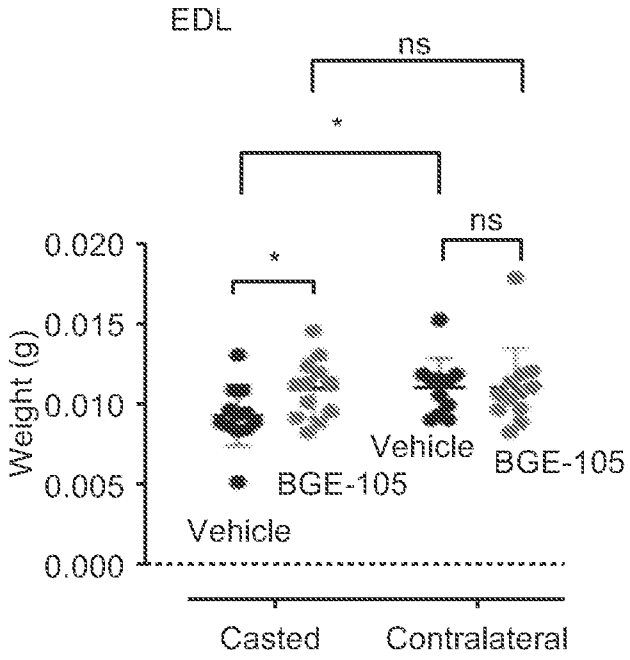


FIG. 9F

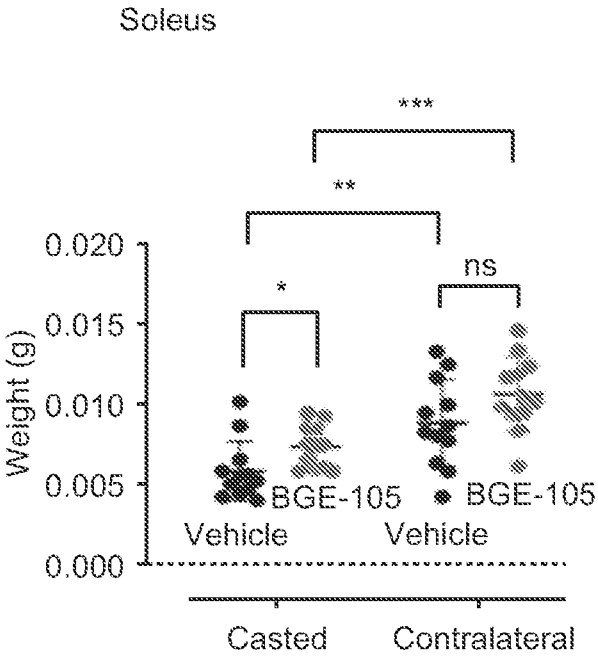


FIG. 9H

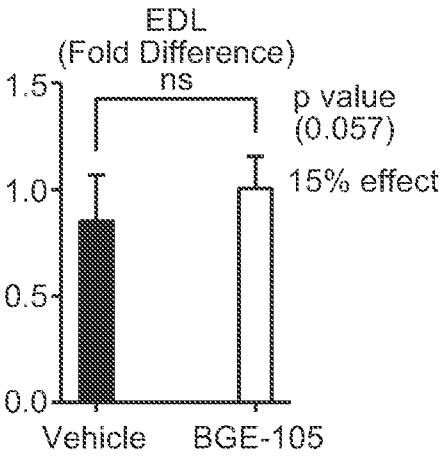


FIG. 9G

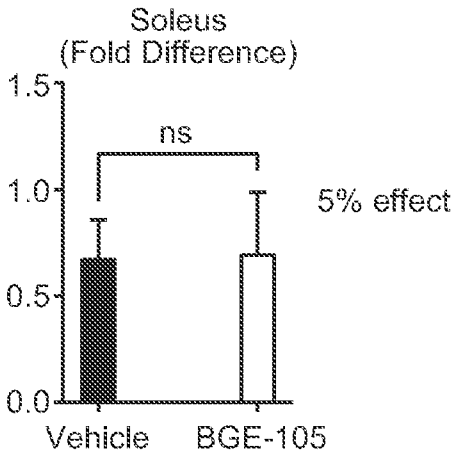


FIG. 9I

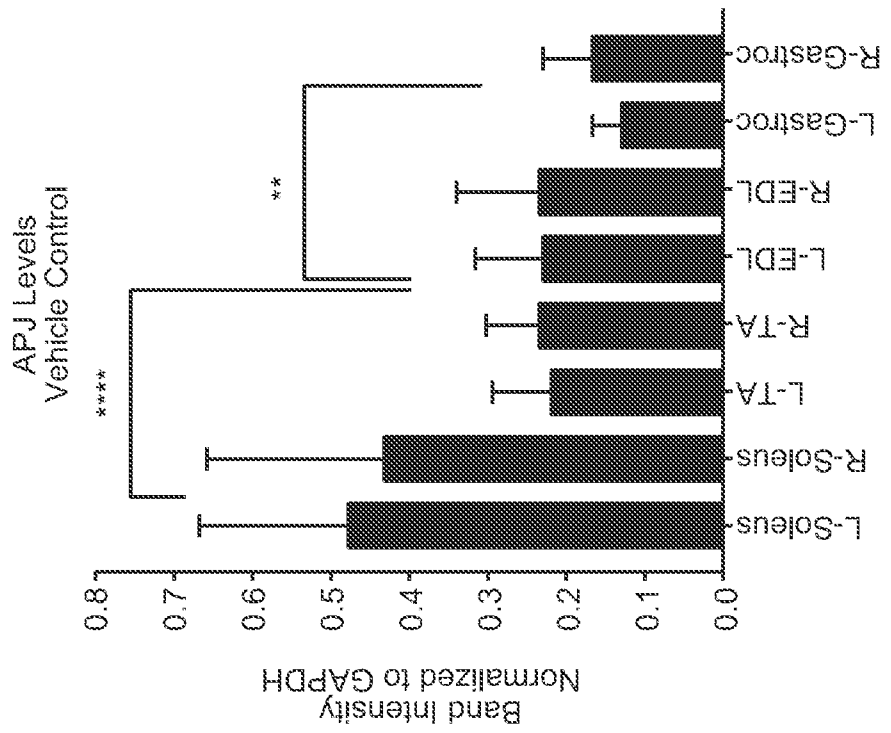

APJ Levels
Vehicle Control
Band Intensity
Normalized to GAPDH
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
****
**
L-Soleus
R-Soleus
L-TA
R-TA
L-EDL
R-EDL
L-Gastroc
R-Gastroc
Mouse Tissue (15 µg)

FIG. 9J

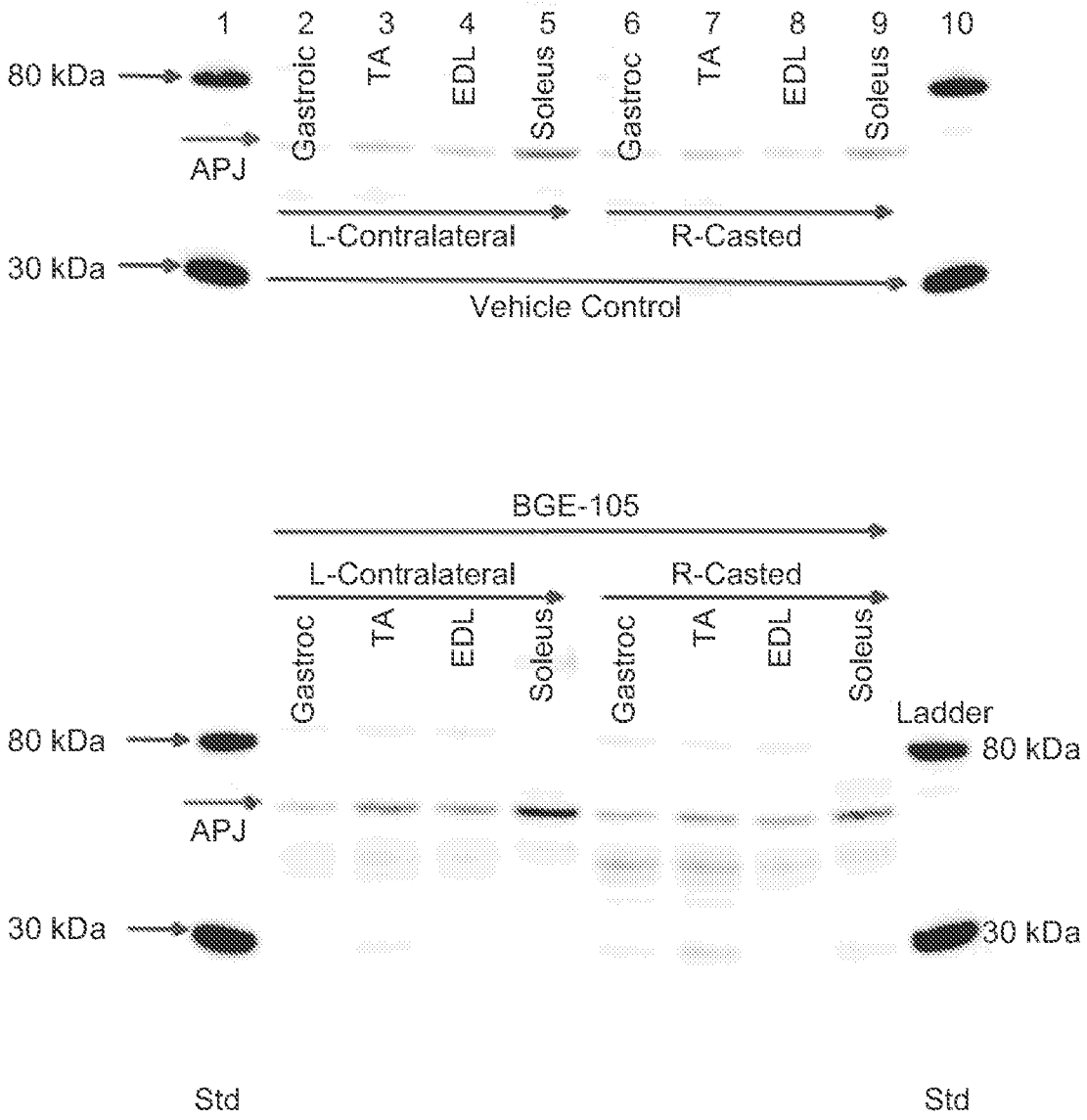

1
2
3
4
5
6
7
8
9
10
80 kDa
APJ
Gastroic
TA
EDL
Soleus
Gastroc
TA
EDL
Soleus
L-Contralateral
R-Casted
30 kDa
Vehicle Control
BGE-105
L-Contralateral
R-Casted
Gastroc
TA
EDL
Soleus
Gastroc
TA
EDL
Soleus
Ladder
80 kDa
80 kDa
APJ
30 kDa
30 kDa
Std
Std

FIG. 9K

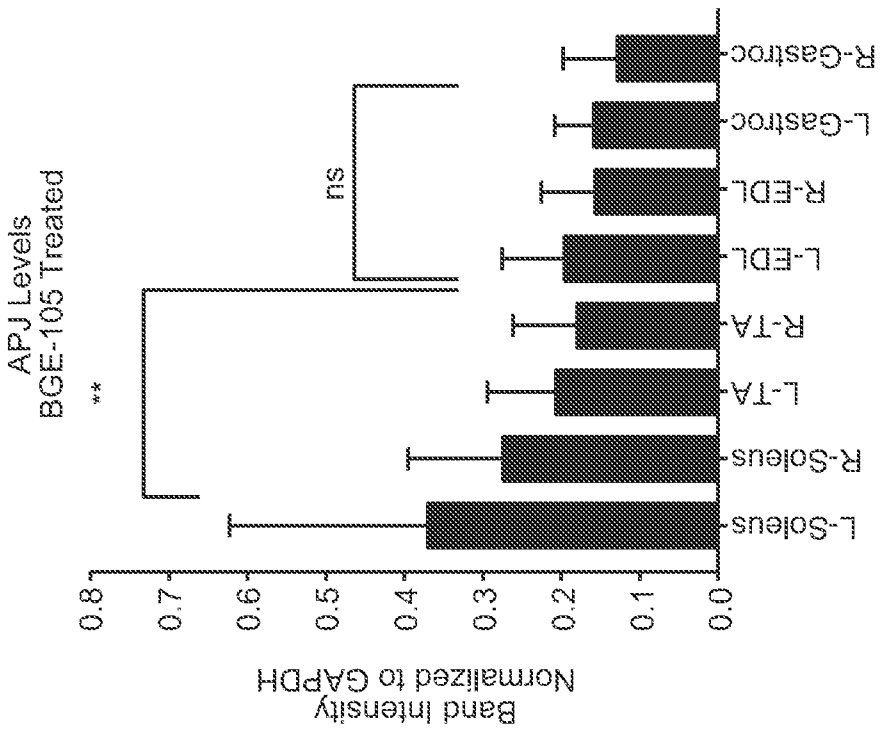

APJ Levels
BGE-105 Treated
**
ns
Band Intensity
Normalized to GAPDH
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
L-Soleus
R-Soleus
L-TA
R-TA
L-EDL
R-EDL
L-Gastroc
R-Gastroc
Mouse Tissue (15 µg)

FIG. 9L

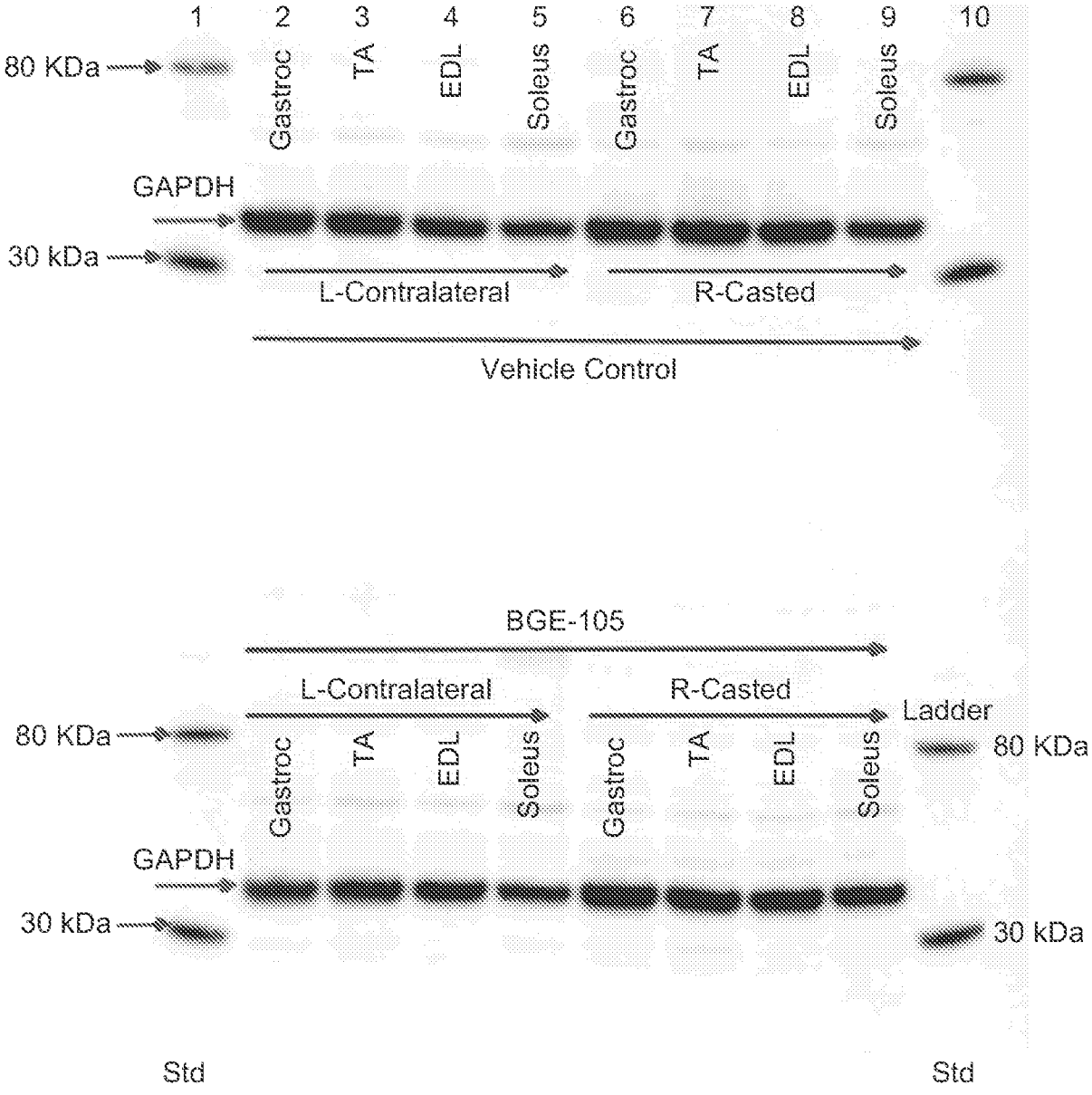

1
2
3
4
5
6
7
8
9
10
80 KDa
Gastroc
TA
EDL
Soleus
Gastroc
TA
EDL
Soleus
GAPDH
30 kDa
L-Contralateral
R-Casted
Vehicle Control
BGE-105
L-Contralateral
R-Casted
Ladder
80 KDa
Gastroc
TA
EDL
Soleus
Gastroc
TA
EDL
Soleus
80 KDa
GAPDH
30 kDa
30 kDa
Std
Std

FIG. 9M