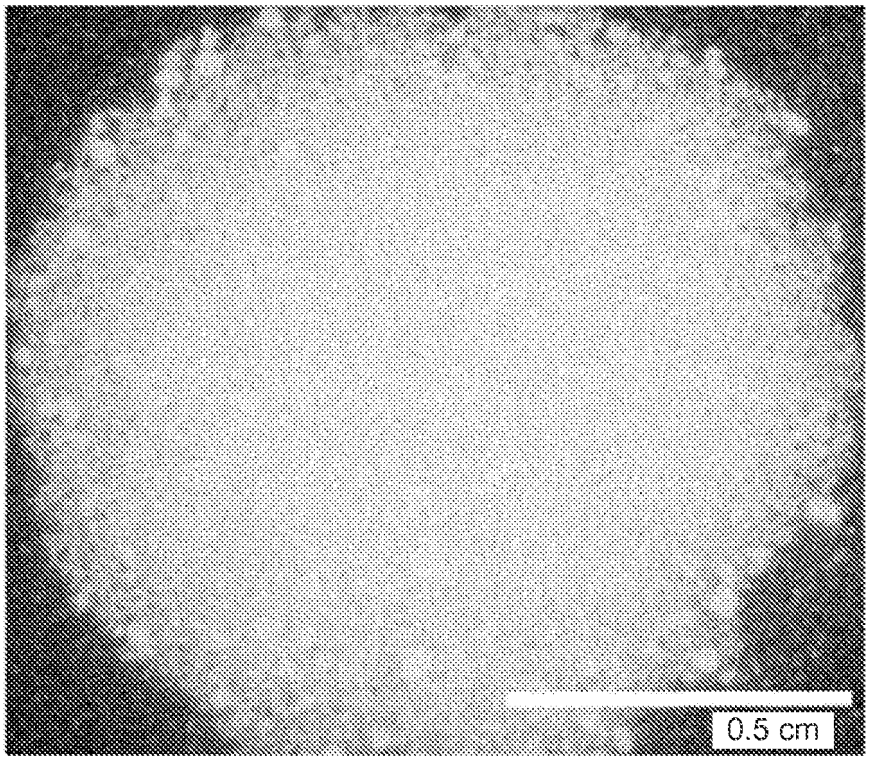


FIG. 1

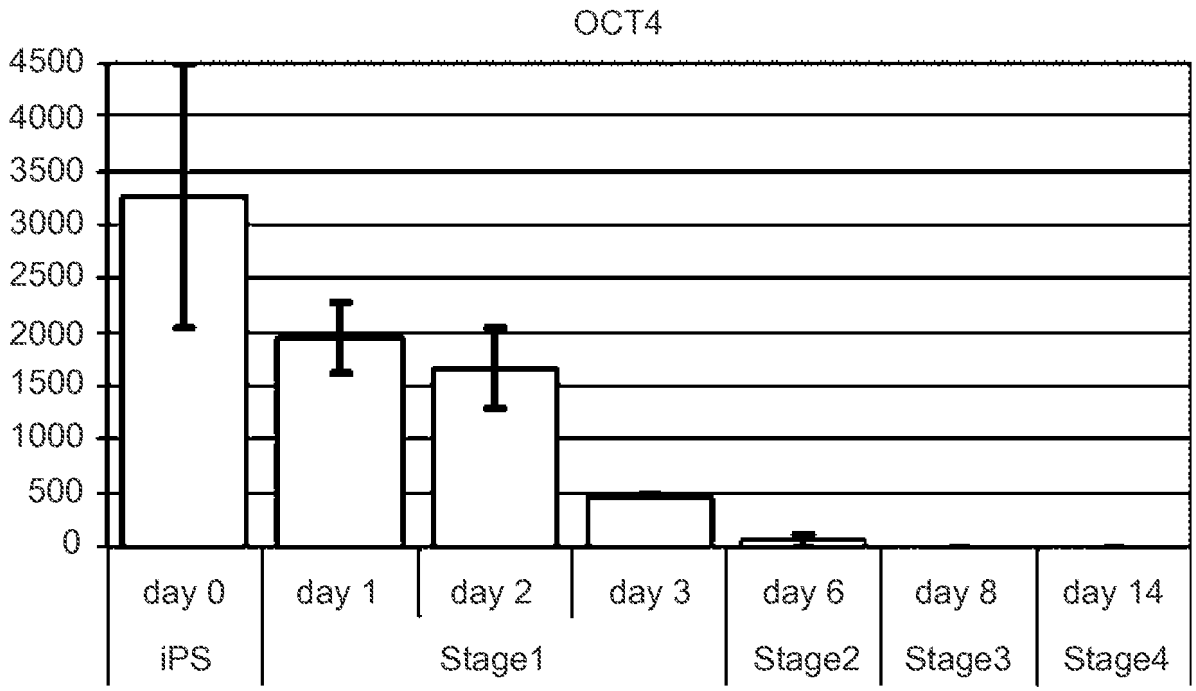

OCT4
4500
4000
3500
3000
2500
2000
1500
1000
500
0
day 0
iPS
day 1
day 2
Stage1
day 3
day 6
Stage2
day 8
Stage3
day 14
Stage4

FIG. 2A

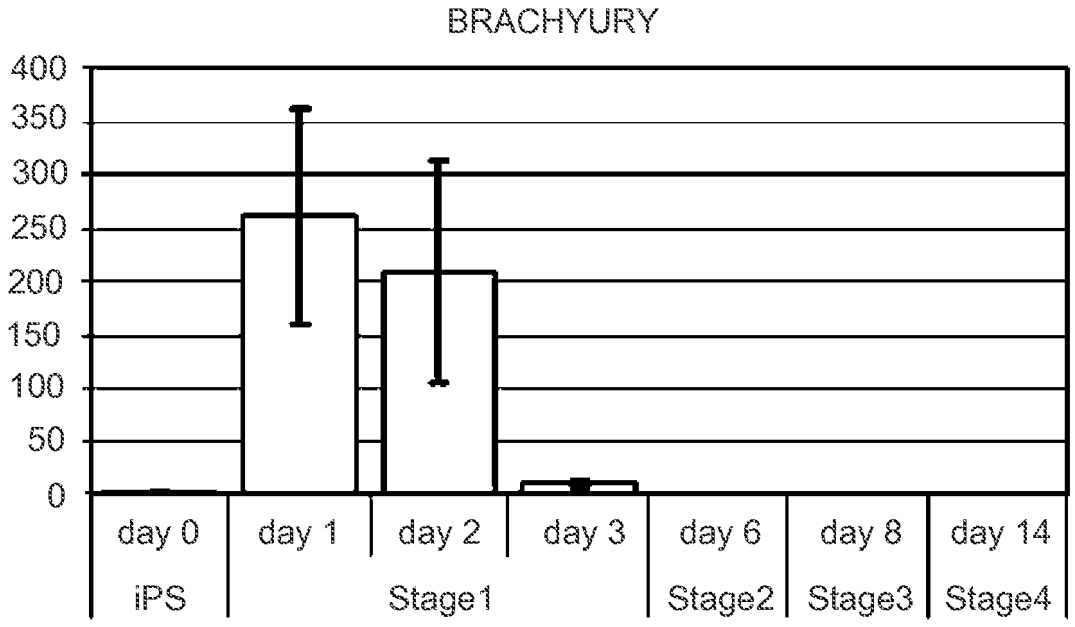

BRACHYURY
400
350
300
250
200
150
100
50
0
day 0
iPS
day 1
day 2
Stage1
day 3
day 6
Stage2
day 8
Stage3
day 14
Stage4

FIG. 2B

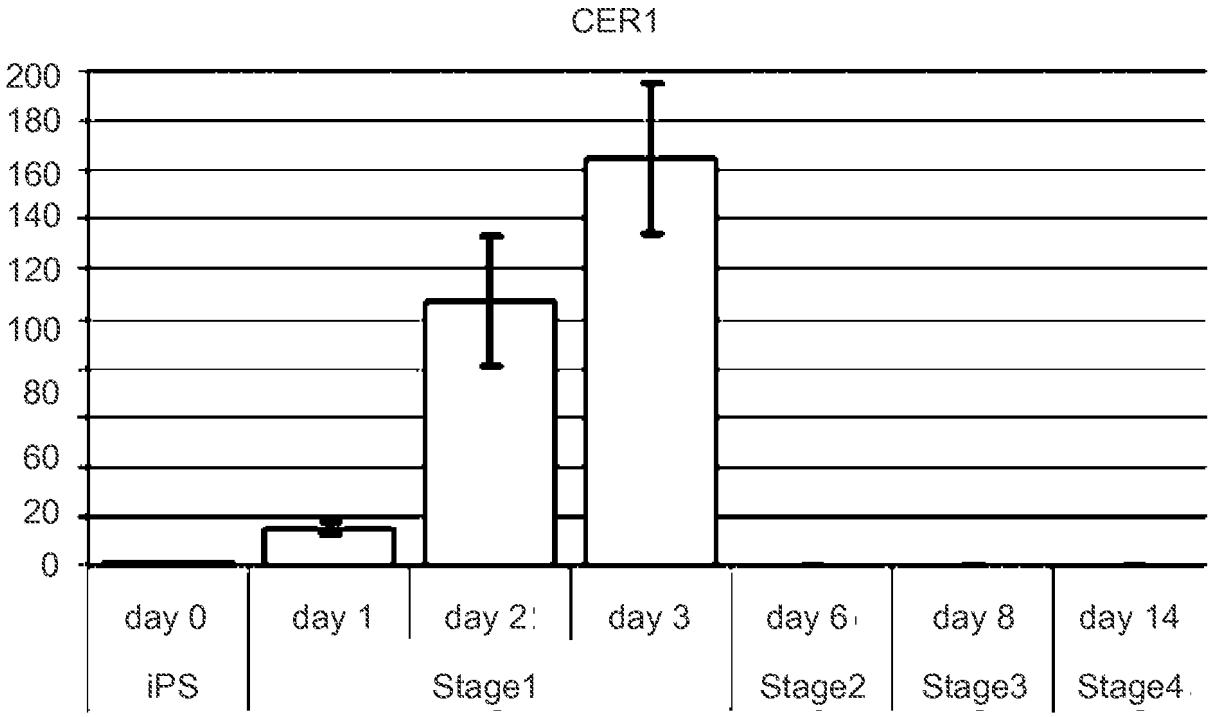

CER1
200
180
160
140
120
100
80
60
20
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

FIG. 2C

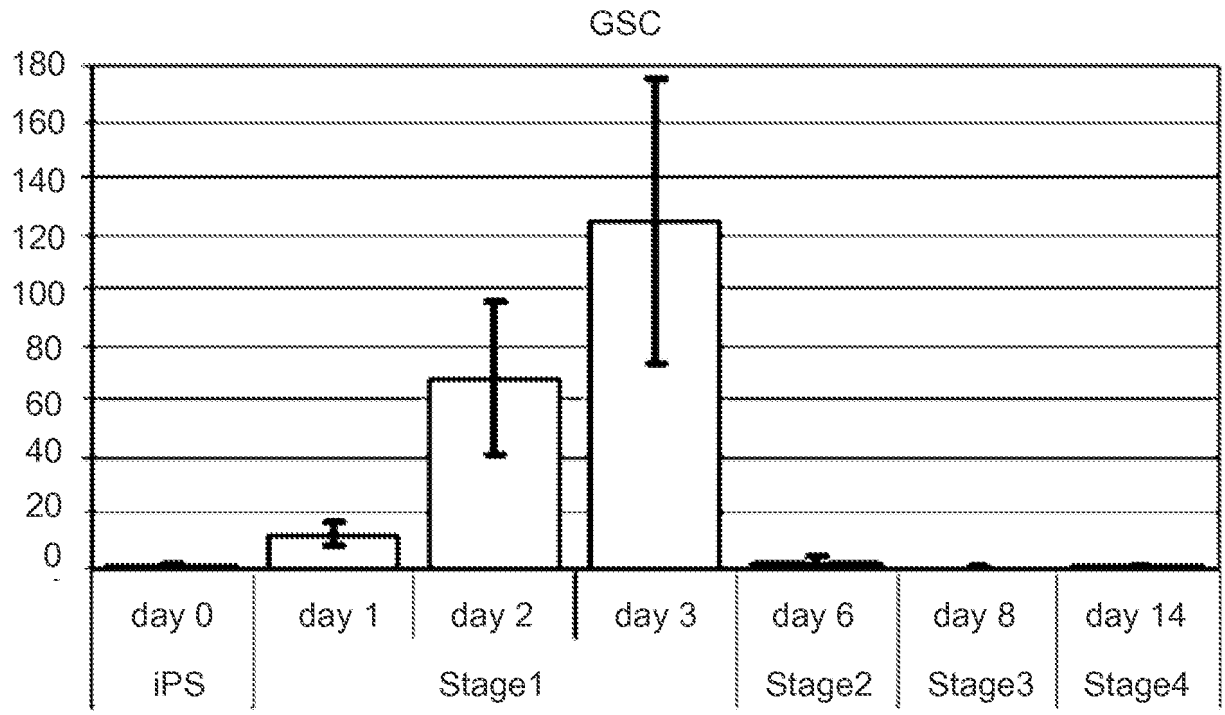

GSC
180
160
140
120
100
80
60
40
20
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

FIG. 2D

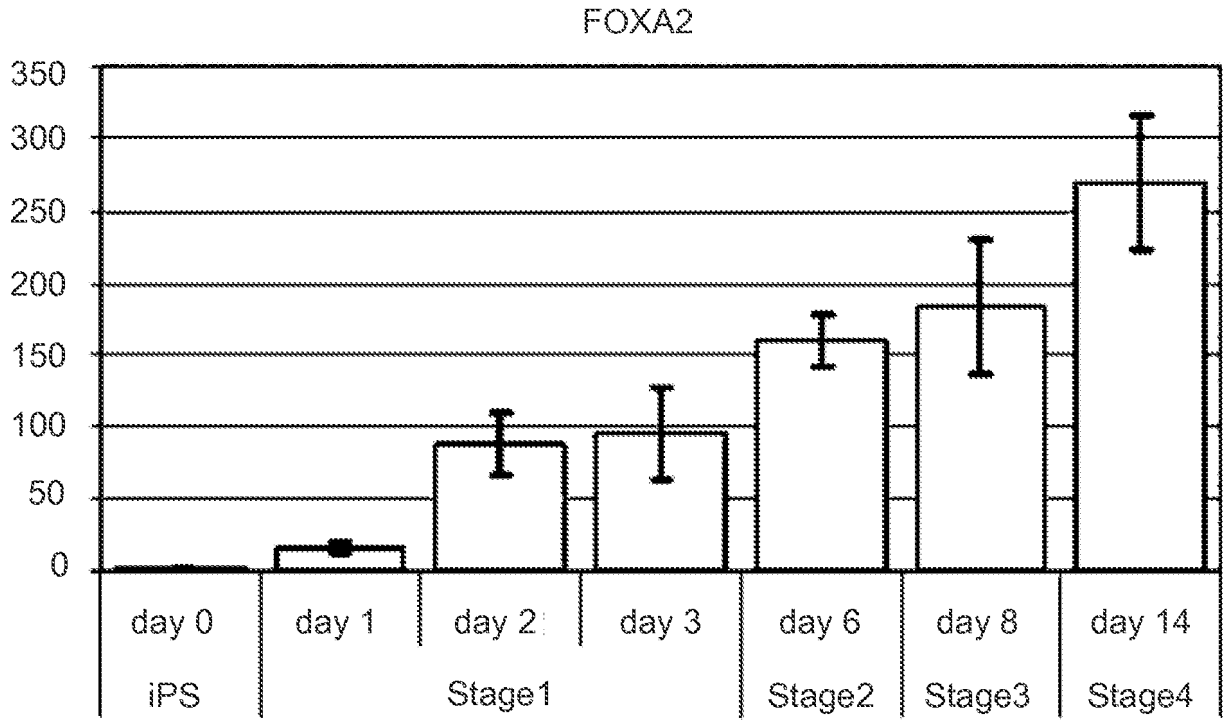

FOXA2
350
300
250
200
150
100
50
0
day 0
iPS
day 1
day 2
day 3
Stage1
day 6
Stage2
day 8
Stage3
day 14
Stage4

FIG. 2E

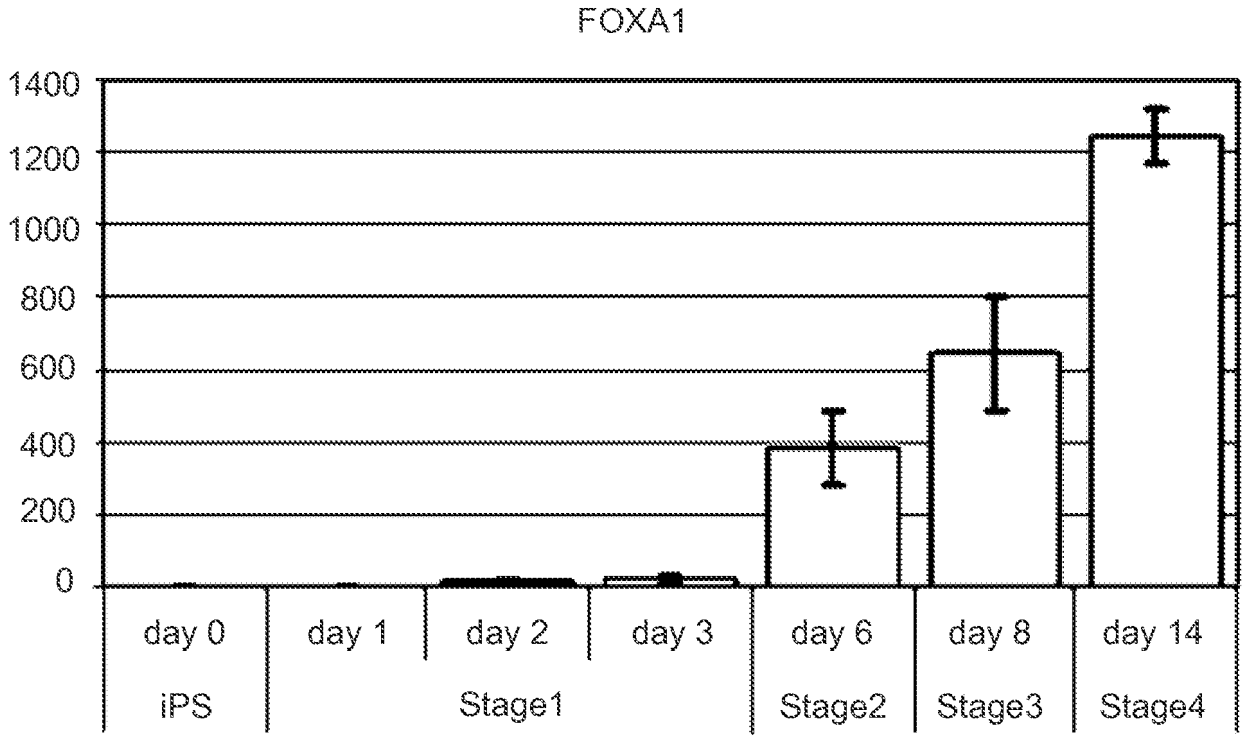

FOXA1
1400
1200
1000
800
600
400
200
0
day 0
iPS
day 1
day 2
day 3
Stage1
day 6
Stage2
day 8
Stage3
day 14
Stage4

FIG. 2F

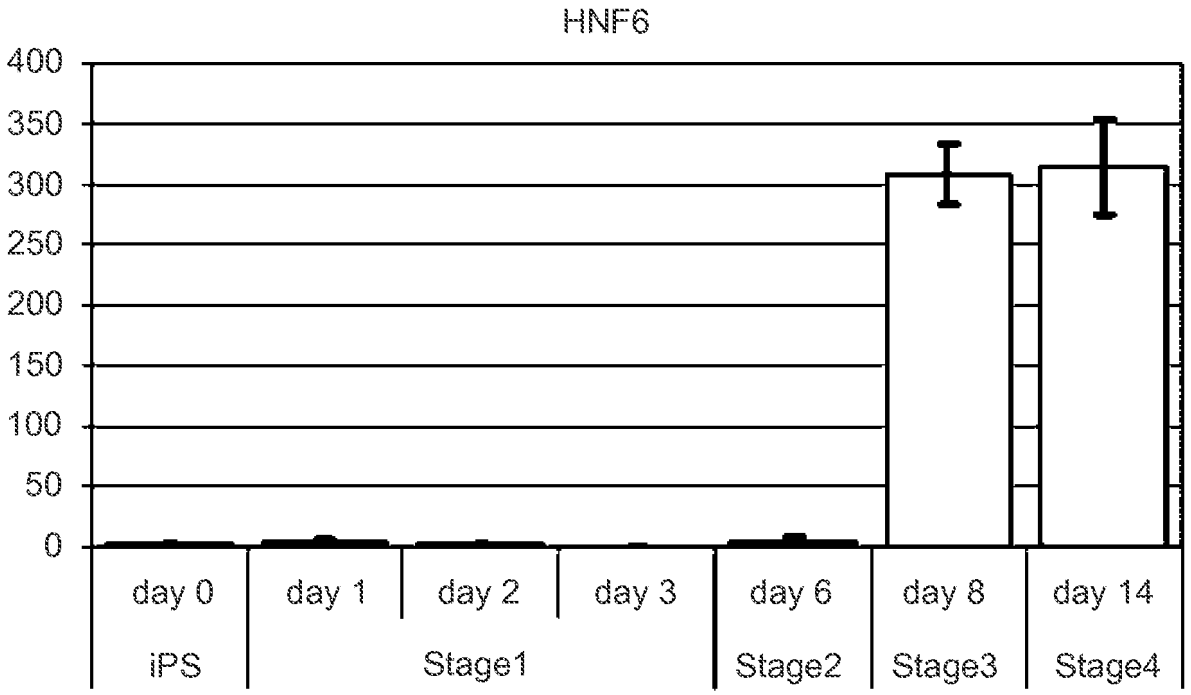

HNF6
400
350
300
250
200
150
100
50
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

FIG. 2G

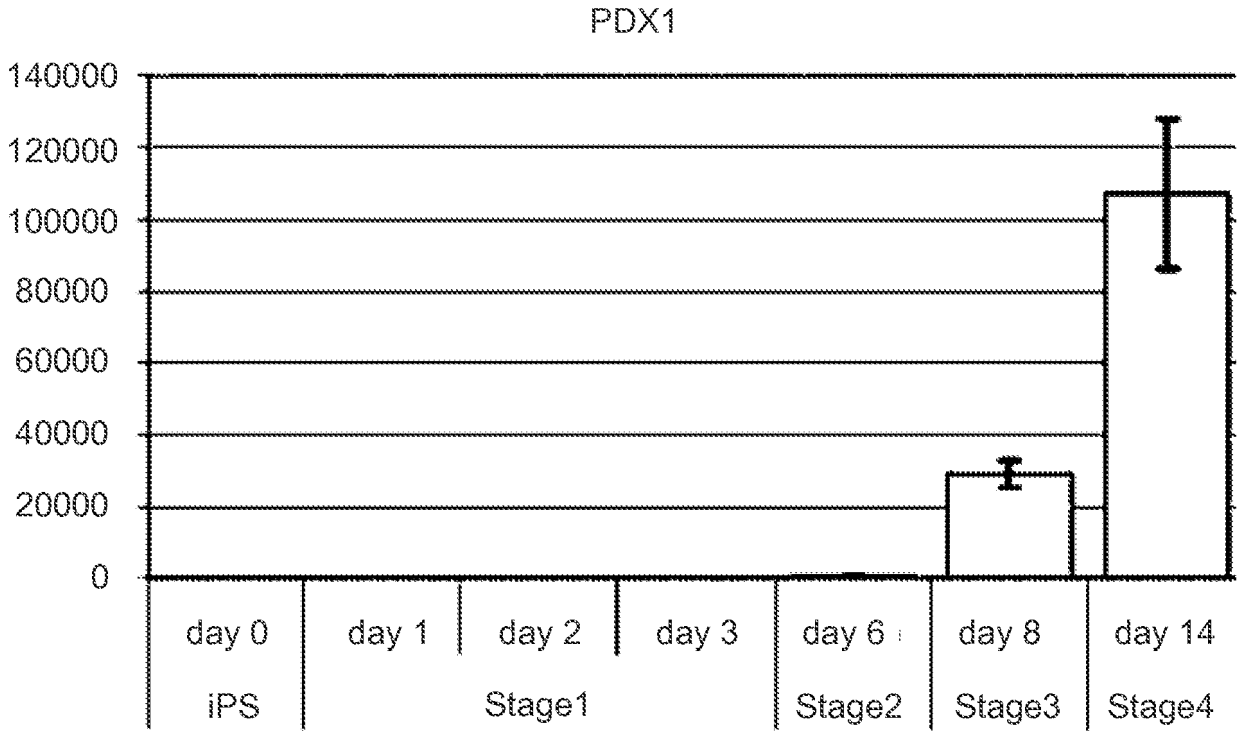

PDX1
140000
120000
100000
80000
60000
40000
20000
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

FIG. 2H

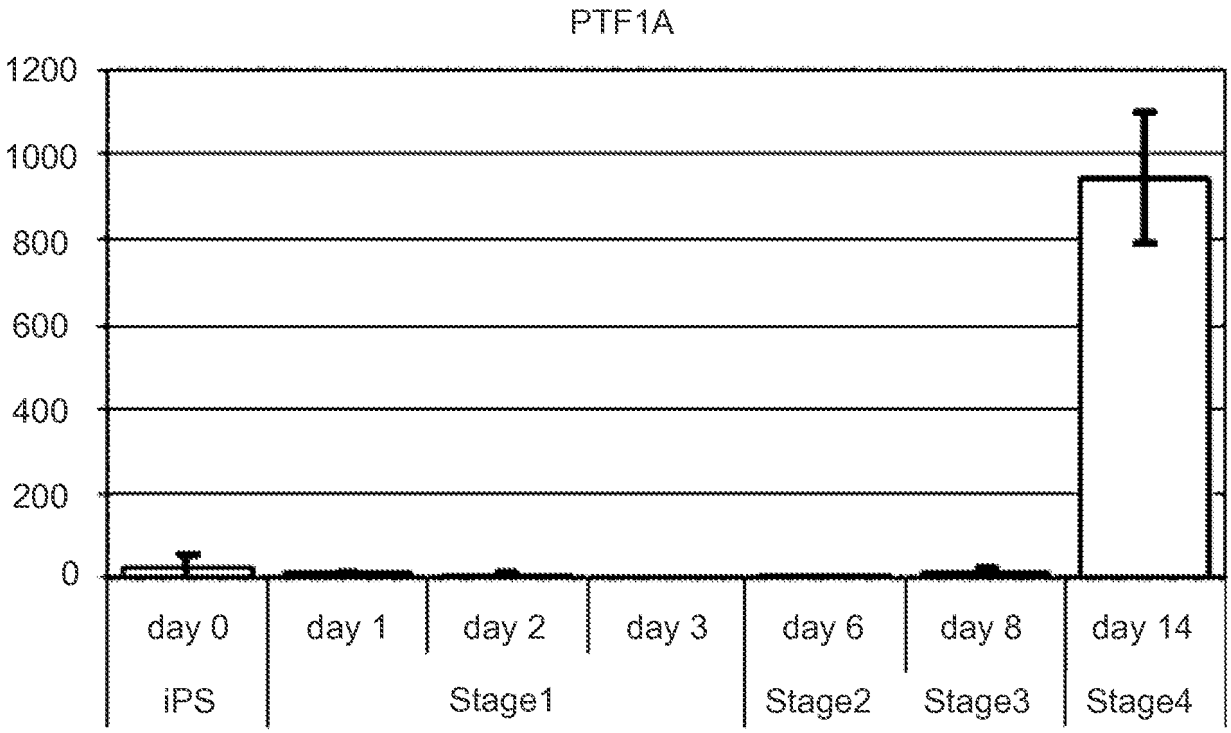

PTF1A
1200
1000
800
600
400
200
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

FIG. 2I

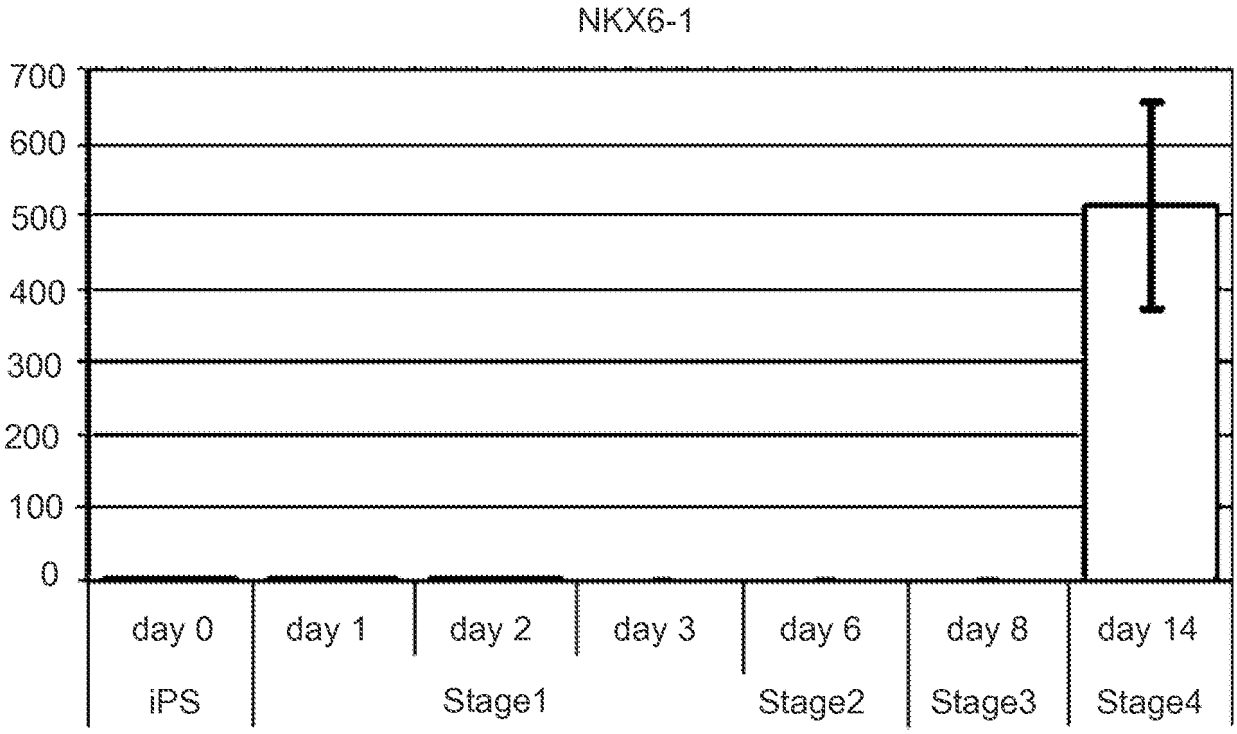

NKX6-1
700
600
500
400
300
200
100
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

FIG. 2J

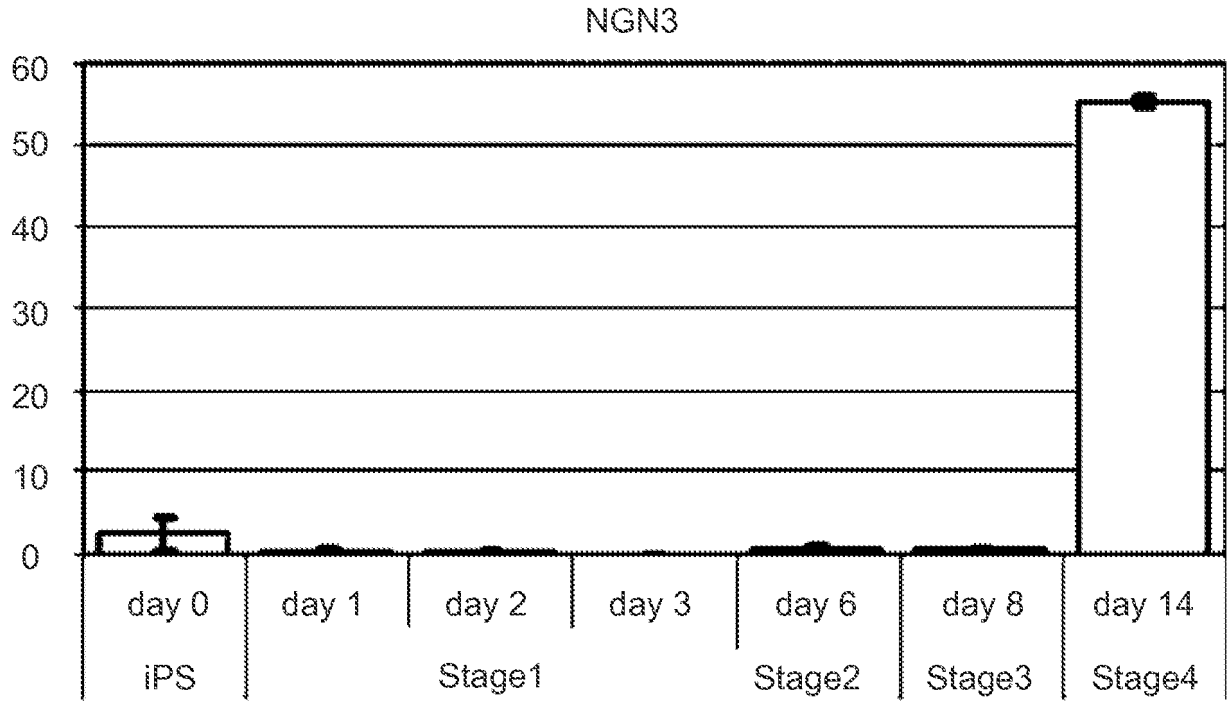

NGN3
60
50
40
30
20
10
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

FIG. 2K

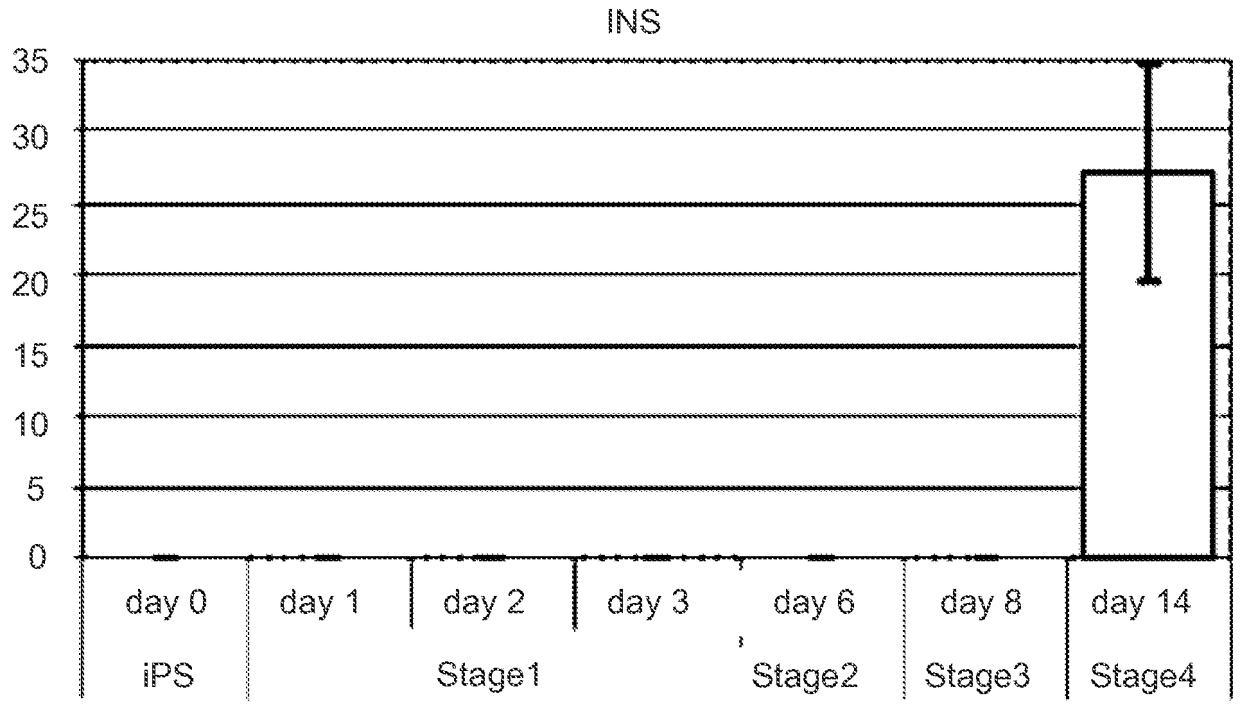
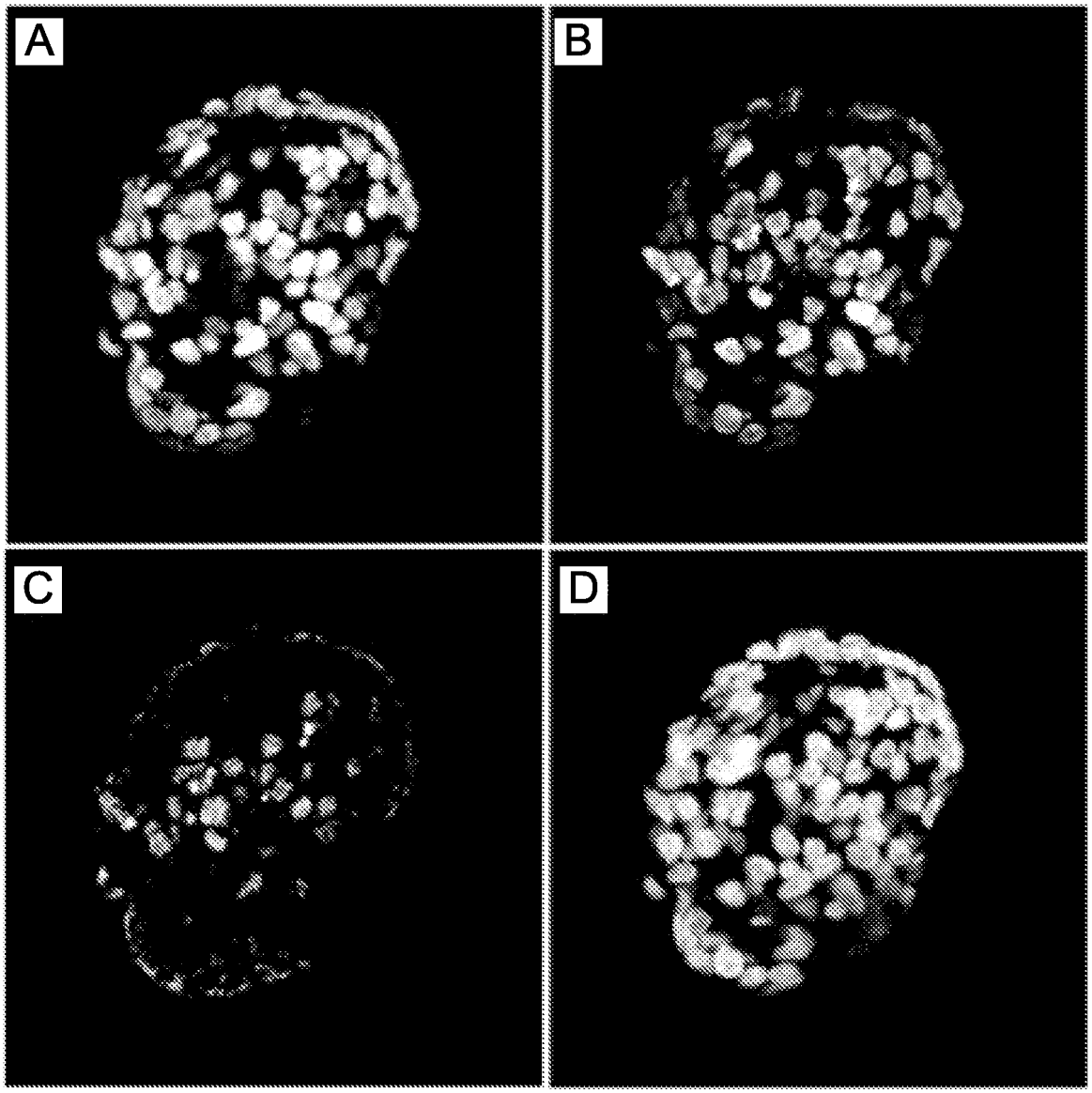

INS
35
30
25
20
15
10
5
0
day 0
day 1
day 2
day 3
day 6
day 8
day 14
iPS
Stage1
Stage2
Stage3
Stage4

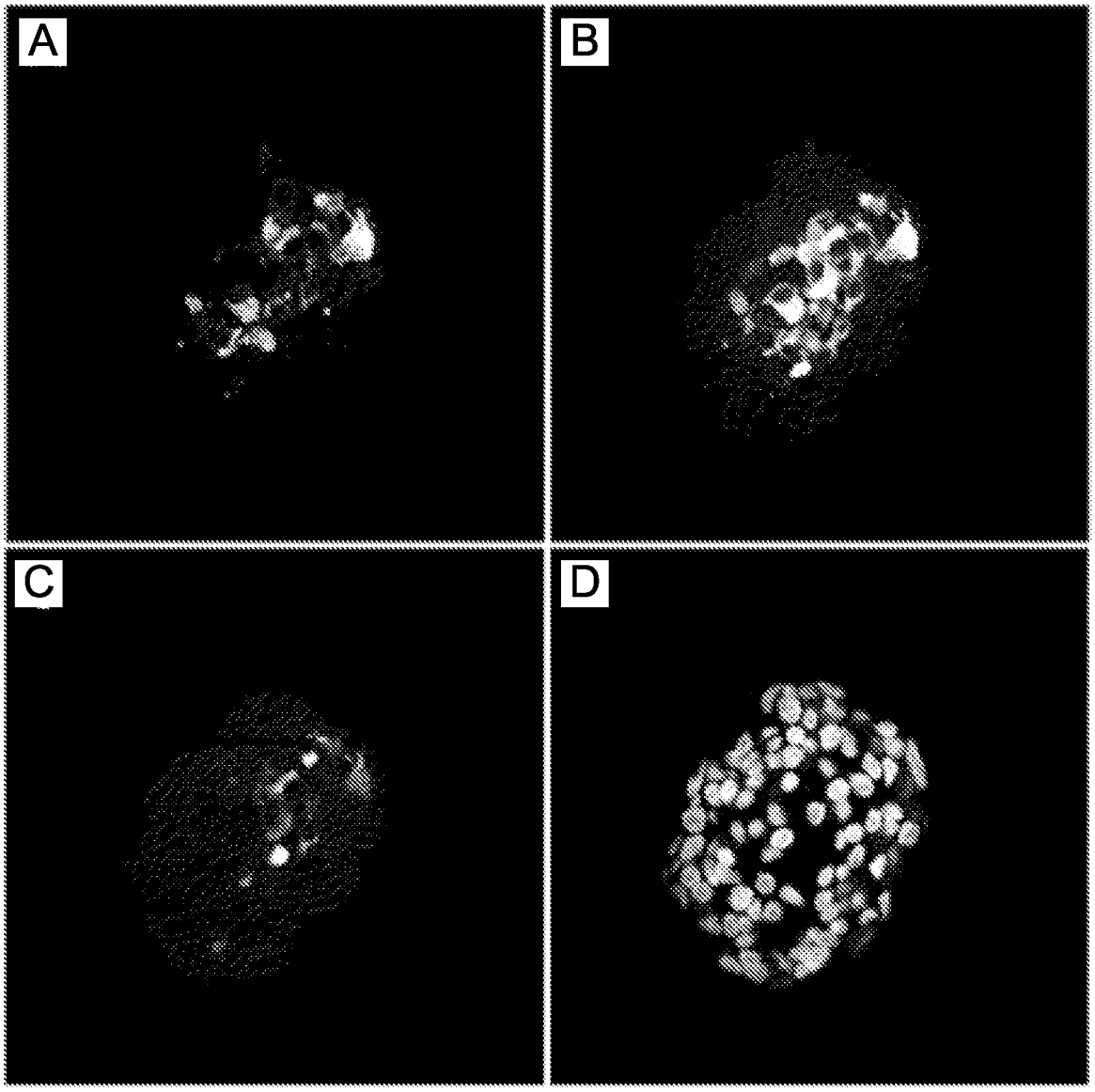
FIG. 2L



E2021 using G4 hIPS cell line at Stage 4 differentiation (PDX1-positive pancreatic endoderm cells)

A) Pdxl
B) Nkx6.1
C) Ptfla
D) Dapi

FIG. 3



E2021 G4 h1PS cell line at Stage 5

A) Glucagon

B) Insulin

C) Somatostatin

D) Dapi

FIG. 4

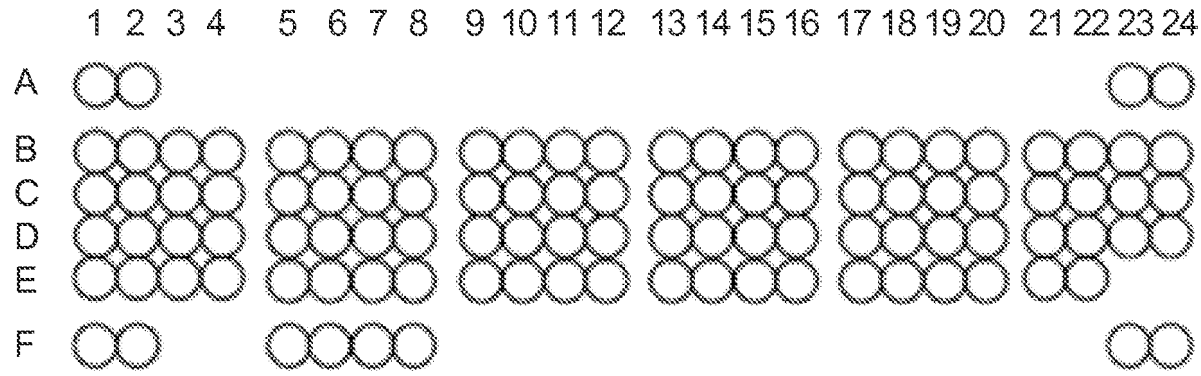


FIG. 5A

Phospho-RTK array key

Coordinate	Family	RTK/Control		Coordinate	Family	RTK/Contrl
A1, A2	Control (+)	PY-Control*		D1, D2	Tie	TIE-2
A23, A24	Control (+)	PY-Control*		D3, D4	NGFR	TRKA
B1, B2	EGFR	EGFR		D5, D6	NGFR	TRKB
B3, B4	EGFR	ERBB2		D7, D8	NGFR	TRKC
B5, B6	EGFR	ERBB3		D9, D10	VEGFR	VEGFR1
B7, B8	EGFR	ERBB4		D11, D12	VEGFR	VEGFR2
B9, B10	FGFR	FGFR1		D13, D14	VEGFR	VEGFR3
B11, B12	FGFR	FGFR2α		D15, D16	MuSK	MuSK
B13, B14	FGFR	FGR3		D17, D18	EphR	EPHA1
B15, B16	FGFR	FGFR4		D19, D20	EphR	EPHA2
B17, B18	Insulin R	IR		D21, D22	EphR	EPHA3
B19, B20	Insulin R	IGF1R		D23, D24	EphR	EPHA4
B21, B22	Axl	AXL		E1, E2	EphR	EPHA6
B23, B24	Axl	DTK		E3, E4	EphR	EPHA7
C1, C2	AXl	MER		E5, E6	EphR	EPHB1
C3, C4	HGFR	HGFR		E7, E8	EphR	EPHB2
C5, C6	HGFR	MSPR		E9, E10	EphR	EPHB4
C7, C8	PDGFR	PDGFRα		E11, E12	EphR	EPHB6
C9, C10	PDGFR	PDGFRβ		E13, E14	Control (-)	Mouse IgG_1
C11, C12	PDGFR	SCFR		E15, E16	Control (-)	Mouse IgG_{2A}
C13, C14	PDGFR	FLT-3		E17, E18	Control (-)	Mouse IgG_{2B}
C15, C16	PDGFR	M-CSFR		E19, E20	Control (-)	Goat IgG
C17, C18	RET	c-RET		E21, E22	Control (-)	PBS
C19, C20	ROR	ROR1		F1, F2	Control (+)	PY-CONTROL*
C21, C22	ROR	ROR2		F23, F24	Control (+)	PYPY-CONTROL*
C23, C24	Tie	TIE-1				

*Phospho-lyrosine positive control

FIG. 5B

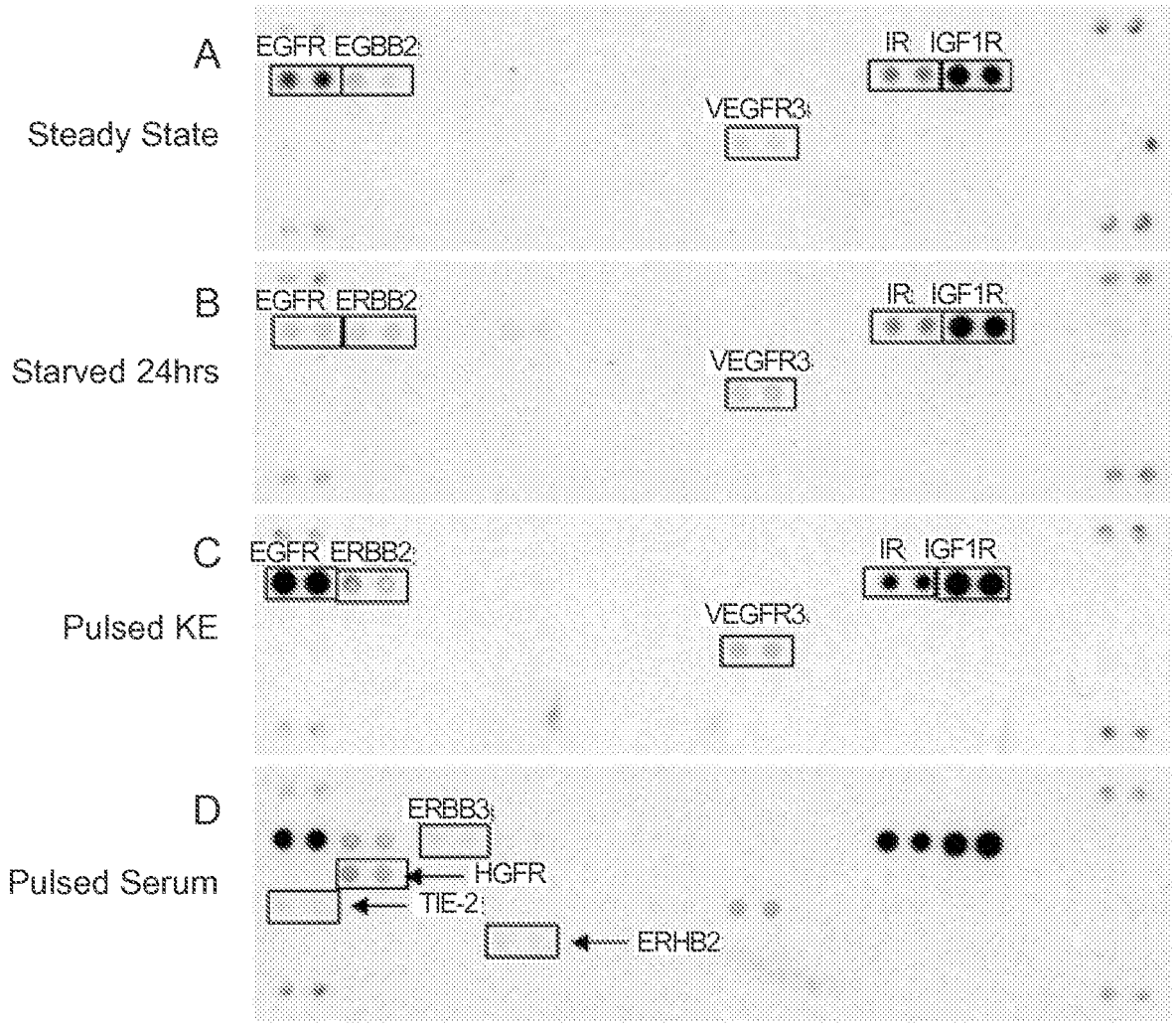

A
Steady State
EGFR EGBB2
VEGFR3
IR IGF1R
B
Starved 24hrs
EGFR ERBB2
VEGFR3
IR IGF1R
C
Pulsed KE
EGFR ERBB2
VEGFR3
IR IGF1R
D
Pulsed Serum
ERBB3
HGFR
TIE-2
ERHB2

FIG. 6

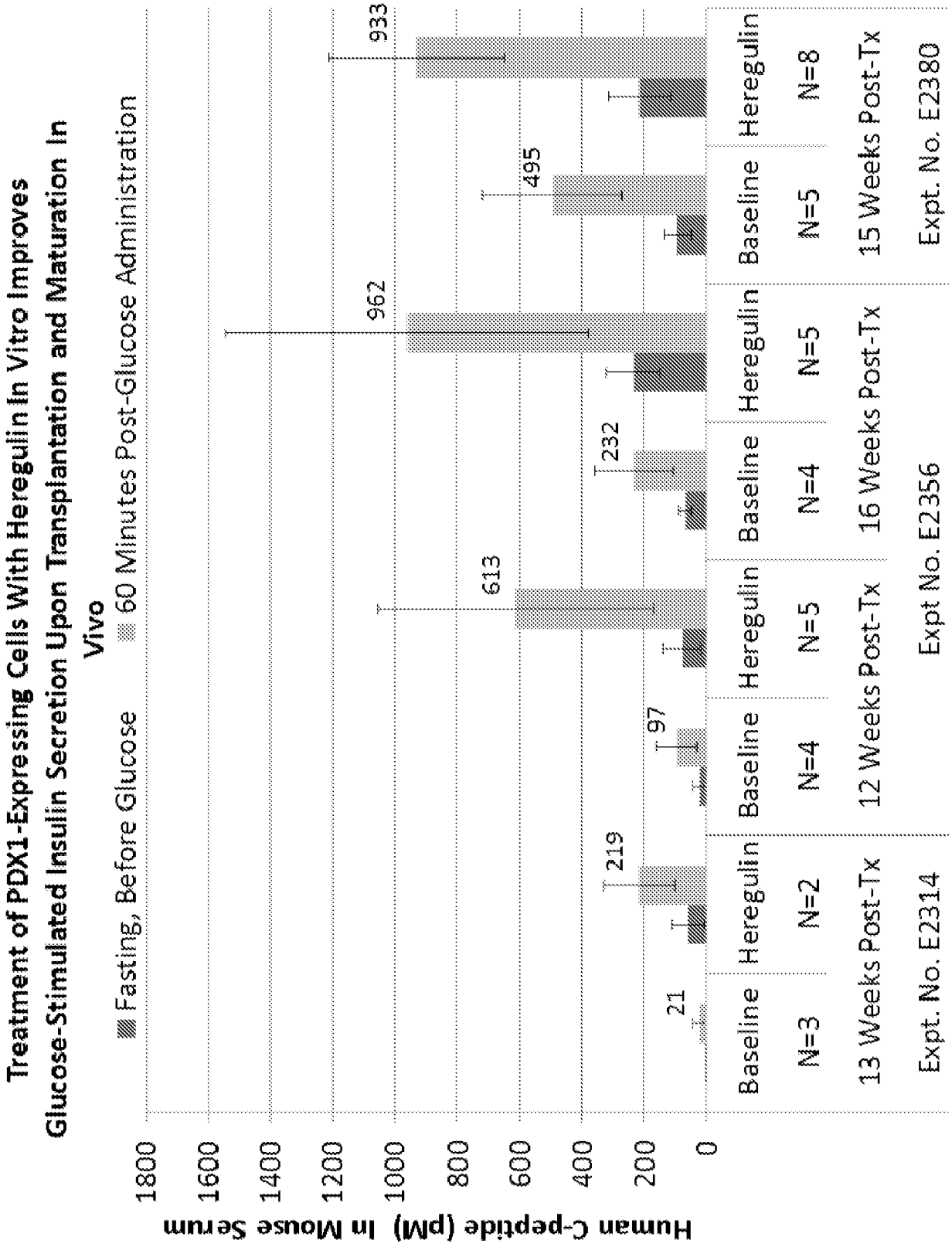

Treatment of PDX1-Expressing Cells With Heregulin In Vitro Improves Glucose-Stimulated Insulin Secretion Upon Transplantation and Maturation In Vivo
Fasting, Before Glucose
60 Minutes Post-Glucose Administration
Human C-peptide (pM) In Mouse Serum
1800
1600
1400
1200
1000
800
600
400
200
0
21
219
97
613
232
962
495
933
Baseline
Heregulin
Baseline
Heregulin
Baseline
Heregulin
Baseline
Heregulin
N=3
N=2
N=4
N=5
N=4
N=5
N=5
N=8
13 Weeks Post-Tx
12 Weeks Post-Tx
16 Weeks Post-Tx
15 Weeks Post-Tx
Expt. No. E2314
Expt No. E2356
Expt. No. E2380

FIG. 7A

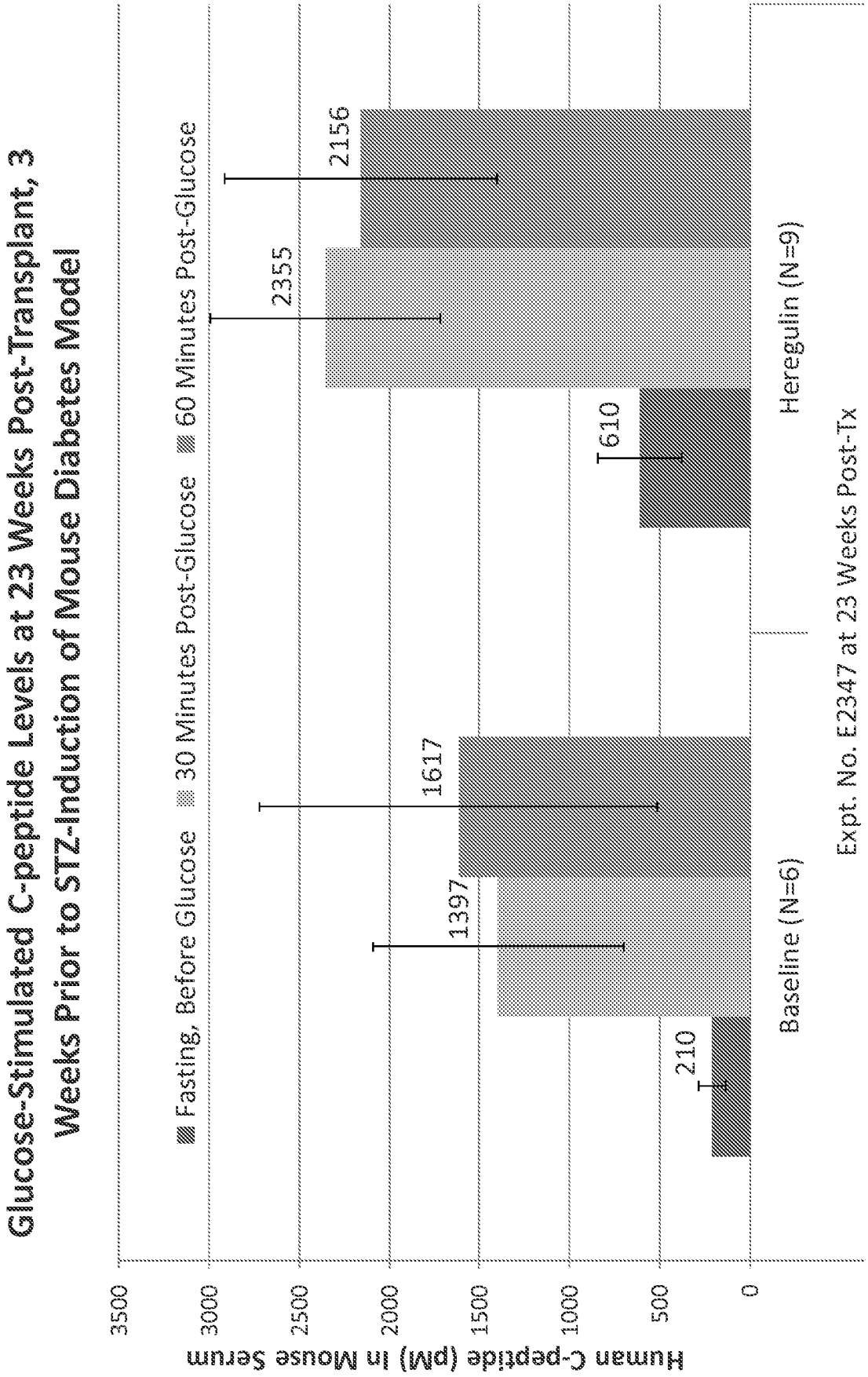

Glucose-Stimulated C-peptide Levels at 23 Weeks Post-Transplant, 3 Weeks Prior to STZ-Induction of Mouse Diabetes Model
Fasting, Before Glucose
30 Minutes Post-Glucose
60 Minutes Post-Glucose
Human C-peptide (pM) in Mouse Serum
3500
3000
2500
2000
1500
1000
500
0
210
1397
1617
610
2355
2156
Baseline (N=6)
Heregulin (N=9)
Expt. No. E2347 at 23 Weeks Post-Tx

FIG. 7B

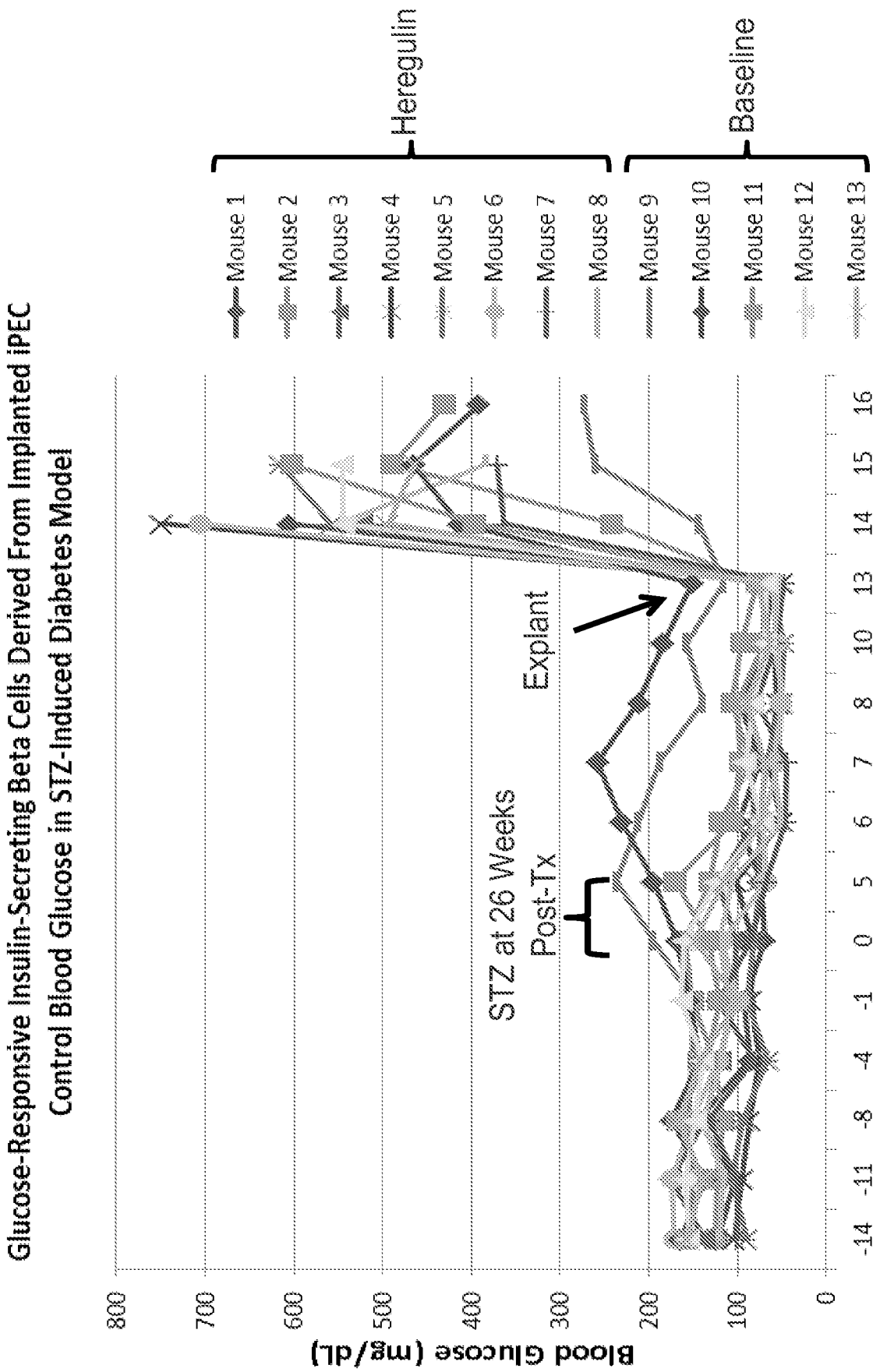

Glucose-Responsive Insulin-Secreting Beta Cells Derived From Implanted iPEC
Control Blood Glucose in STZ-Induced Diabetes Model
Heregulin
Baseline
Mouse 1
Mouse 2
Mouse 3
Mouse 4
Mouse 5
Mouse 6
Mouse 7
Mouse 8
Mouse 9
Mouse 10
Mouse 11
Mouse 12
Mouse 13
STZ at 26 Weeks
Post-Tx
Explant
Blood Glucose (mg/dL)
800
700
600
500
400
300
200
100
0
-14 -11 -8 -4 -1 0 5 6 7 8 10 13 14 15 16
Days Pre and Post-STZ Treatment
Expt No. E2347

FIG. 8A

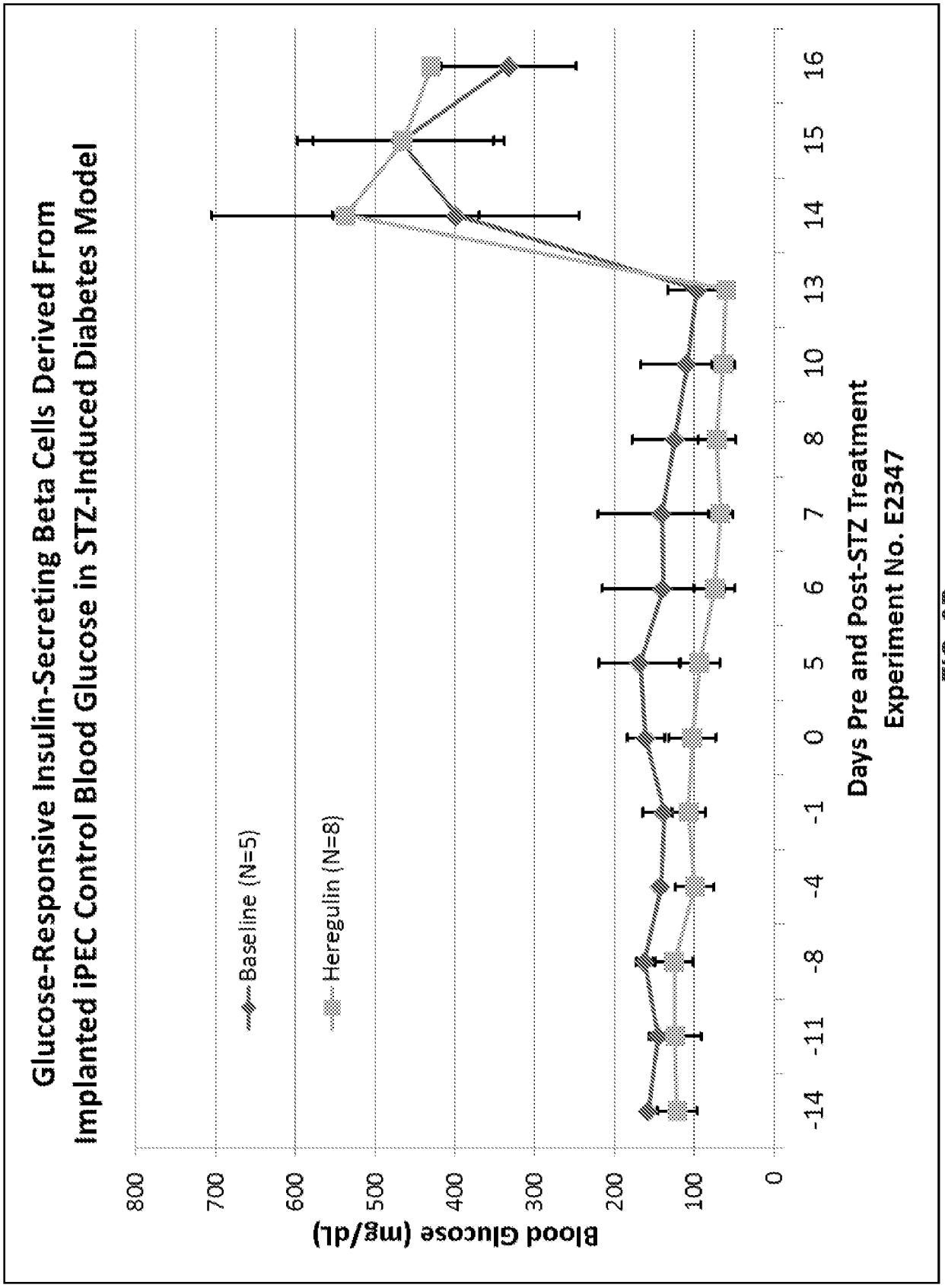

Glucose-Responsive Insulin-Secreting Beta Cells Derived From Implanted iPEC Control Blood Glucose in STZ-Induced Diabetes Model
Baseline (N=5)
Heregulin (N=8)
Blood Glucose (mg/dL)
0
100
200
300
400
500
600
700
800
-14
-11
-8
-4
-1
0
5
6
7
8
10
13
14
15
16
Days Pre and Post-STZ Treatment
Experiment No. E2347

FIG. 8B

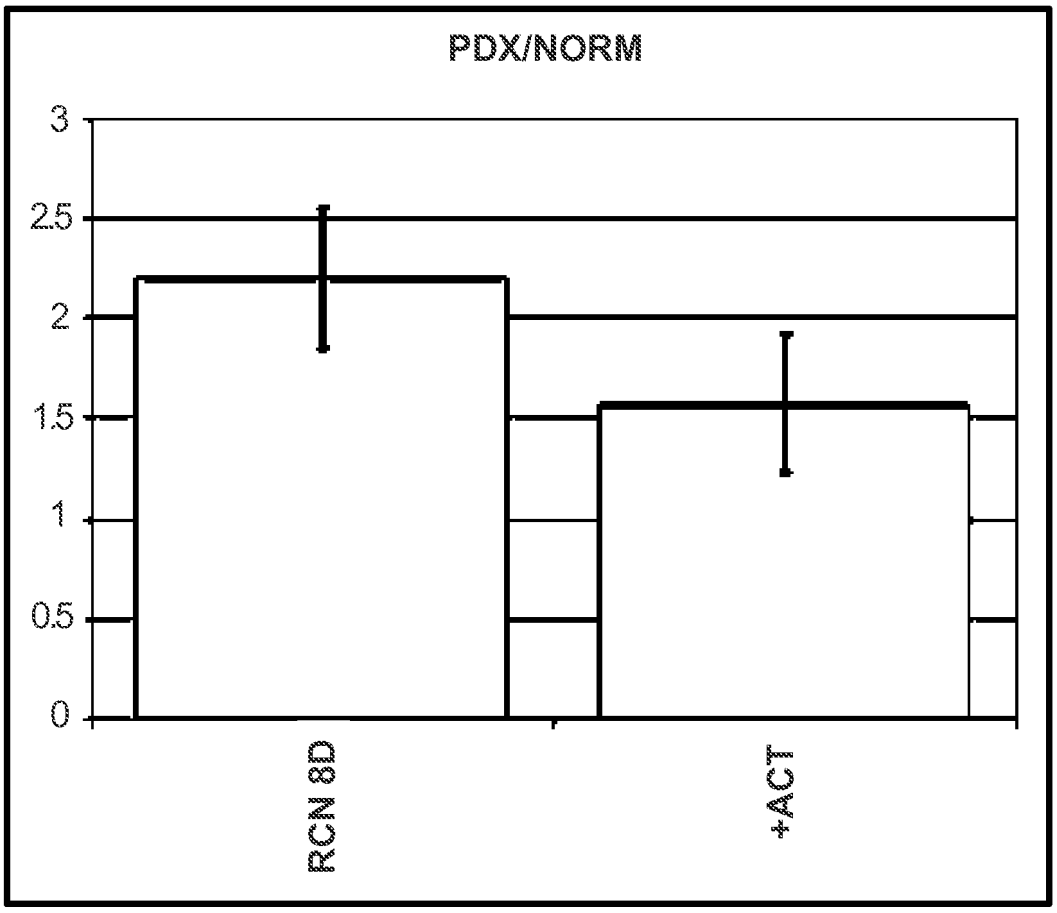


FIG. 9A

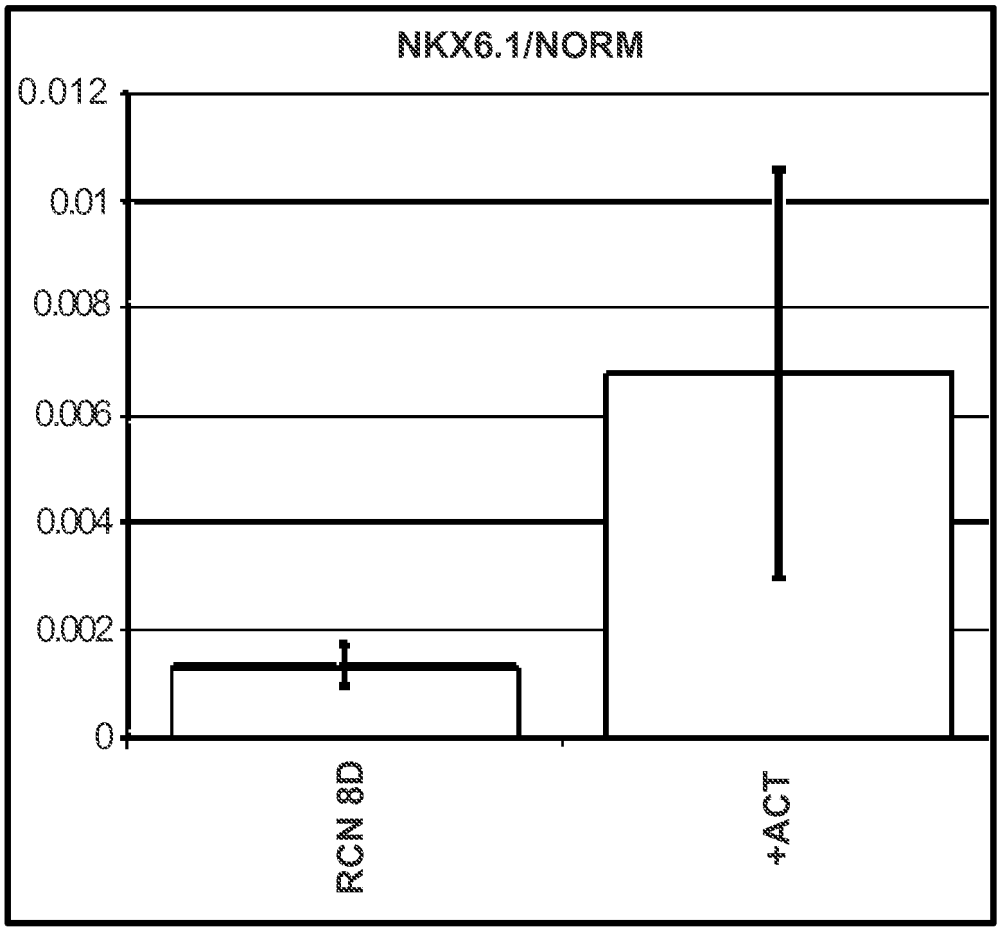


FIG. 9B

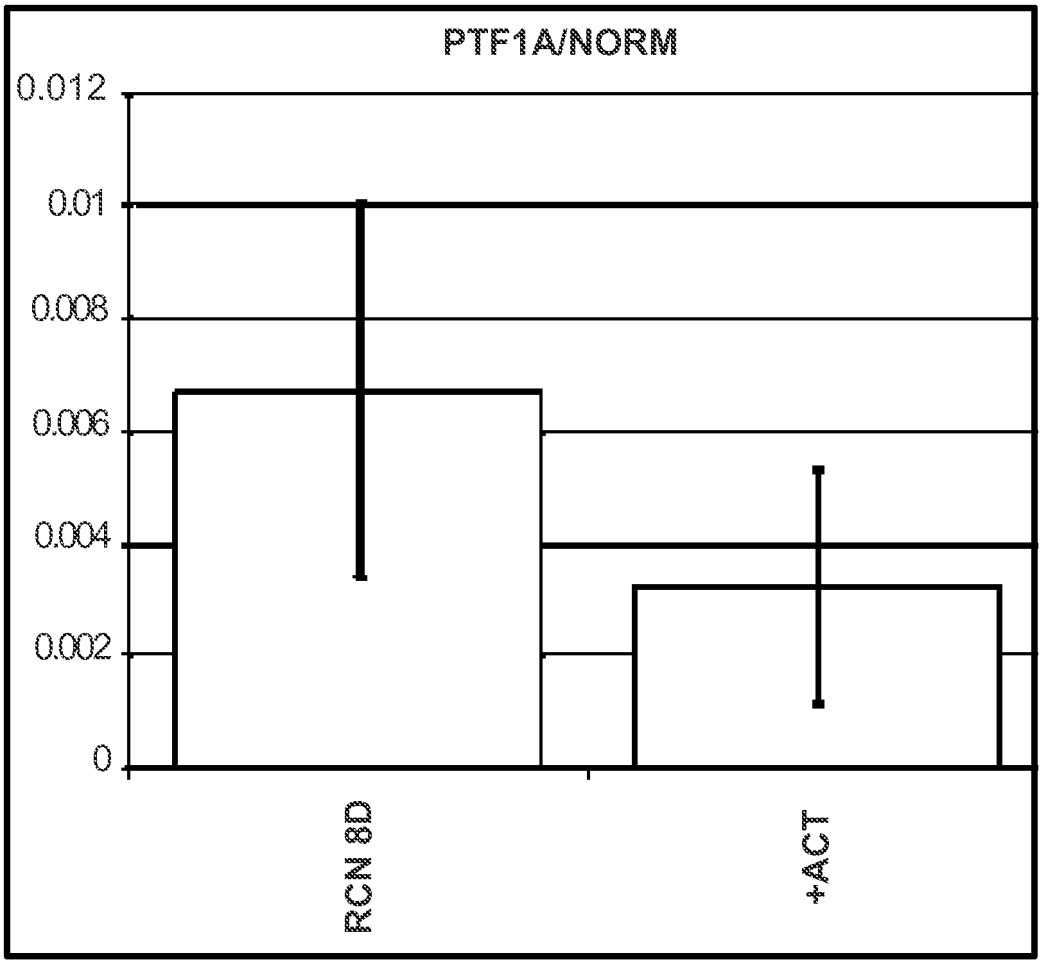


FIG. 9C

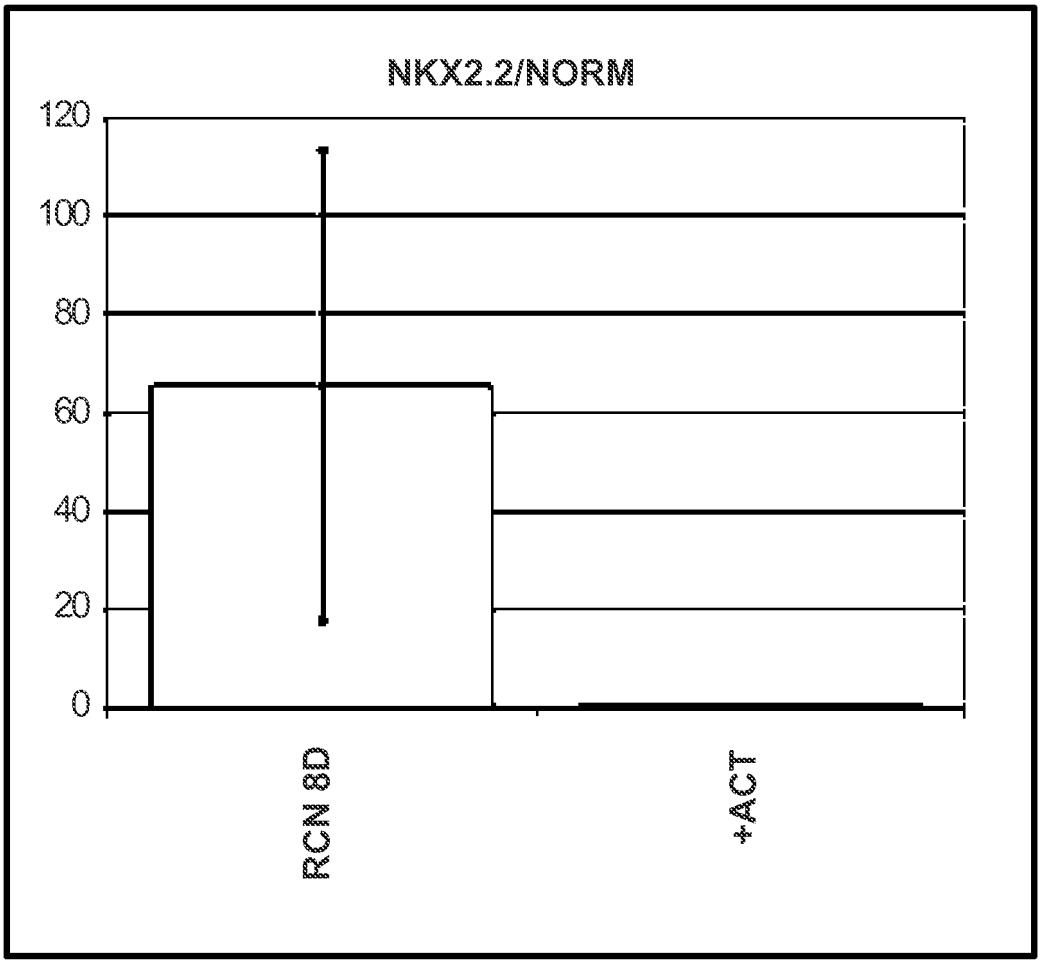


FIG. 9D

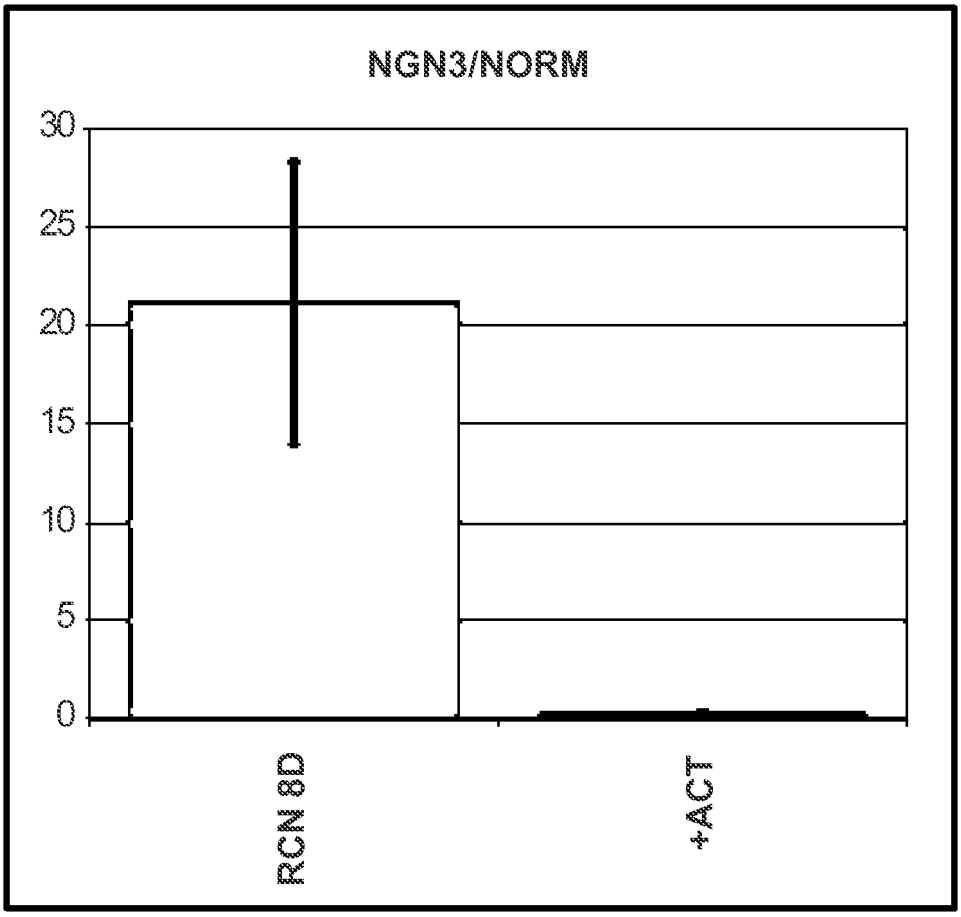


FIG. 9E

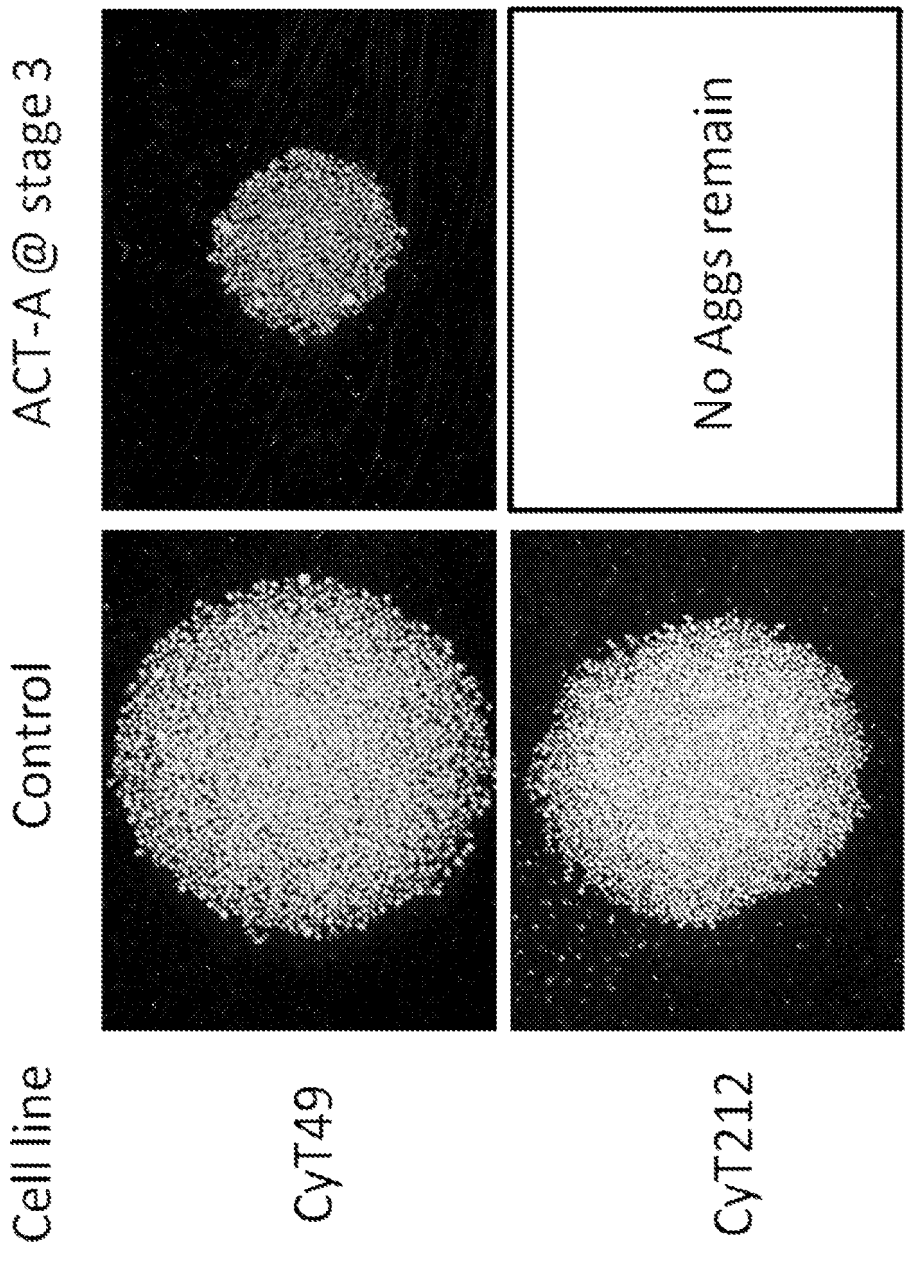

Cell line
Control
ACT-A @ stage 3
CyT49
No Aggs remain
CyT212
Magnification=6.3x

FIG. 10

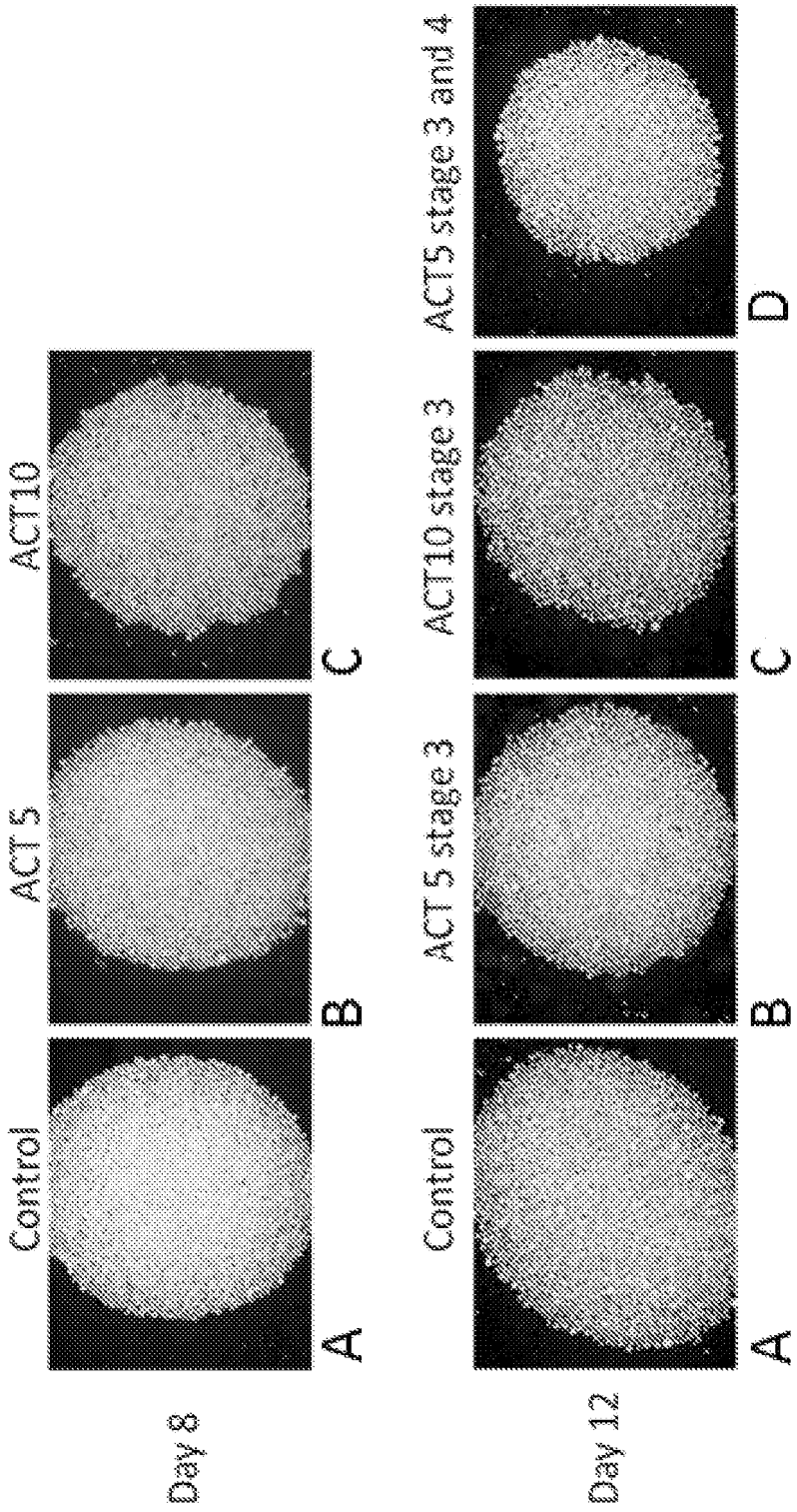

Day 8
Control
A
ACT 5
B
ACT10
C
Day 12
Control
A
ACT 5 stage 3
B
ACT10 stage 3
C
ACT5 stage 3 and 4
D

FIG. 11

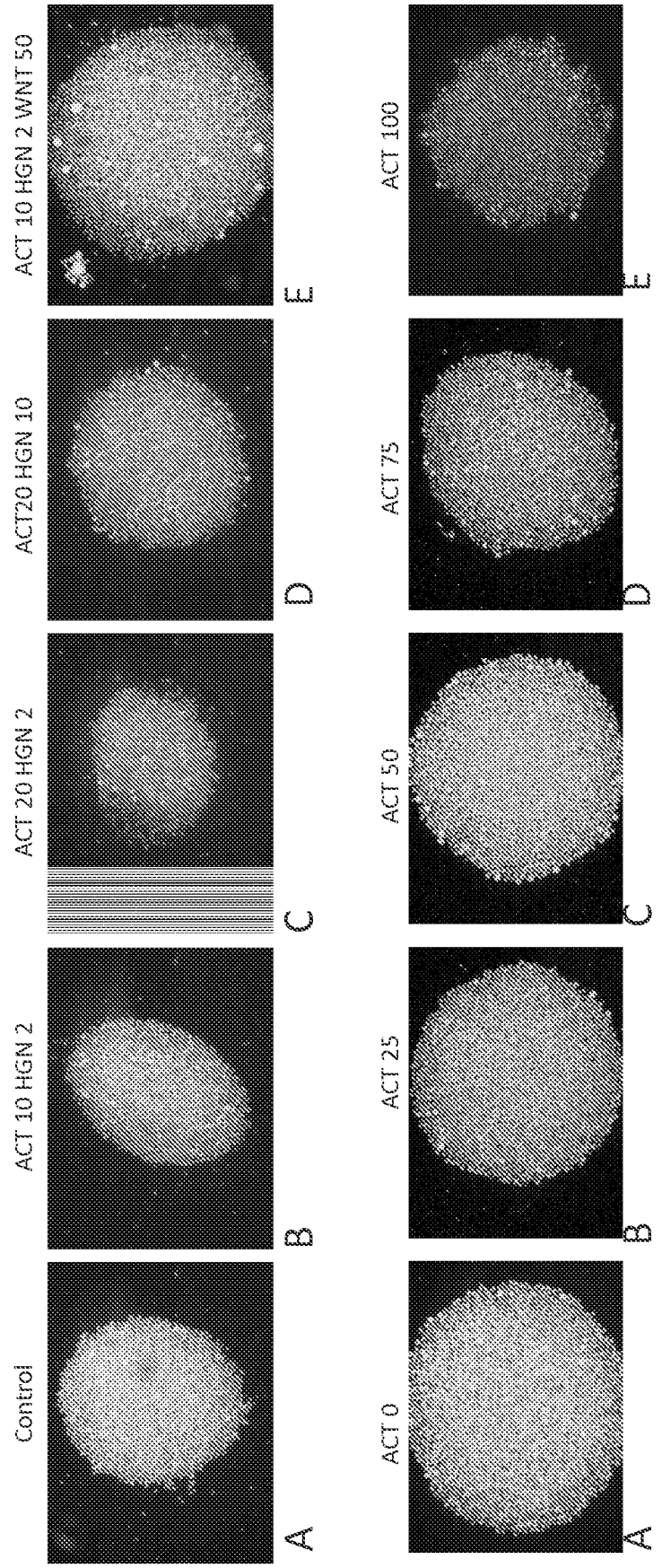

Control
A
ACT 10 HGN 2
B
ACT 20 HGN 2
C
ACT20 HGN 10
D
ACT 10 HGN 2 WNT 50
E
ACT 0
A
ACT 25
B
ACT 50
C
ACT 75
D
ACT 100
E

FIG. 12

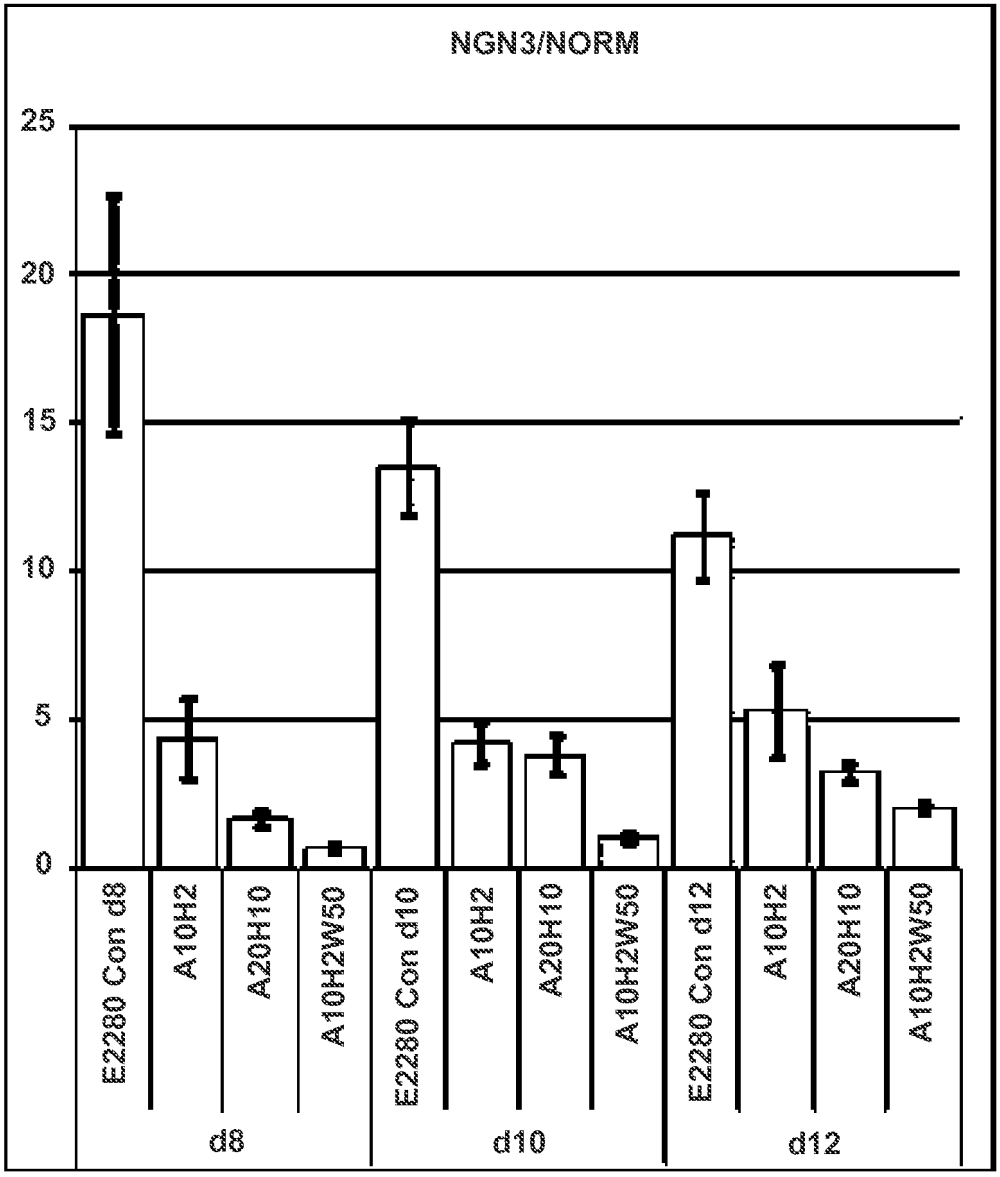

NGN3/NORM
25
20
15
10
5
0
E2280 Con d8
A10H2
A20H10
A10H2W50
E2280 Con d10
A10H2
A20H10
A10H2W50
E2280 Con d12
A10H2
A20H10
A10H2W50
d8
d10
d12

FIG. 13A

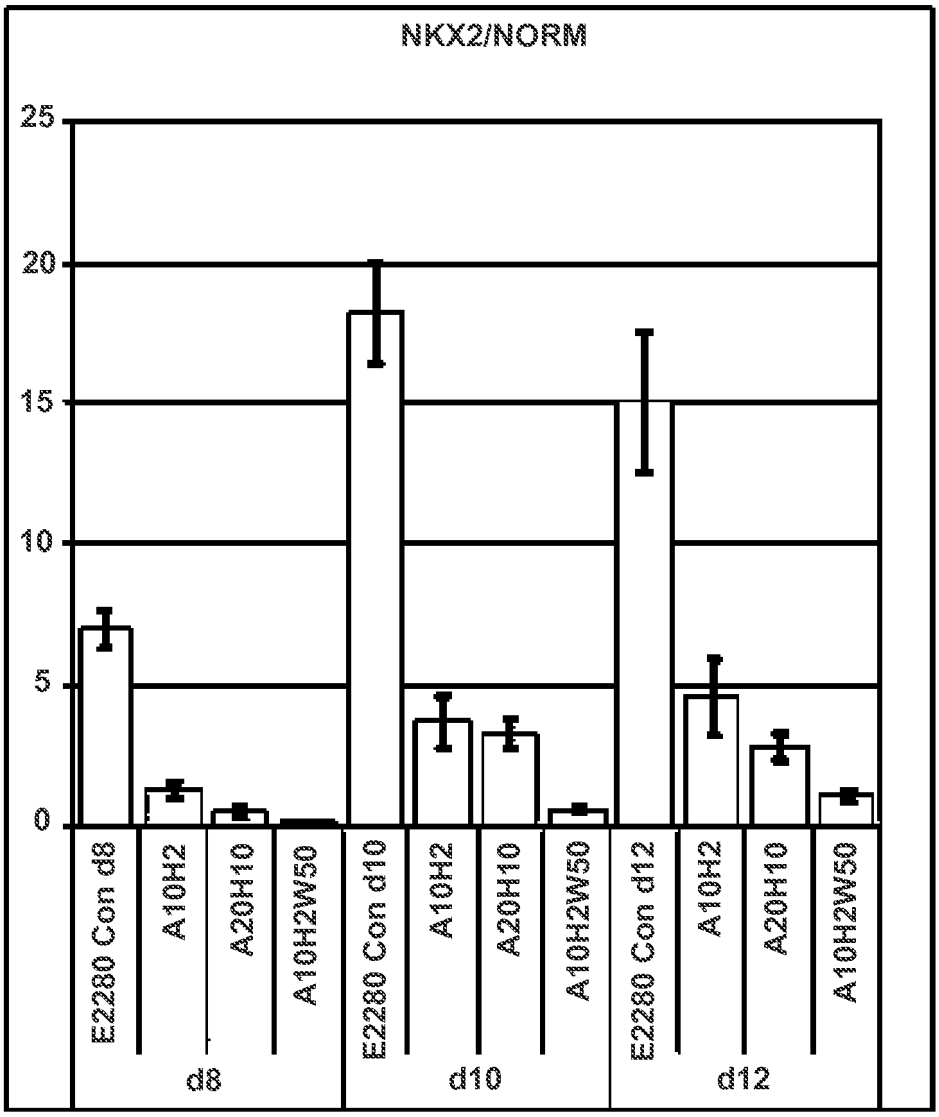

NKX2/NORM
25
20
15
10
5
0
E2280 Con d8
A10H2
A20H10
A10H2W50
E2280 Con d10
A10H2
A20H10
A10H2W50
E2280 Con d12
A10H2
A20H10
A10H2W50
d8
d10
d12

FIG. 13B

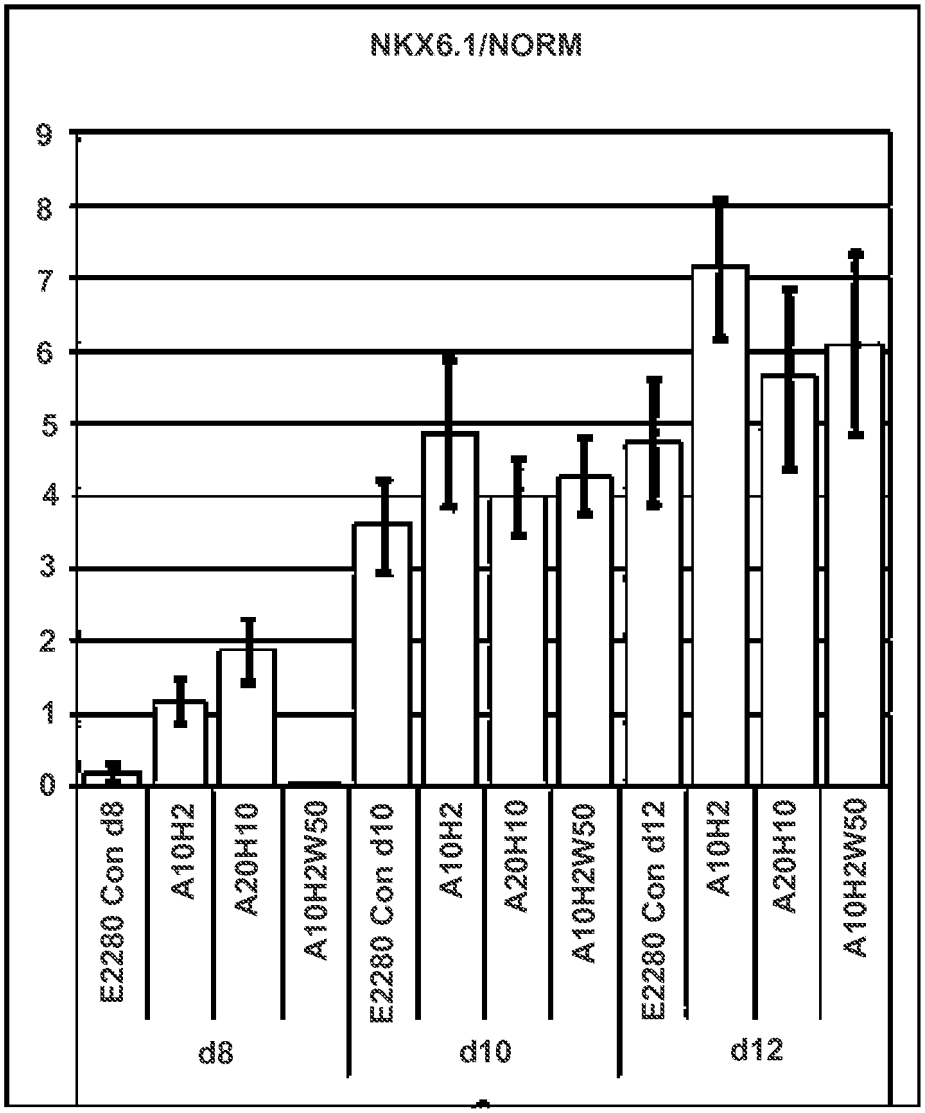

NKX6.1/NORM
9
8
7
6
5
4
3
2
1
0
E2280 Con d8
A10H2
A20H10
A10H2W50
E2280 Con d10
A10H2
A20H10
A10H2W50
E2280 Con d12
A10H2
A20H10
A10H2W50
d8
d10
d12

FIG. 13C

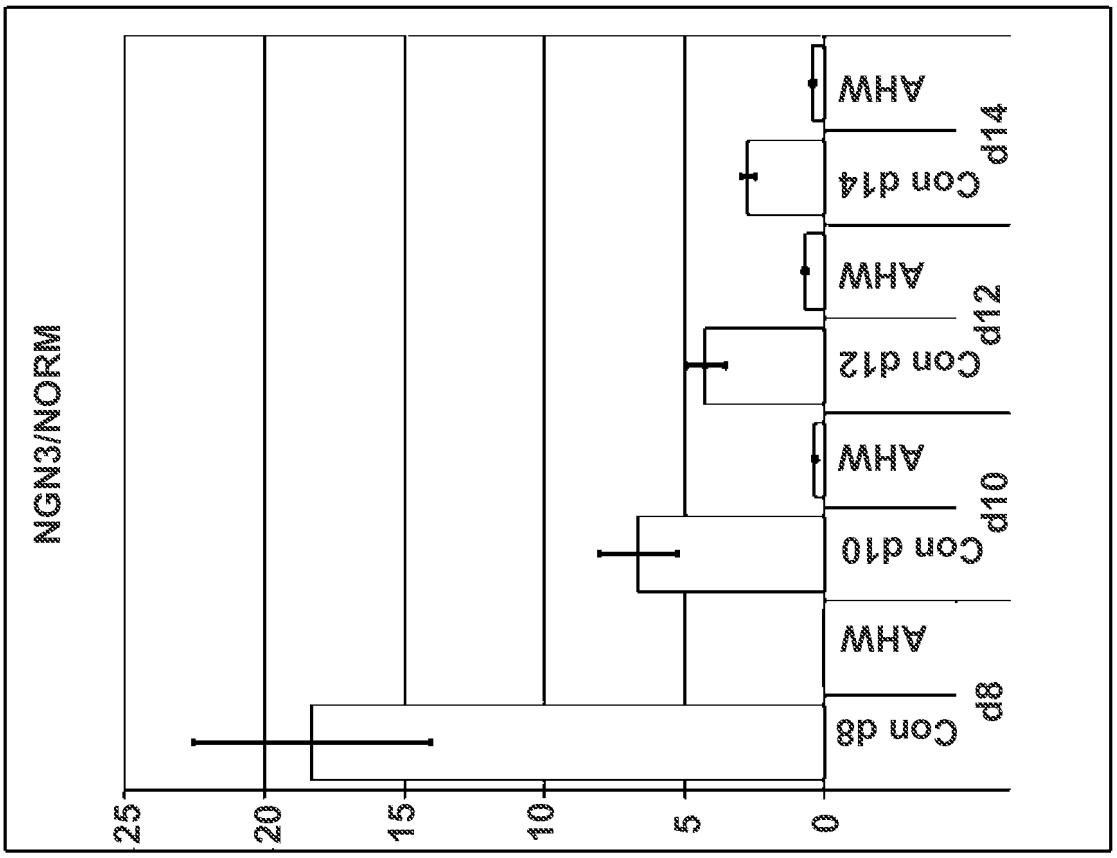


FIG. 14B

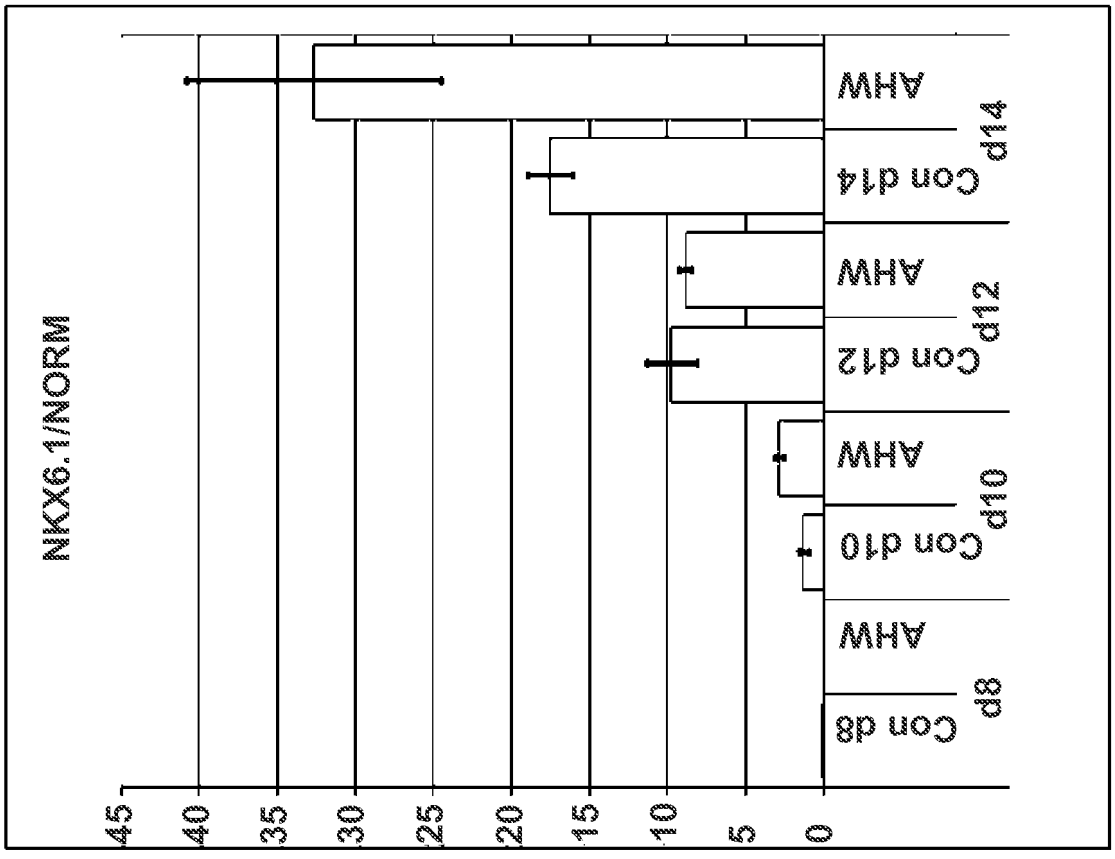


FIG. 14A

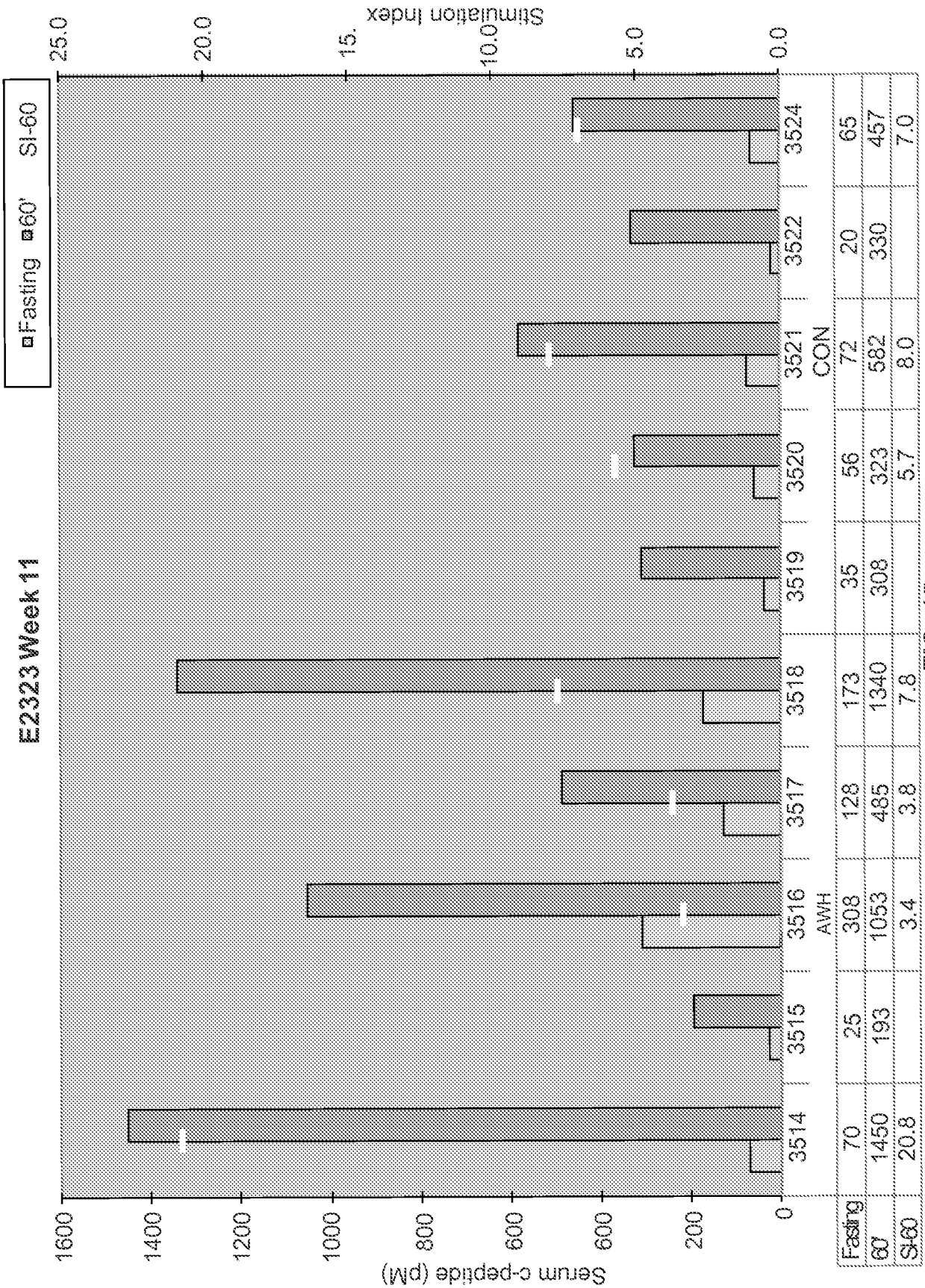

E2323 Week 11
Fasting
60'
SI-60
Serum c-peptide (pM)
Stimulation Index
0
200
600
800
1000
1200
1400
1600
0.0
5.0
10.0
15.
20.0
25.0
3514
3515
3516
3517
3518
3519
3520
3521
3522
3524
AWH
CON
Fasting 70 25 308 128 173 35 56 72 20 65
60' 1450 193 1053 485 1340 308 323 582 330 457
SI-60 20.8 3.4 3.8 7.8 5.7 8.0 7.0

FIG. 15

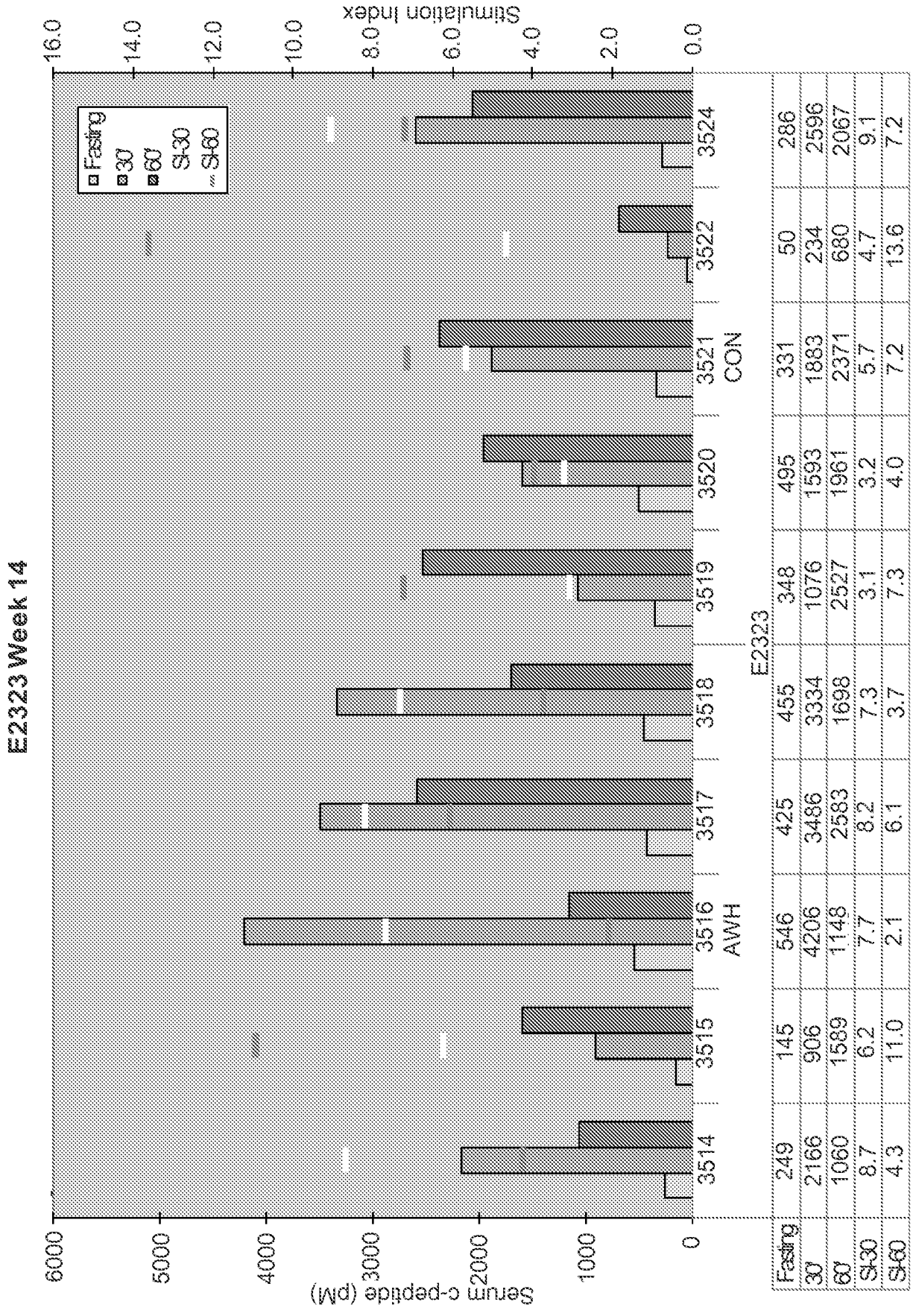

E2323 Week 14
Serum c-peptide (pM)
Stimulation Index
Fasting
30'
60'
SI-30
SI-60
AWH
CON
E2323
0
1000
2000
3000
4000
5000
6000
0.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
3514 3515 3516 3517 3518 3519 3520 3521 3522 3524
Fasting 249 145 546 425 455 348 495 331 50 286
30' 2166 906 4206 3486 3334 1076 1593 1883 234 2596
60' 1060 1589 1148 2583 1698 2527 1961 2371 680 2067
SI-30 8.7 6.2 7.7 8.2 7.3 3.1 3.2 5.7 4.7 9.1
SI-60 4.3 11.0 2.1 6.1 3.7 7.3 4.0 7.2 13.6 7.2

FIG. 16

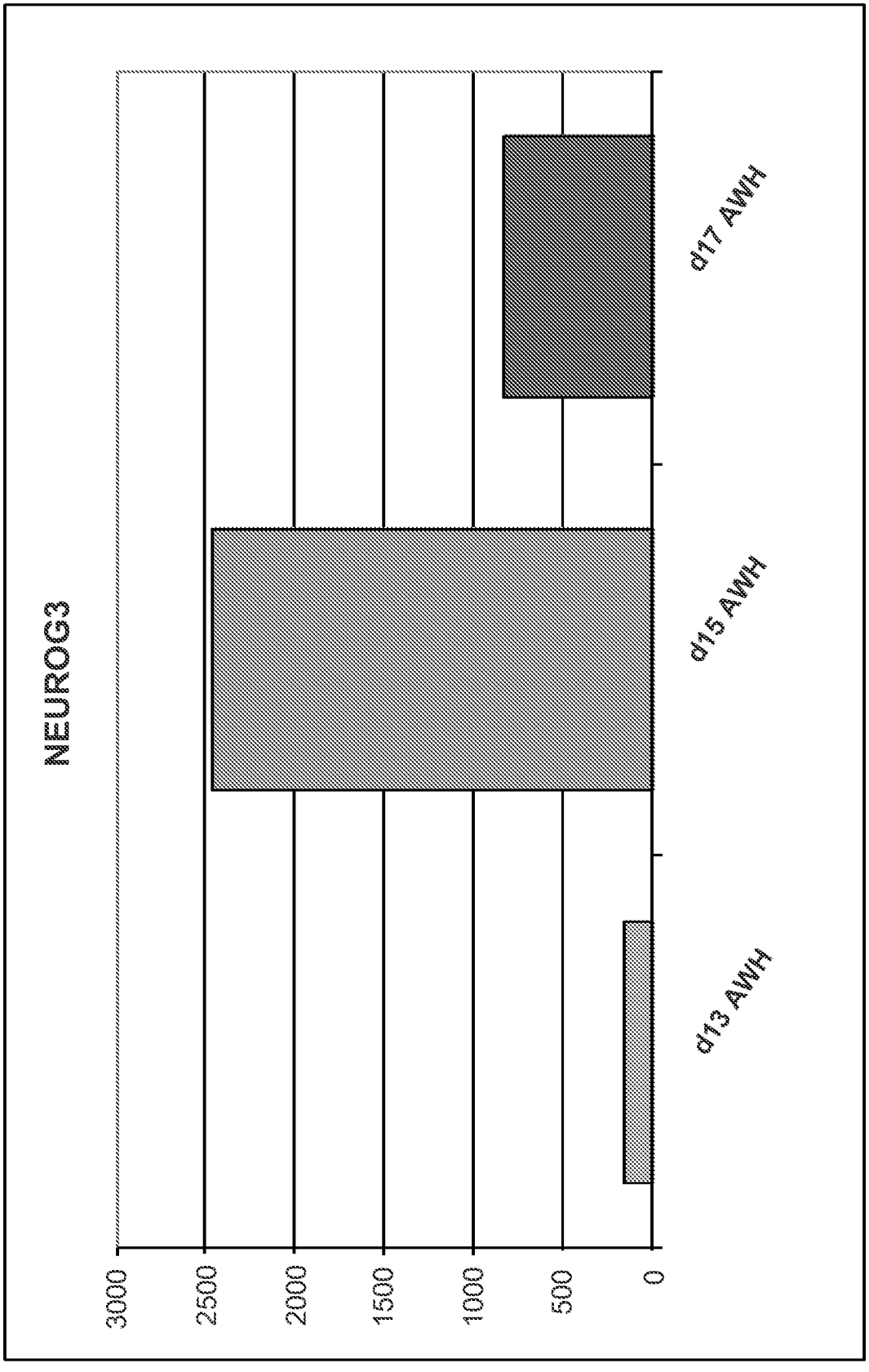


FIG. 17

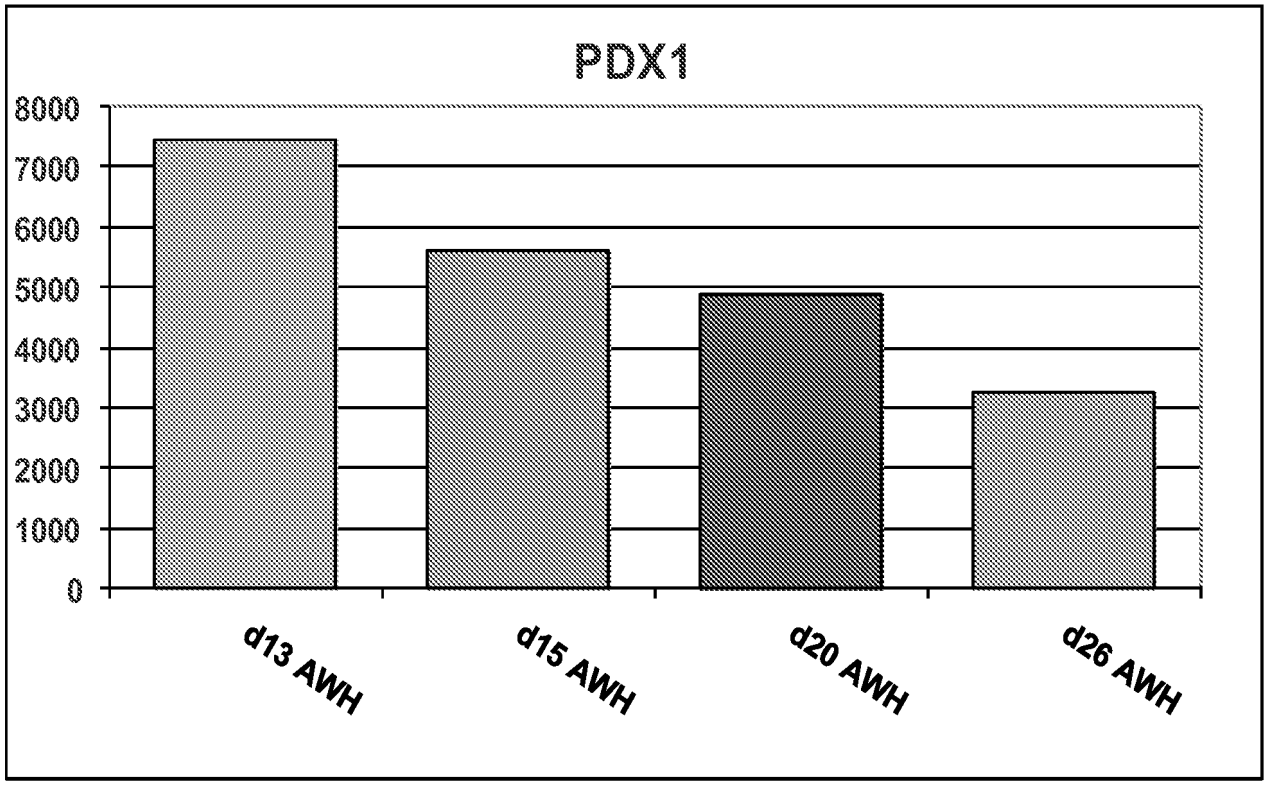

PDX1
8000
7000
6000
5000
4000
3000
2000
1000
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 18A

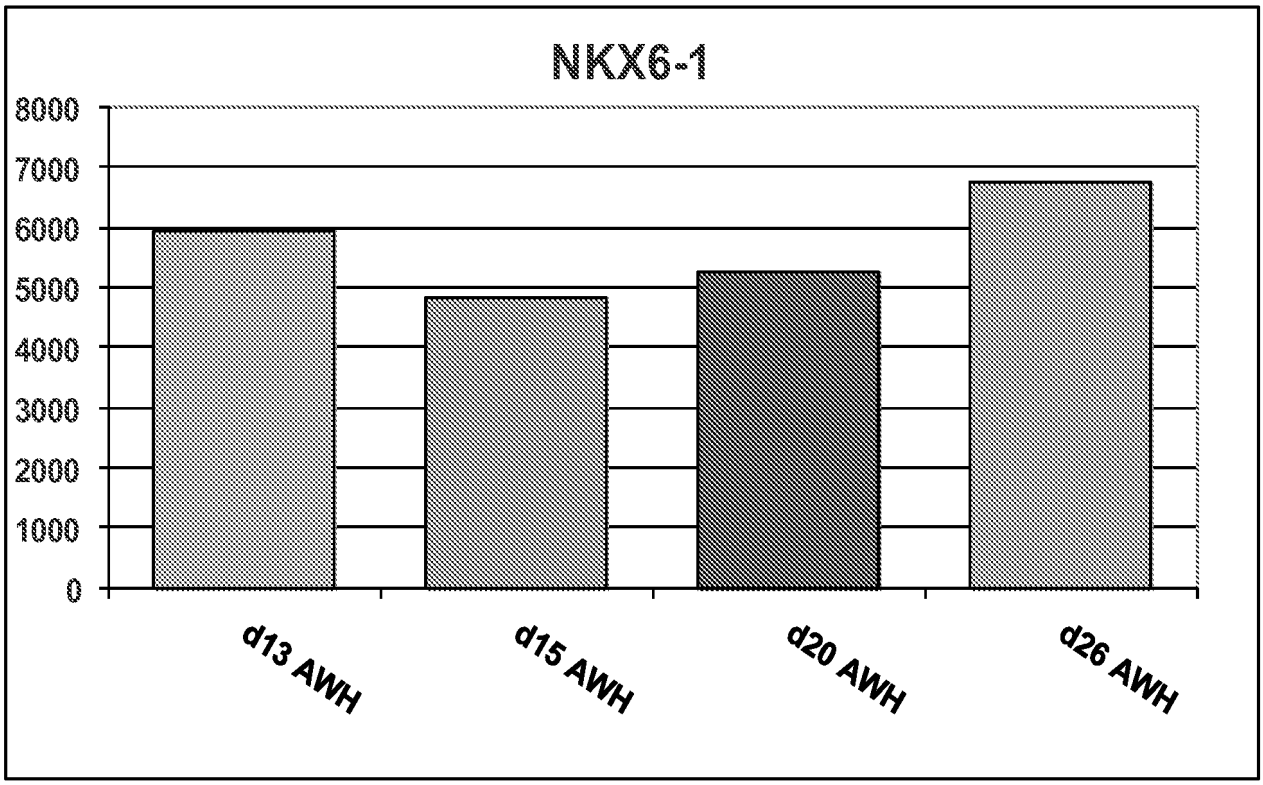

NKX6-1
8000
7000
6000
5000
4000
3000
2000
1000
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 18B

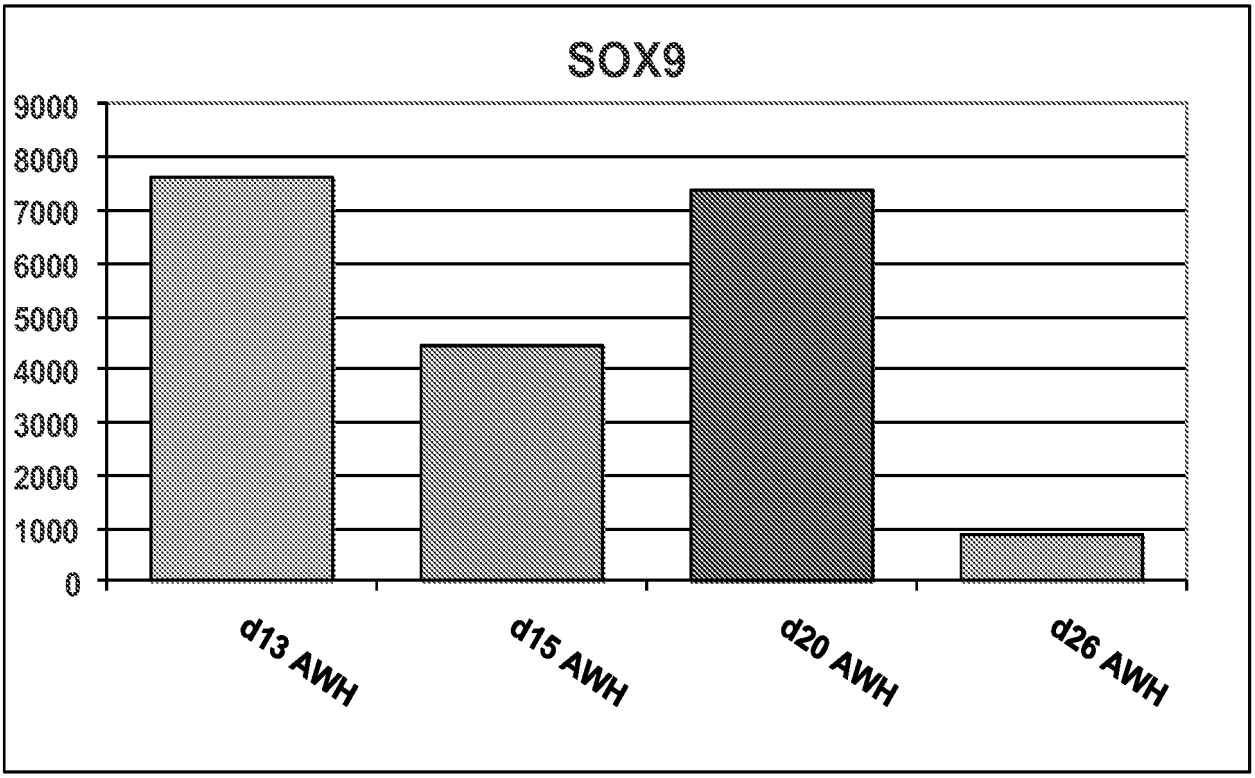

SOX9
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 18C

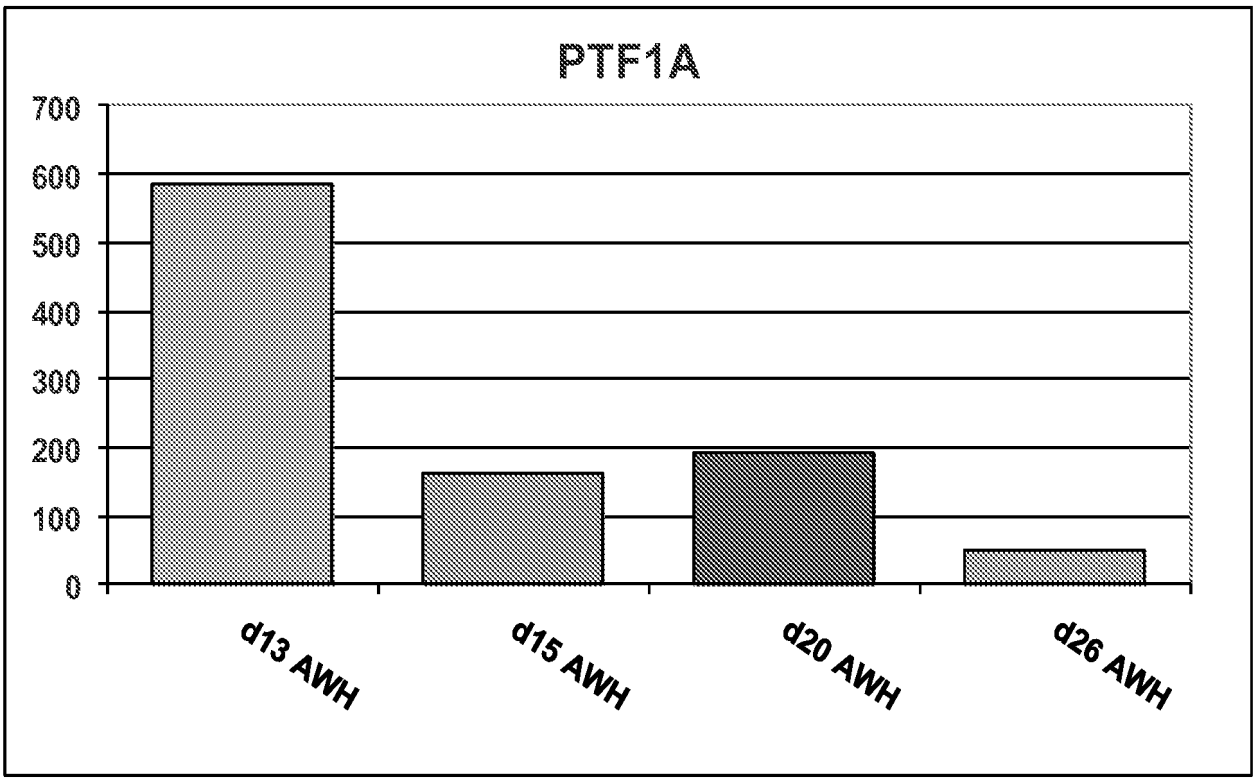

PTF1A
700
600
500
400
300
200
100
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 18D

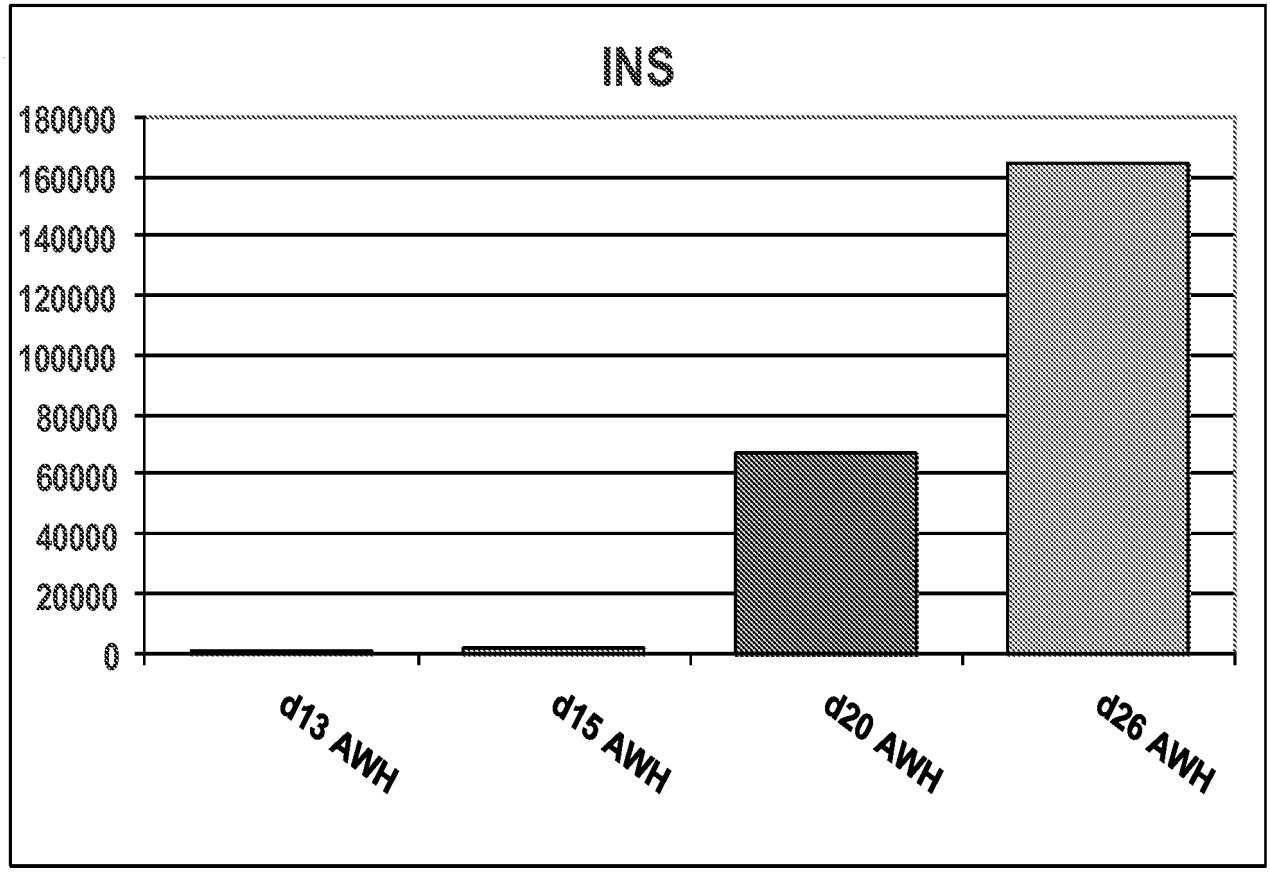

INS
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 19A

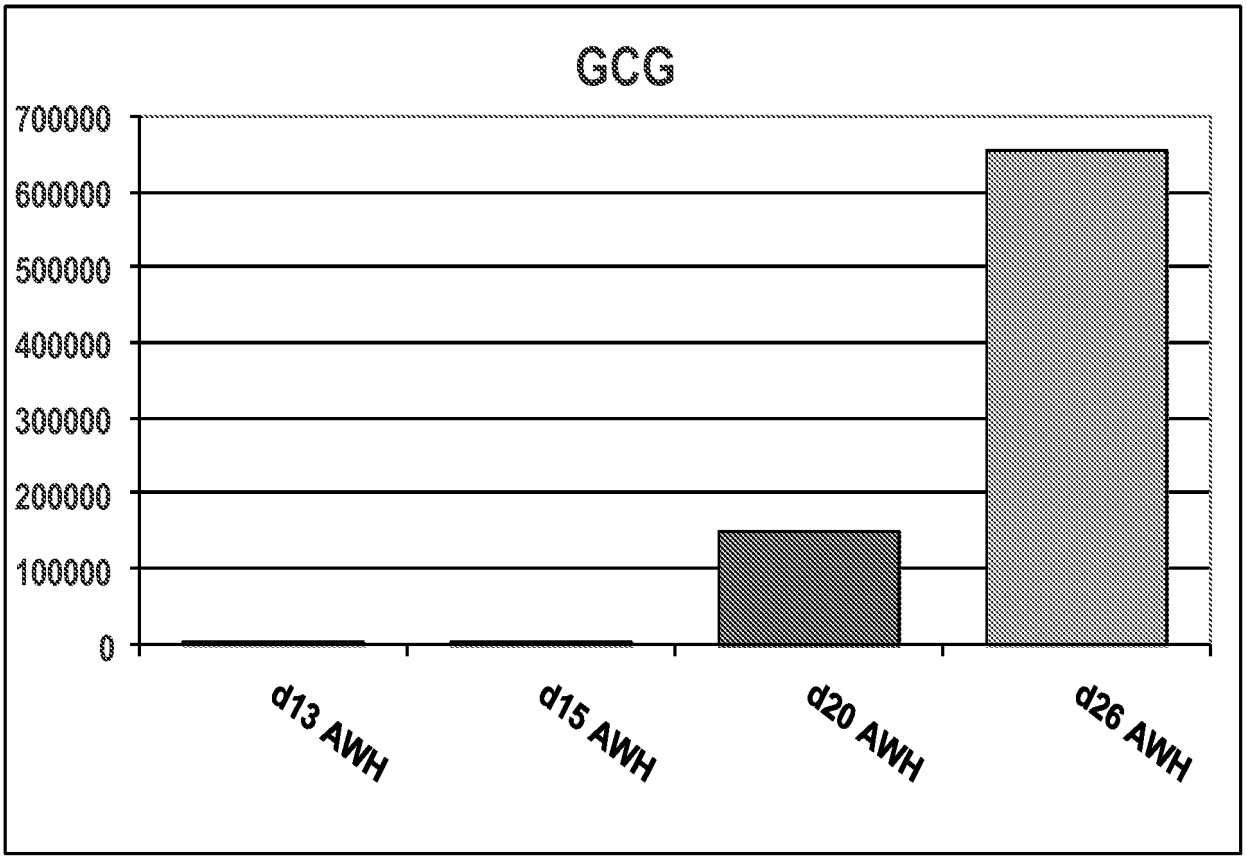

GCG
700000
600000
500000
400000
300000
200000
100000
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 19B

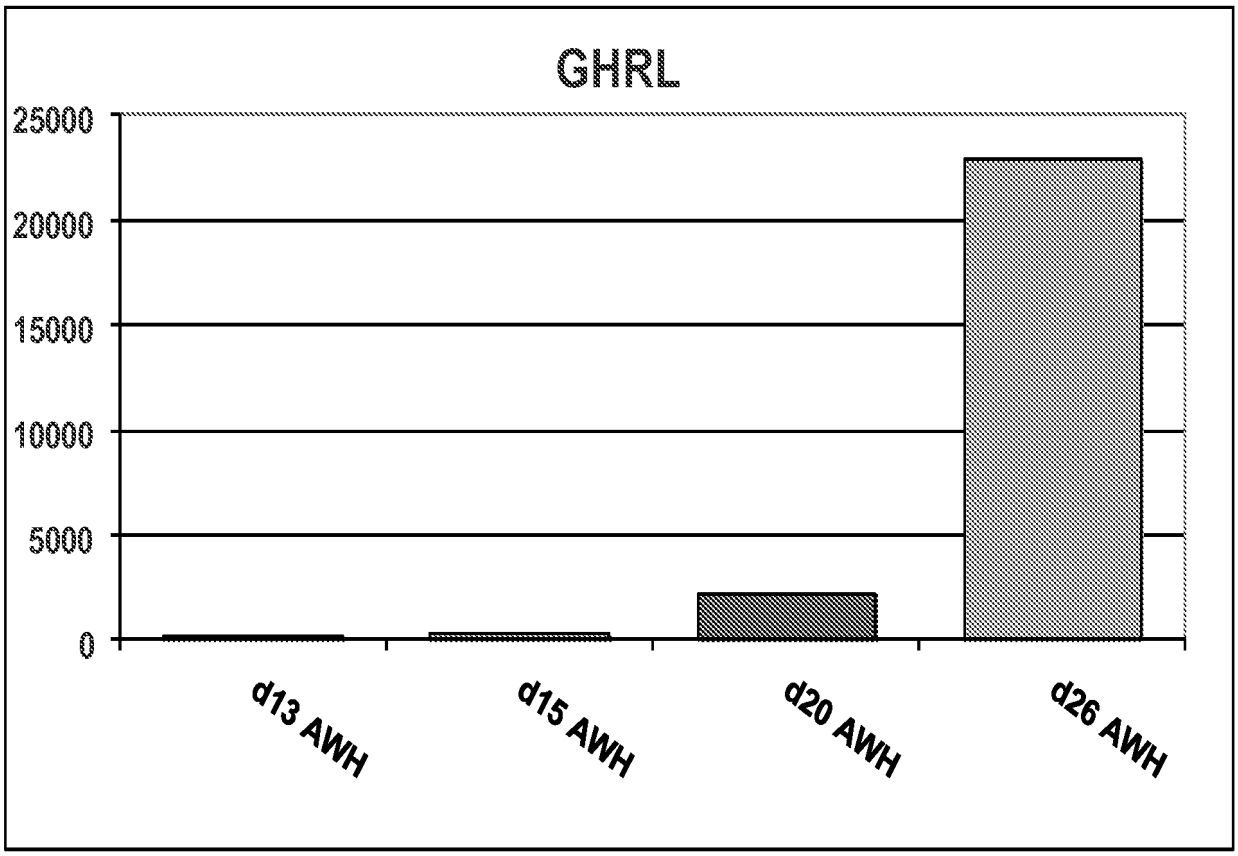

GHRL
25000
20000
15000
10000
5000
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 19C

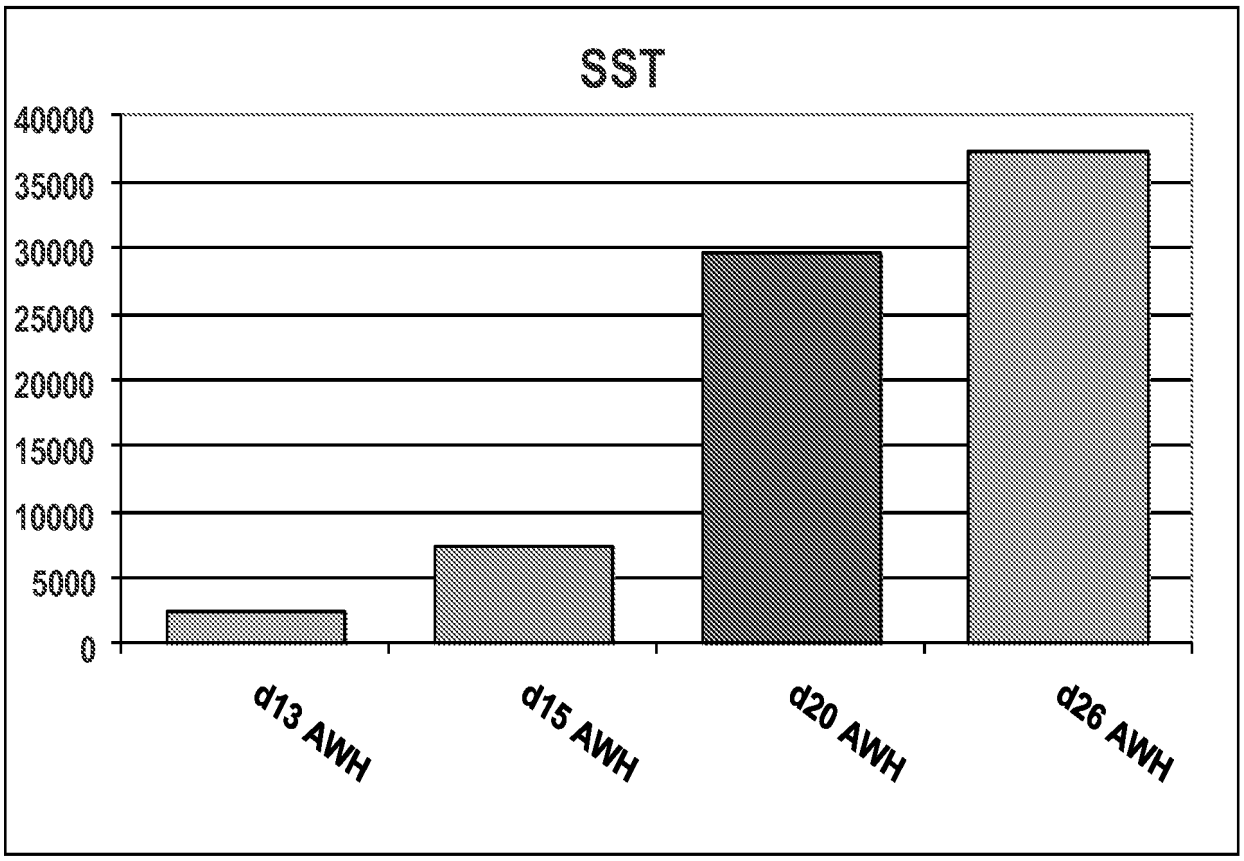

SST
40000
35000
30000
25000
20000
15000
10000
5000
0
d13 AWH
d15 AWH
d20 AWH
d26 AWH

FIG. 19D

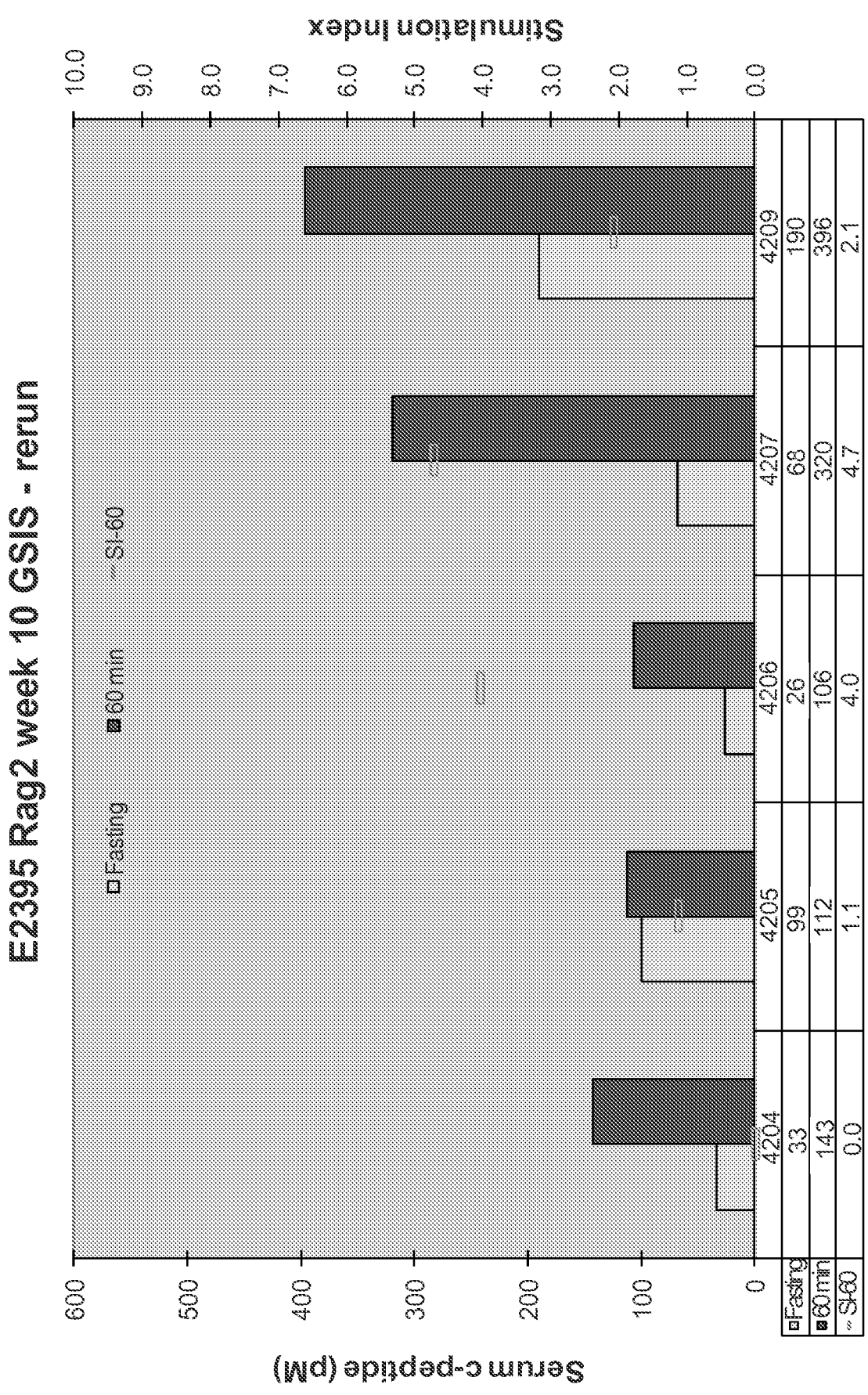

E2395 Rag2 week 10 GSIS - rerun
Fasting
60 min
SI-60
Serum c-peptide (pM)
Stimulation Index
0
100
200
300
400
500
600
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
4204
4205
4206
4207
4209
Fasting 33 99 26 68 190
60 min 143 112 106 320 396
SI-60 0.0 1.1 4.0 4.7 2.1

FIG. 20

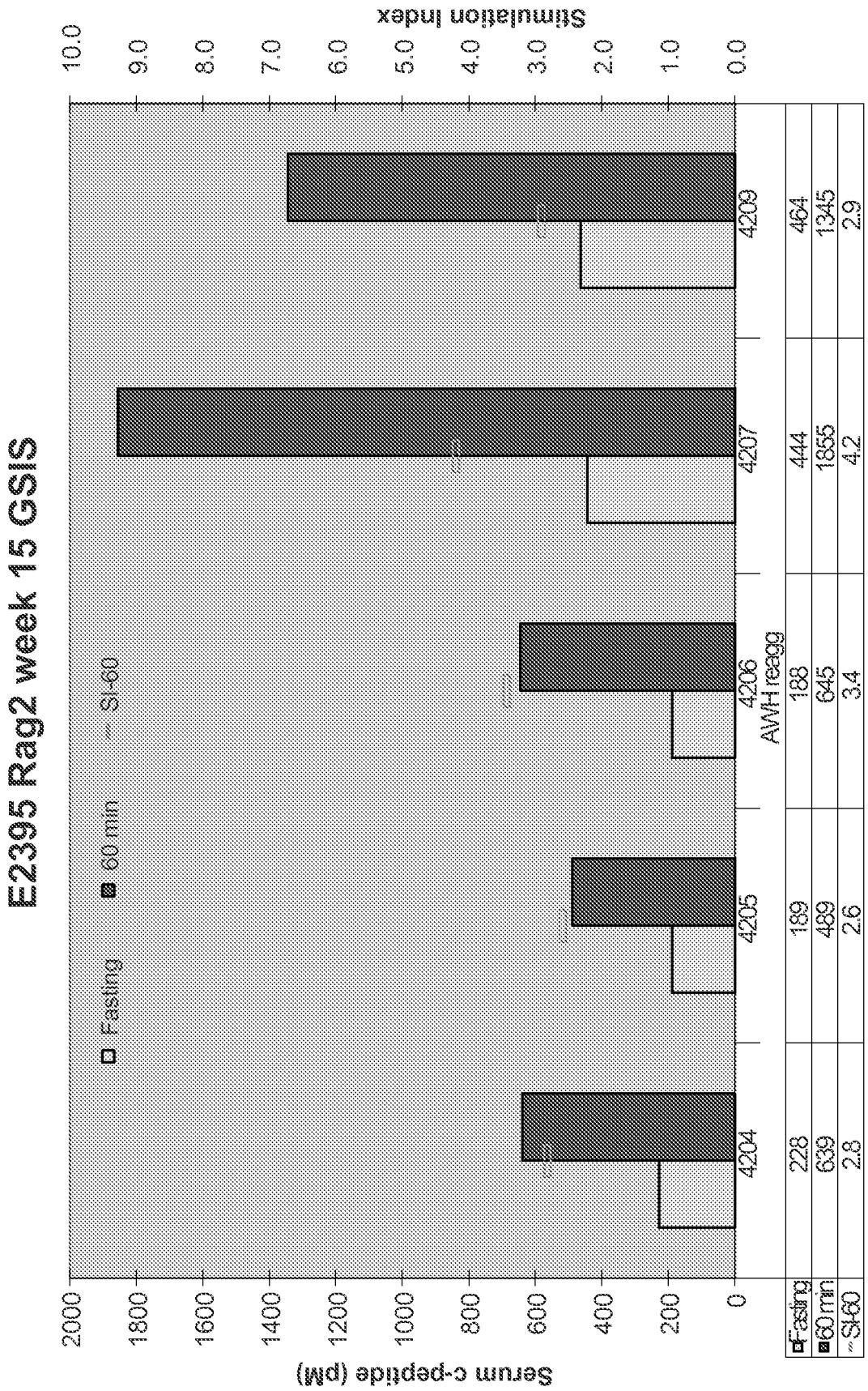

E2395 Rag2 week 15 GSIS
Fasting
60 min
SI-60
Serum c-peptide (pM)
Stimulation Index
2000
1800
1600
1400
1200
1000
800
600
400
200
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
4204
4205
4206
4207
4209
AWH reagg
Fasting 228 189 188 444 464
60 min 639 489 645 1855 1345
SI60 2.8 2.6 3.4 4.2 2.9

FIG. 21

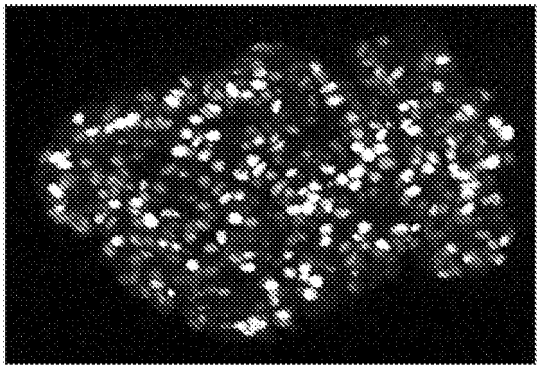


FIG. 22C

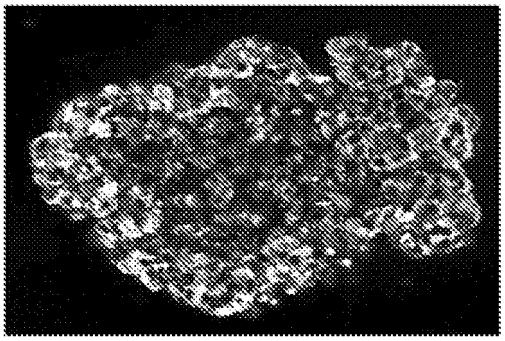


FIG. 22D

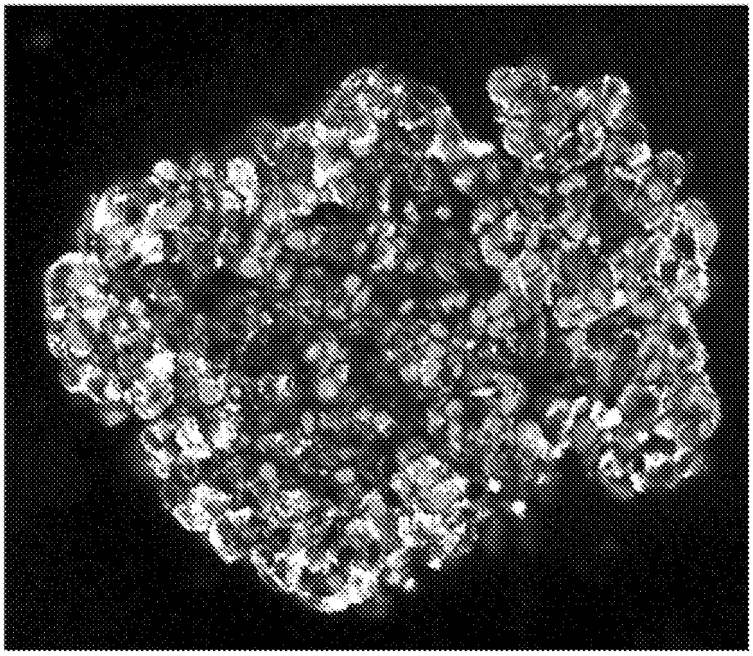


FIG. 22B

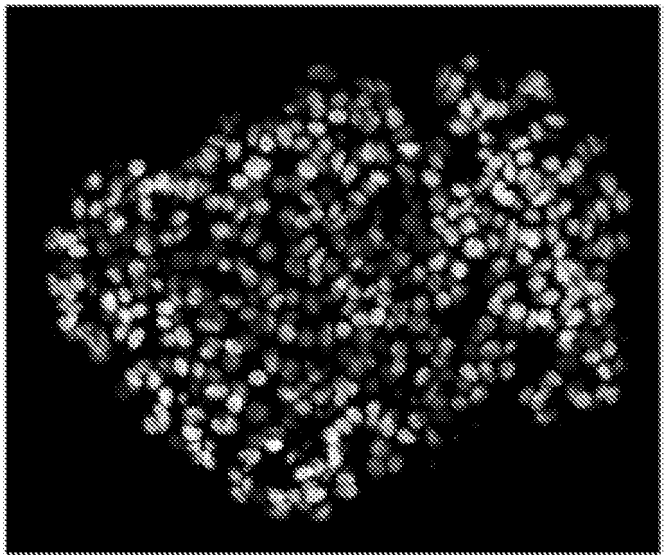


FIG. 22A

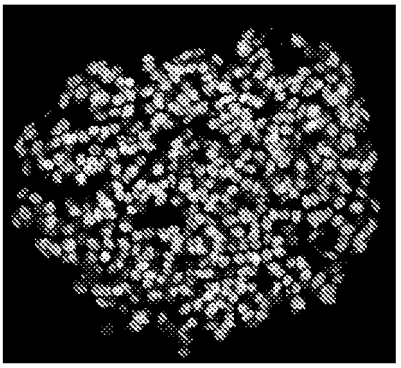


FIG. 23C

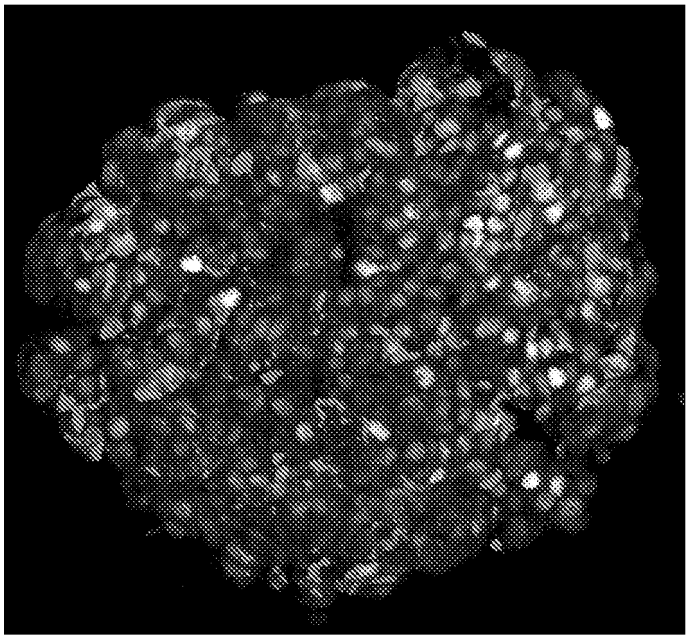


FIG. 23B

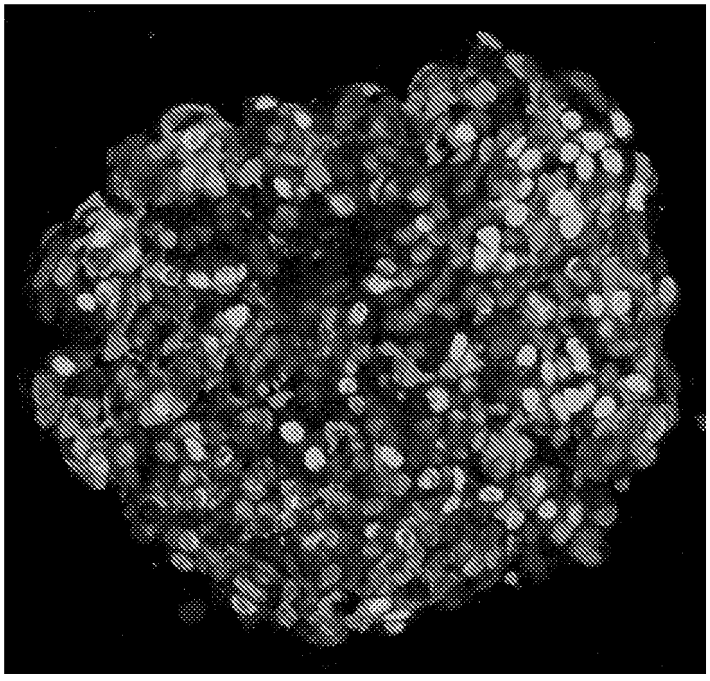


FIG. 23A

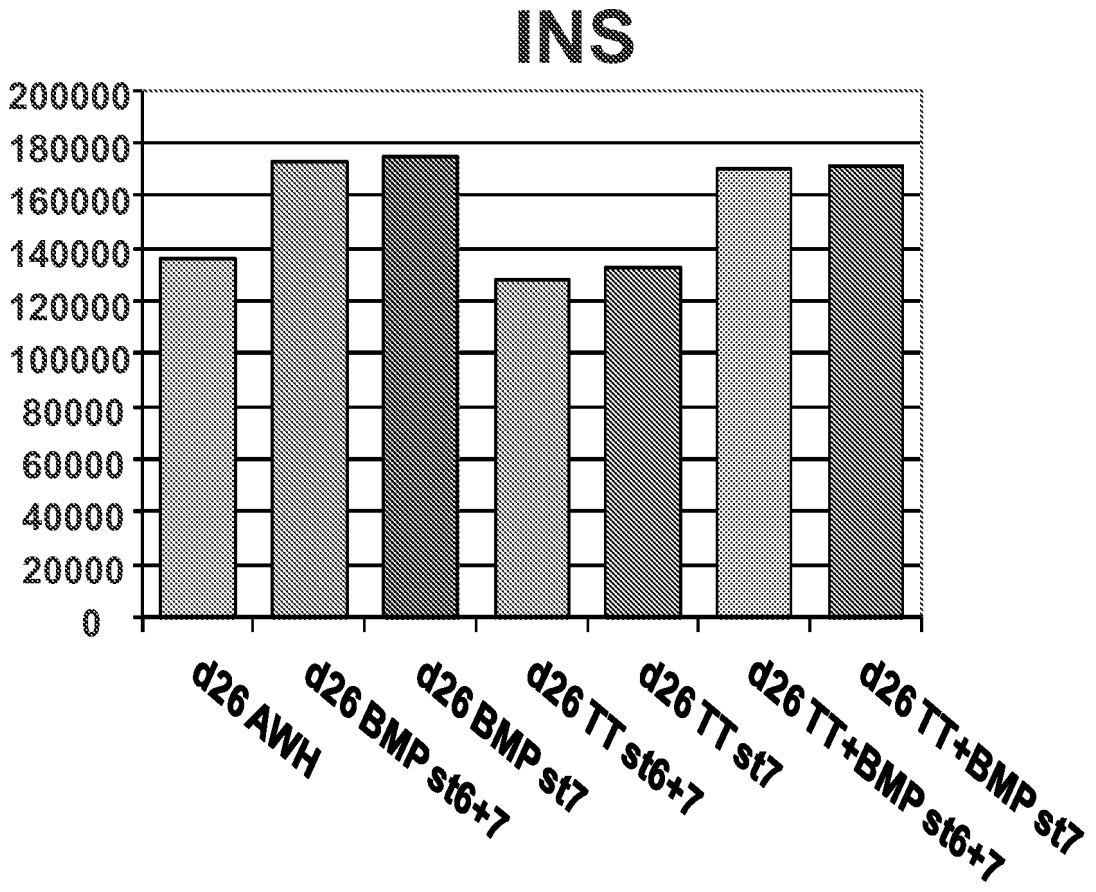

INS
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
d26 AWH
d26 BMP st6+7
d26 BMP st7
d26 TT st6+7
d26 TT st7
d26 TT+BMP st6+7
d26 TT+BMP st7

FIG. 24A

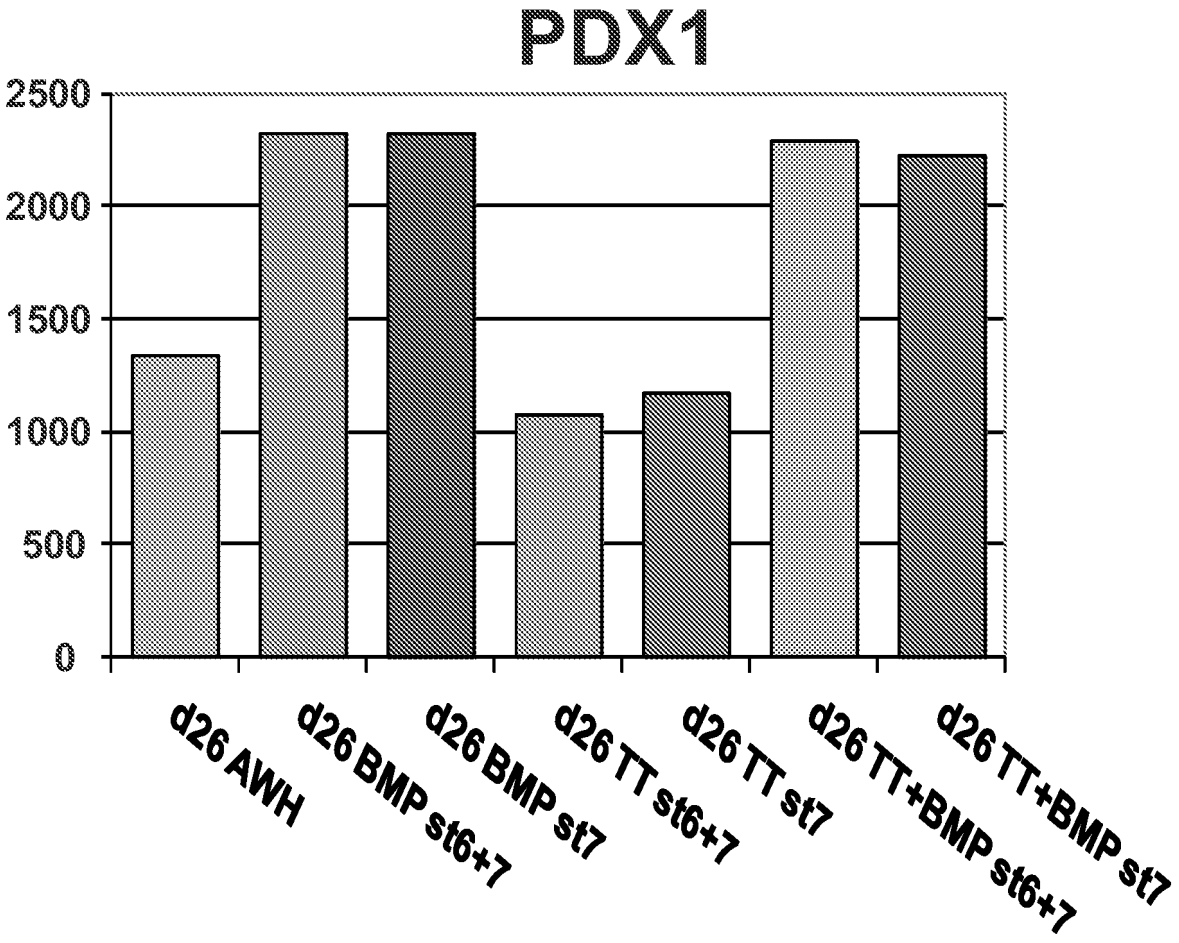

PDX1
2500
2000
1500
1000
500
0
d26 AWH
d26 BMP st6+7
d26 BMP st7
d26 TT st6+7
d26 TT st7
d26 TT+BMP st6+7
d26 TT+BMP st7

FIG. 24B

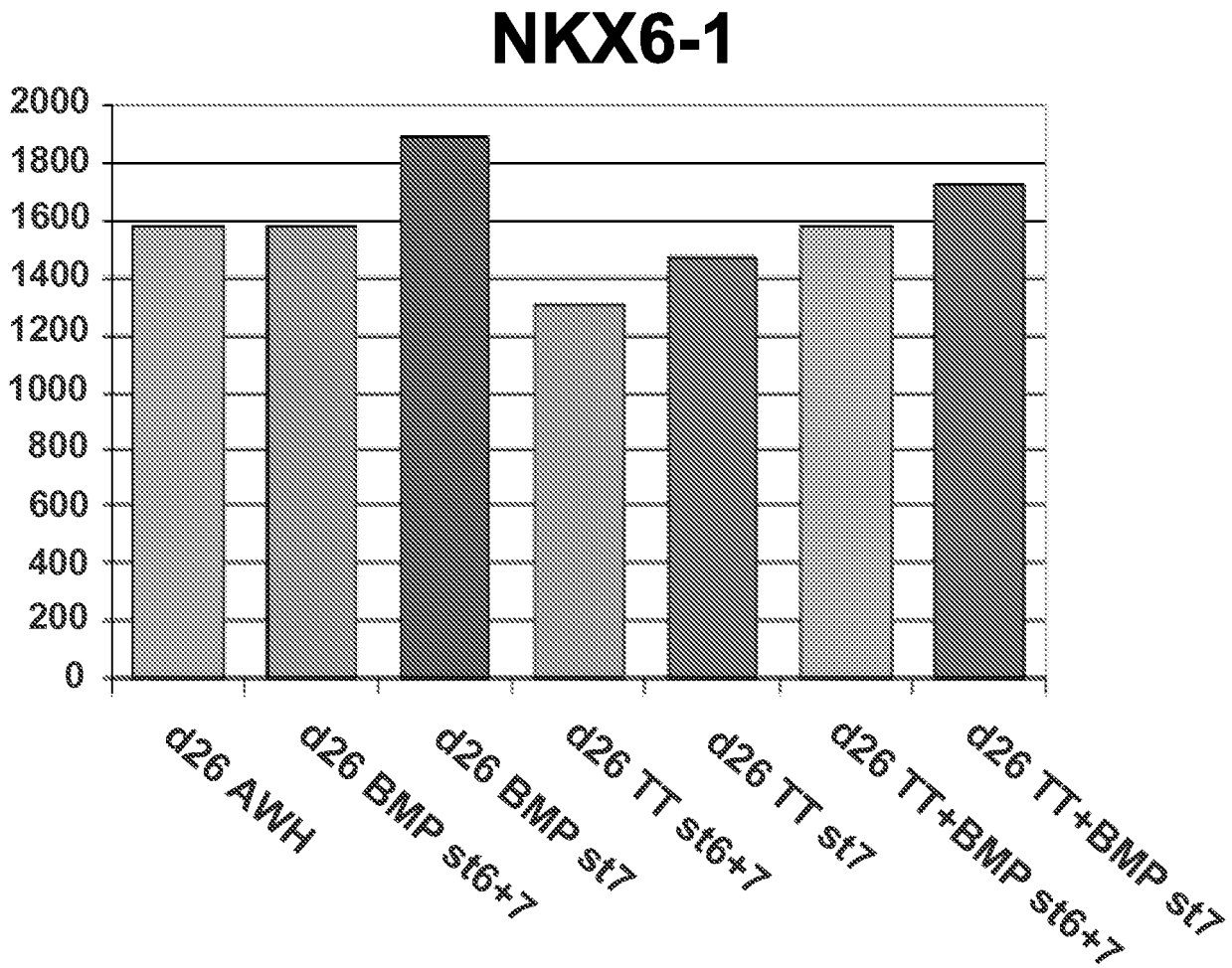

NKX6-1
2000
1800
1600
1400
1200
1000
800
600
400
200
0
d26 AWH
d26 BMP st6+7
d26 BMP st7
d26 TT st6+7
d26 TT st7
d26 TT+BMP st6+7
d26 TT+BMP st7

FIG. 24C

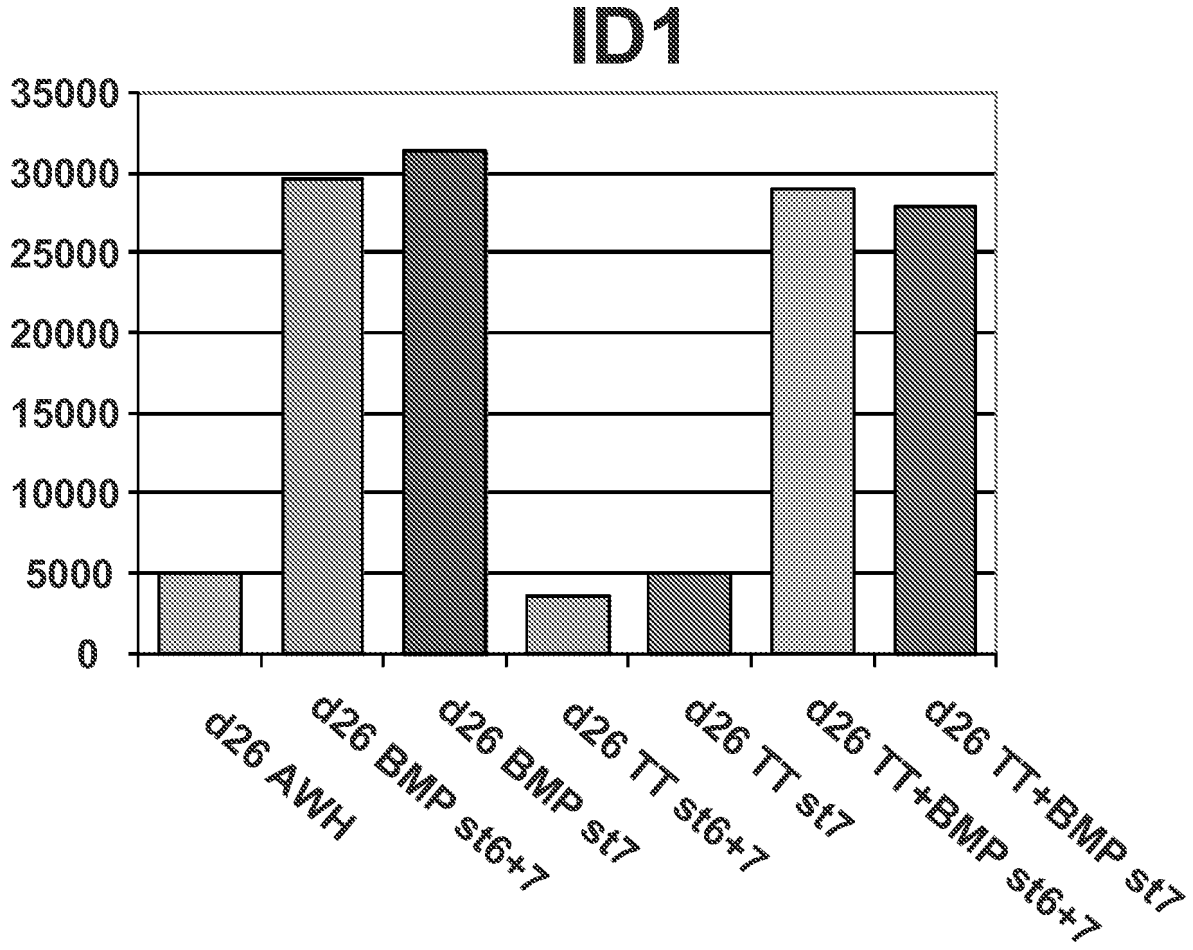

ID1
35000
30000
25000
20000
15000
10000
5000
0
d26 AWH
d26 BMP st6+7
d26 BMP st7
d26 TT st6+7
d26 TT st7
d26 TT+BMP st6+7
d26 TT+BMP st7

FIG. 24D

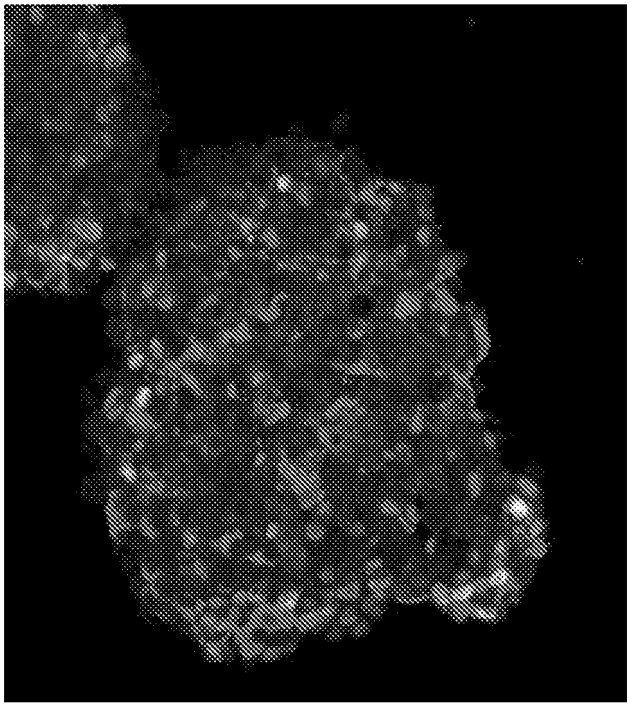


FIG. 25B

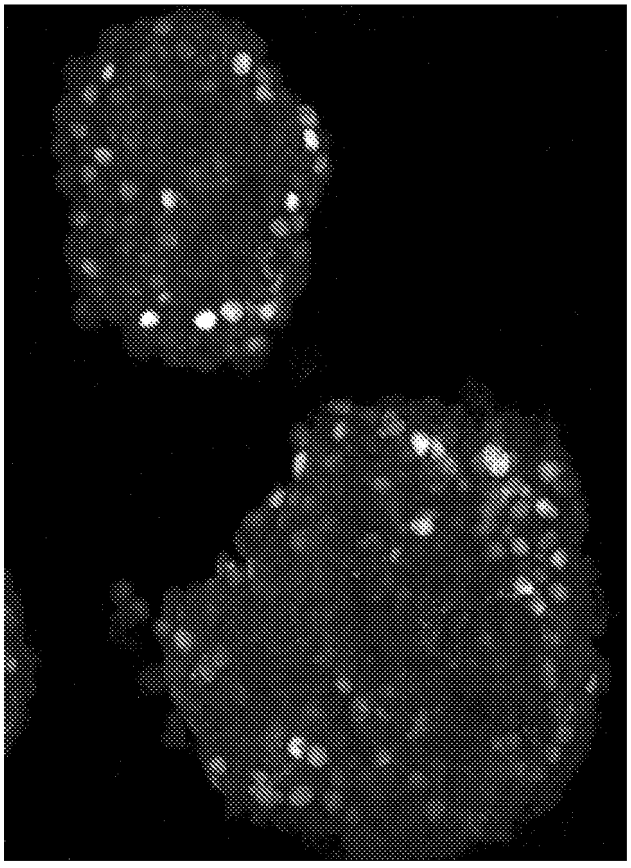


FIG. 25A

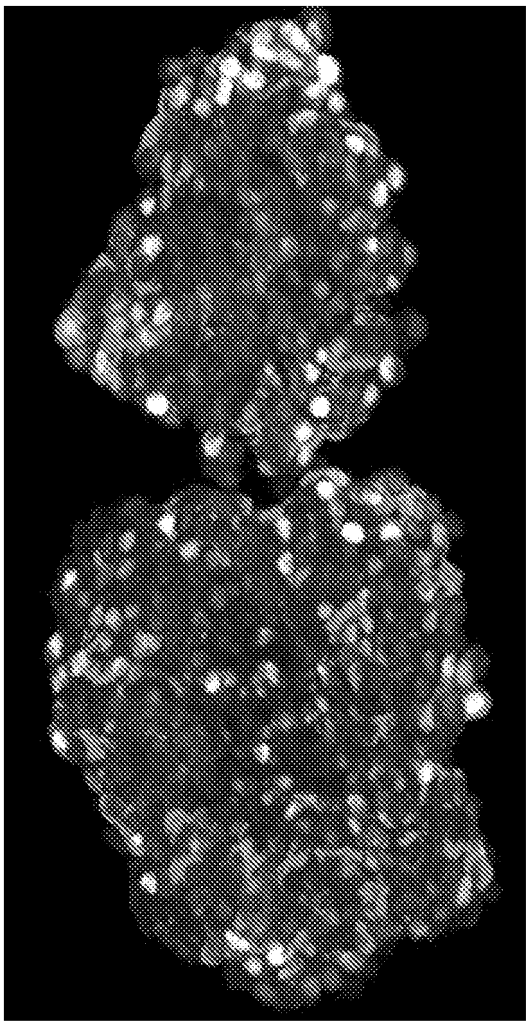


FIG. 25C

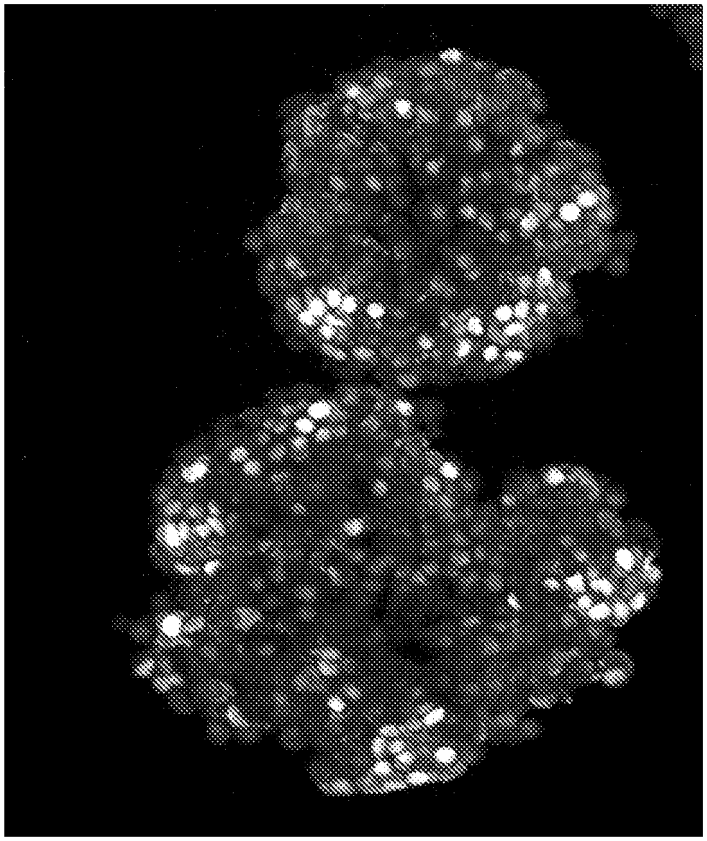


FIG. 26B

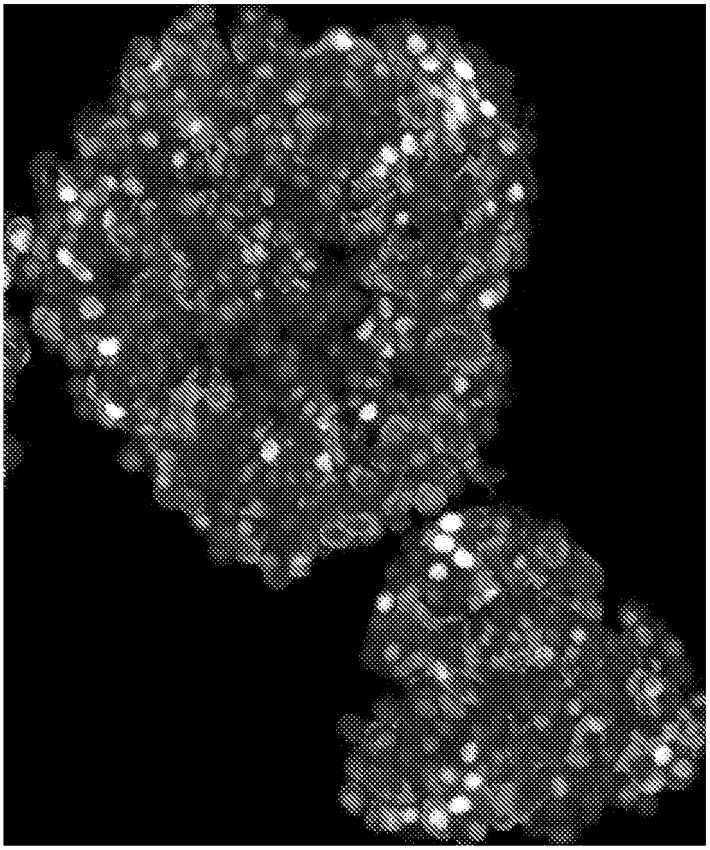


FIG. 26A

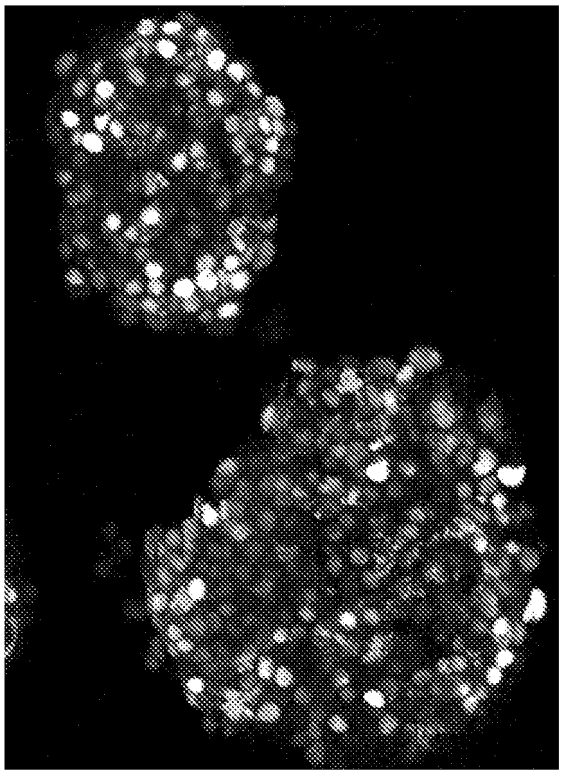


FIG. 27A

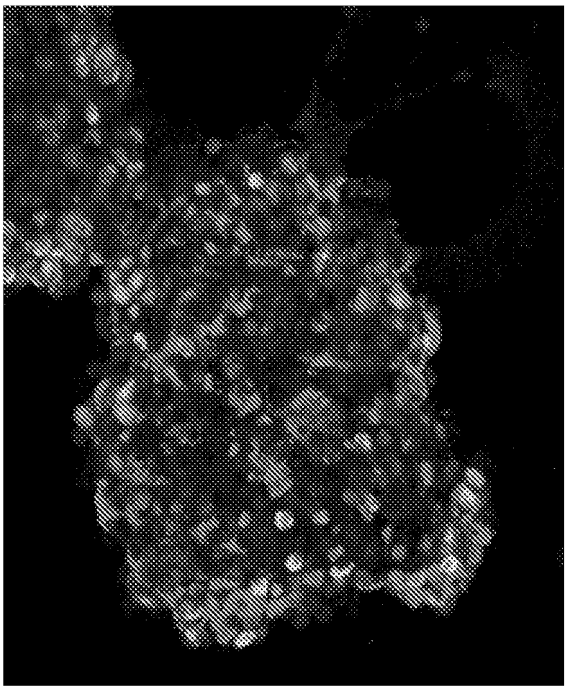


FIG. 27B

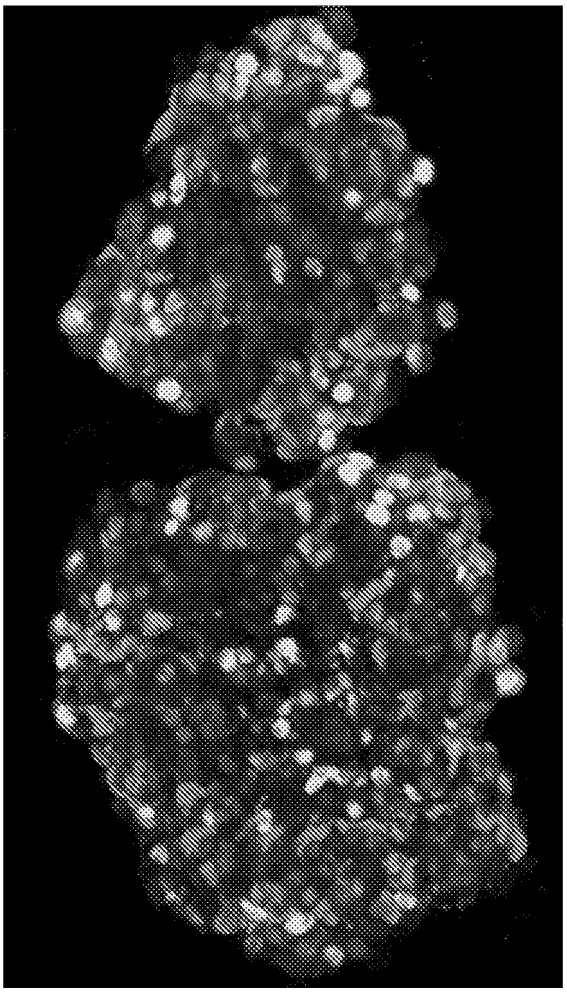


FIG. 27C

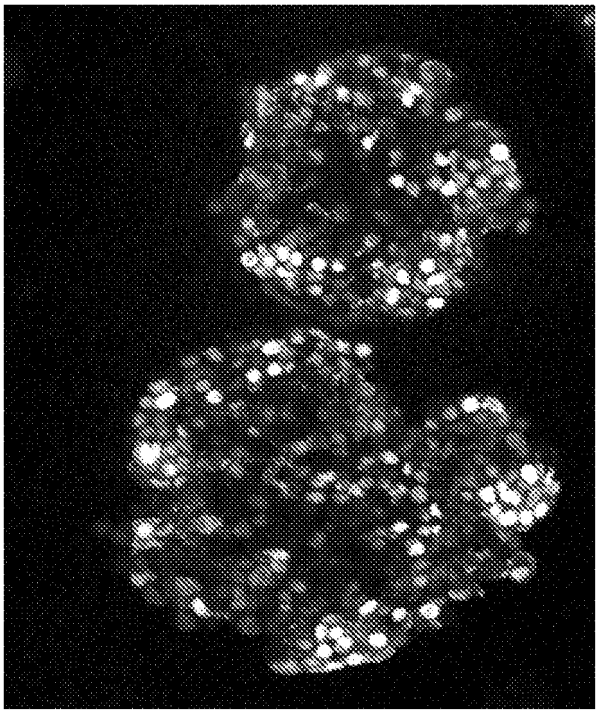


FIG. 28B

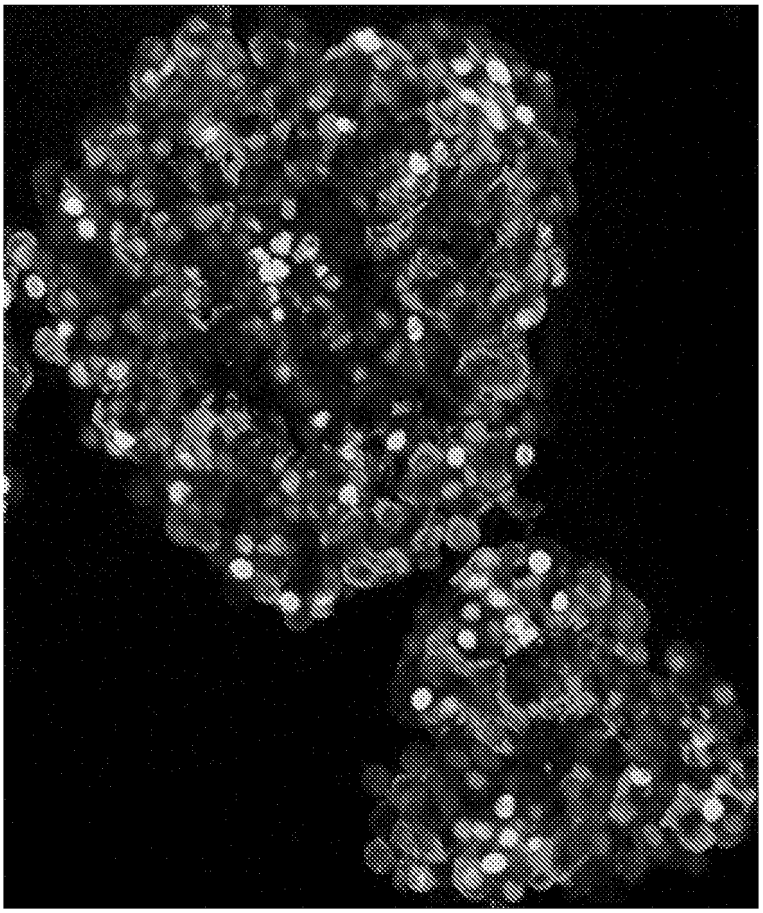


FIG. 28A

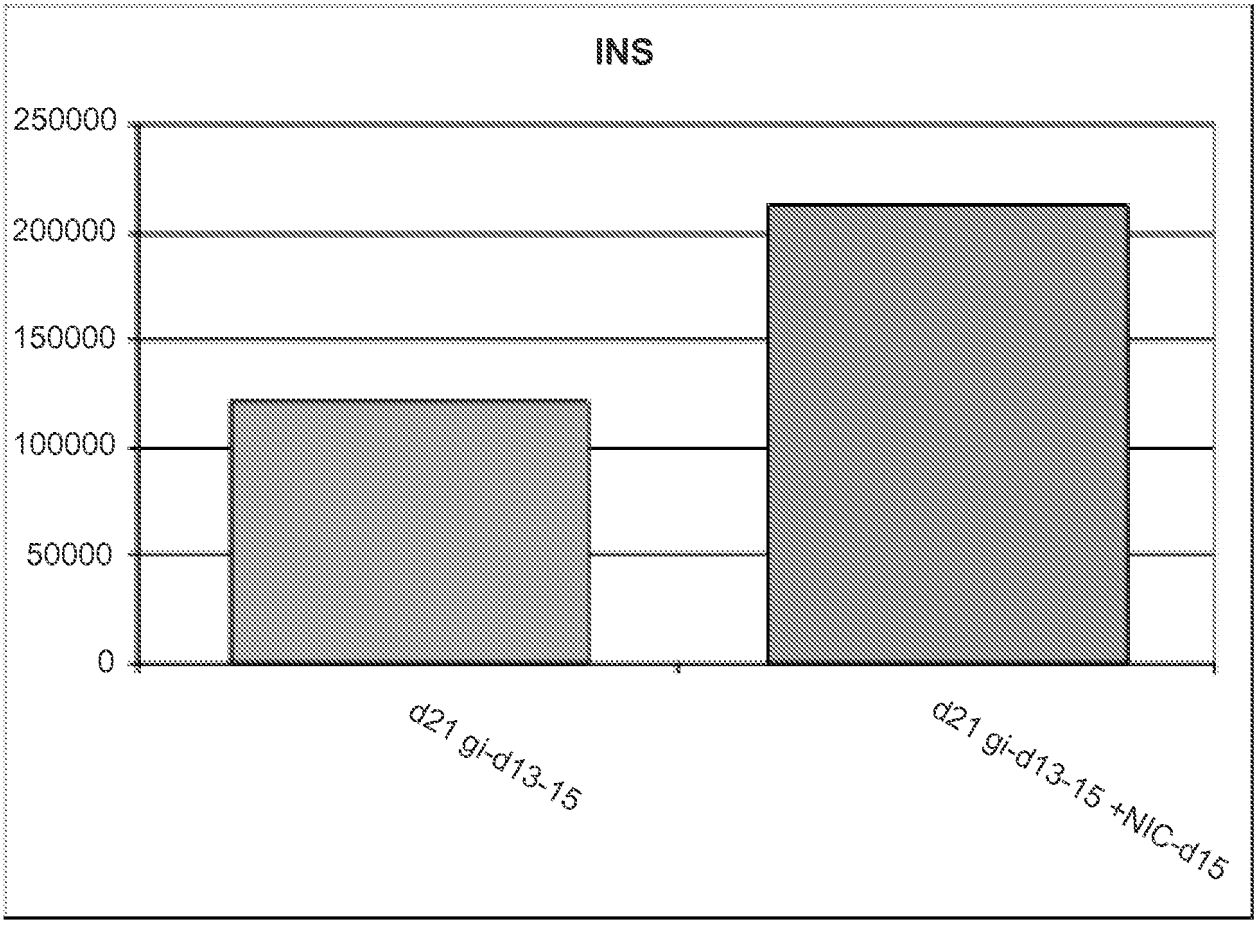

INS
250000
200000
150000
100000
50000
0
d21 gi-d13-15
d21 gi-d13-15 +NIC-d15

FIG. 29A

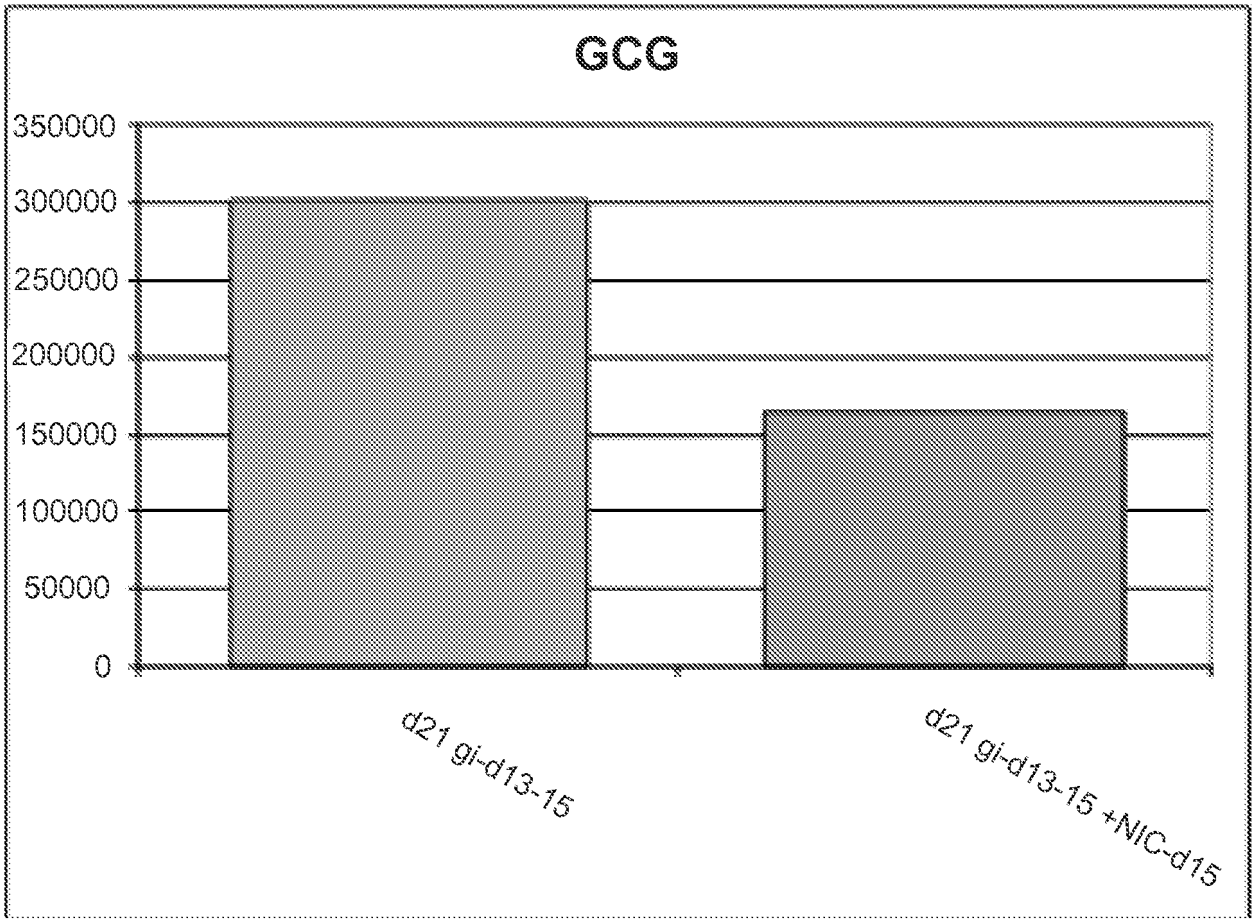

GCG
350000
300000
250000
200000
150000
100000
50000
0
d21 gi-d13-15
d21 gi-d13-15 +NIC-d15

FIG. 29B

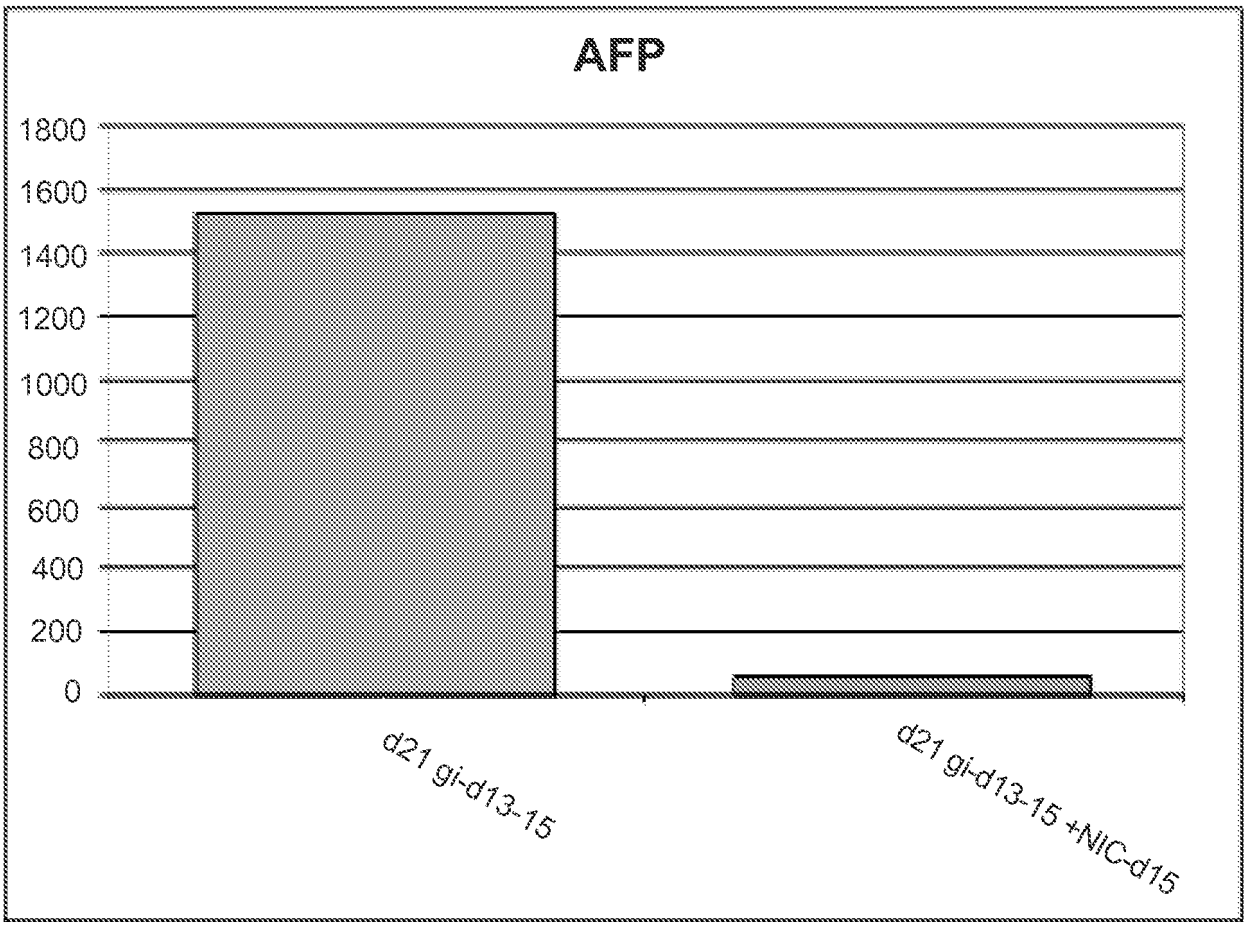

AFP
1800
1600
1400
1200
1000
800
600
400
200
0
d21 gi-d13-15
d21 gi-d13-15 +NIC-d15

FIG. 29C

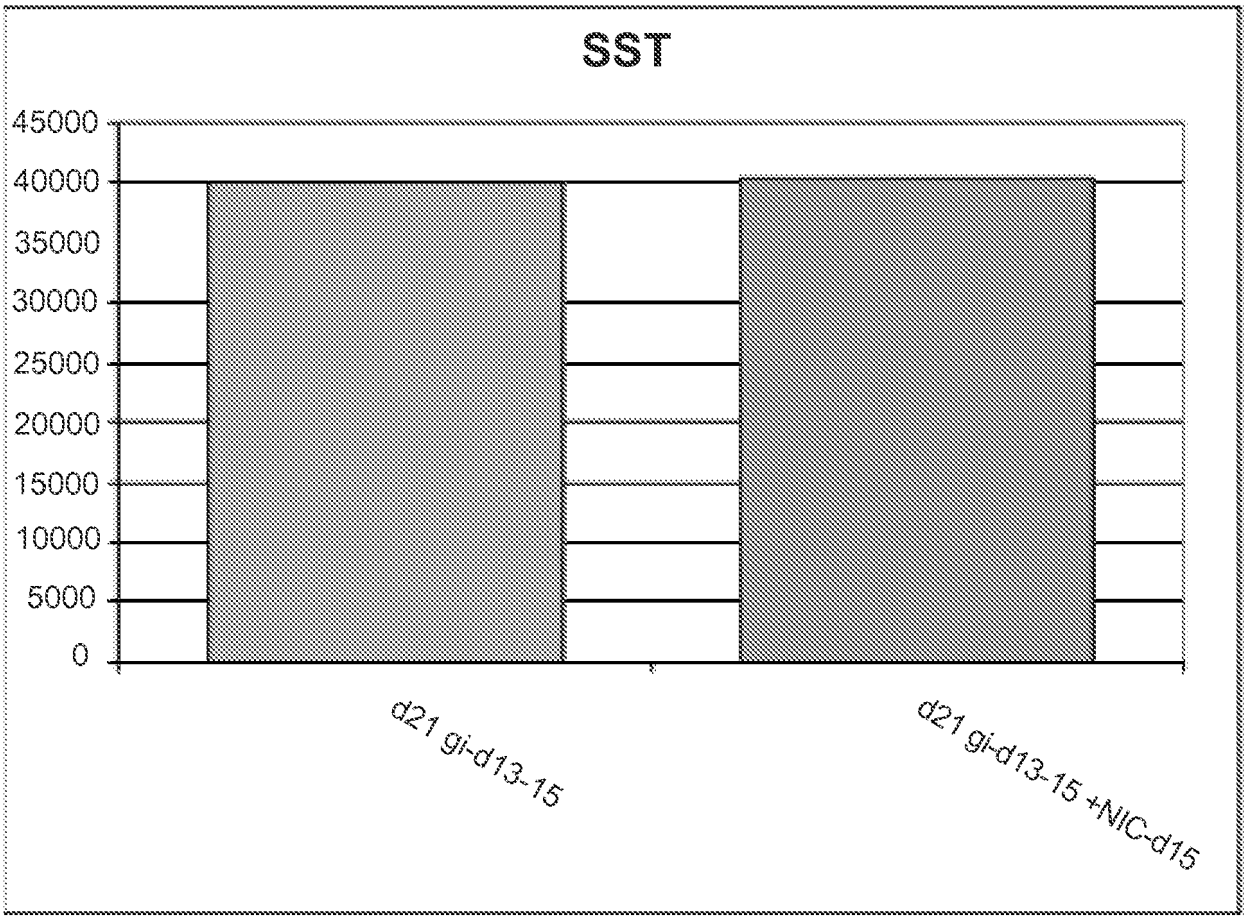

SST
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
d21 gi-d13-15
d21 gi-d13-15 +NIC-d15

FIG. 29D

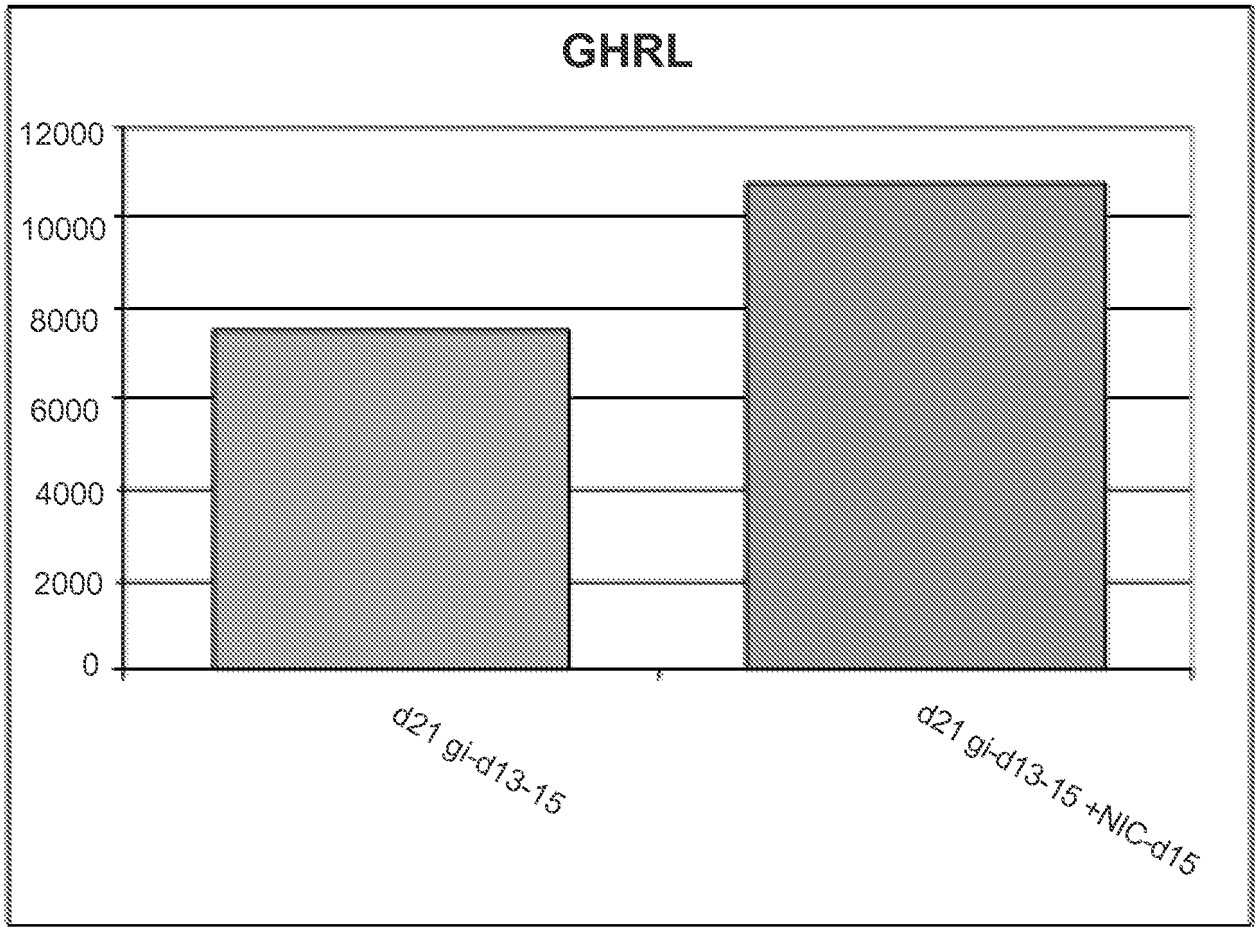

GHRL
12000
10000
8000
6000
4000
2000
0
d21 gi-d13-15
d21 gi-d13-15 +NIC-d15

FIG. 29E

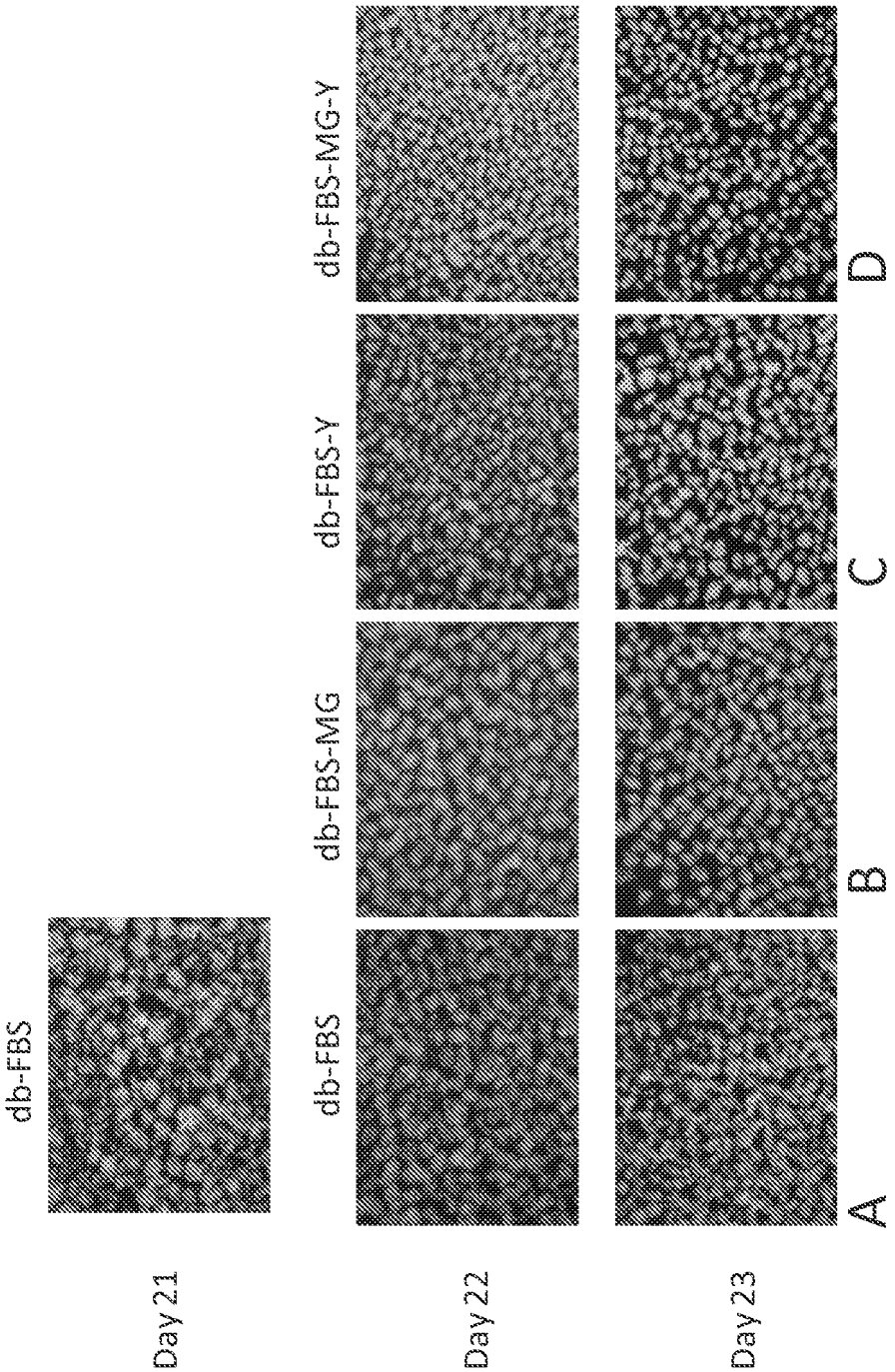

db-FBS
db-FBS
db-FBS-MG
db-FBS-Y
db-FBS-MG-Y
Day 21
Day 22
Day 23
A
B
C
D

FIG. 30

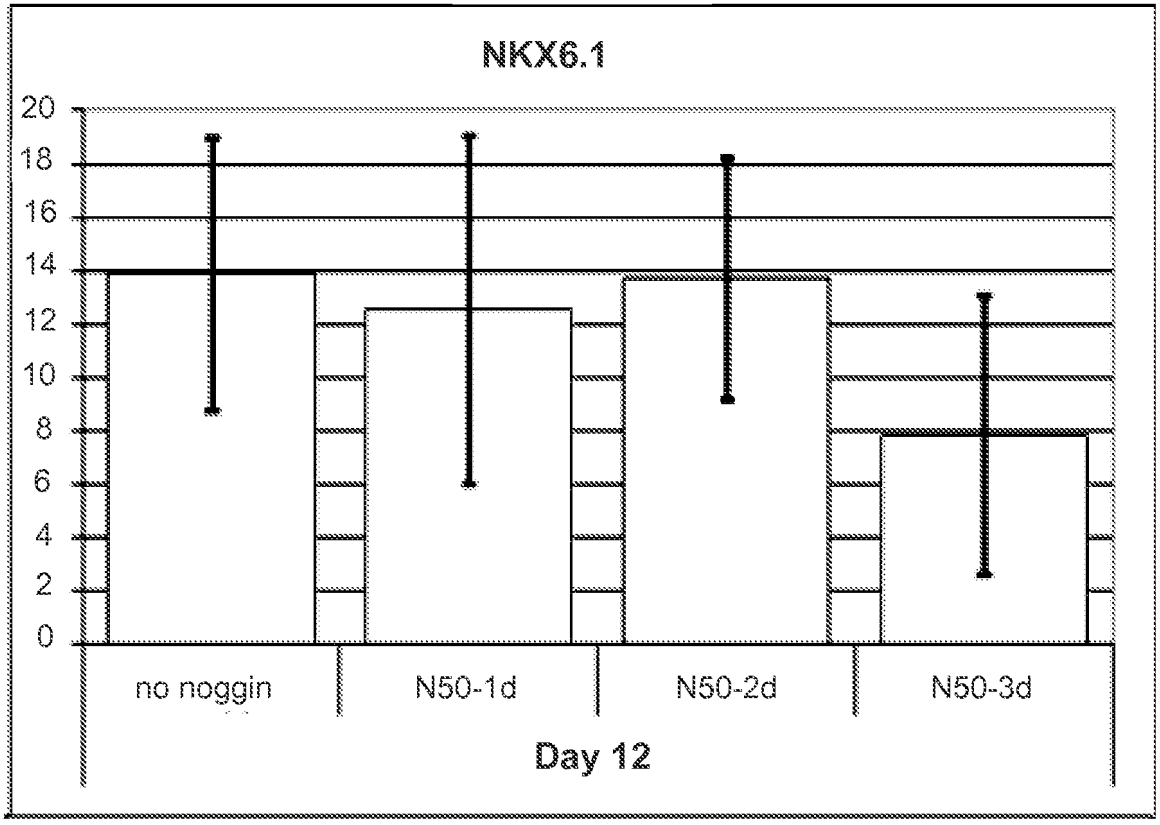


FIG. 31A

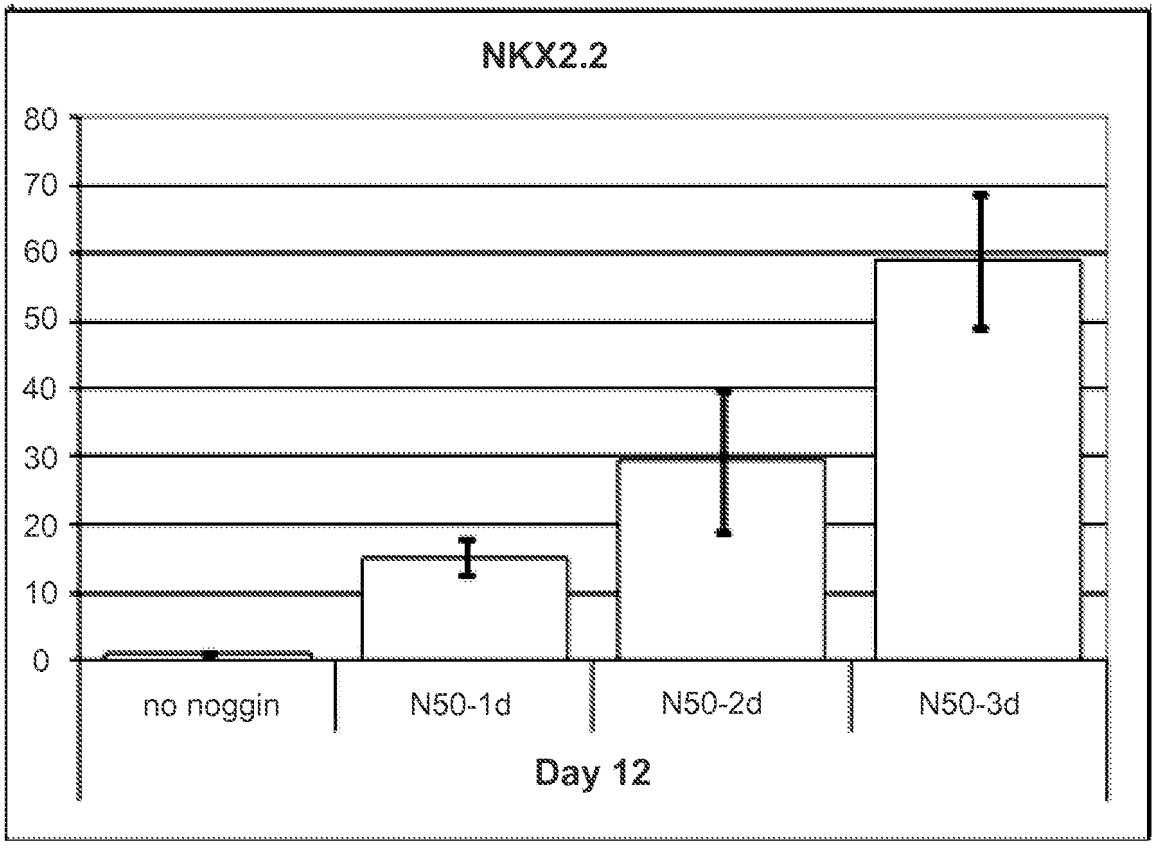


FIG. 31B

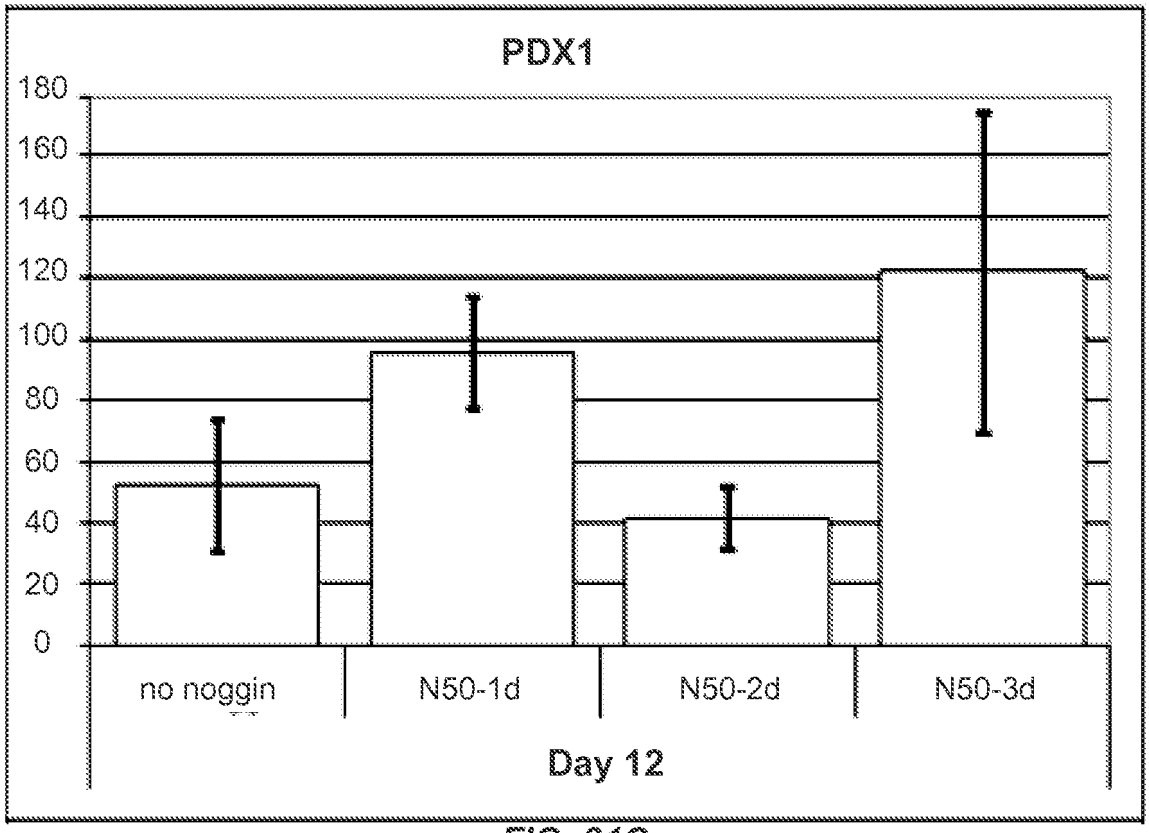


FIG. 31C

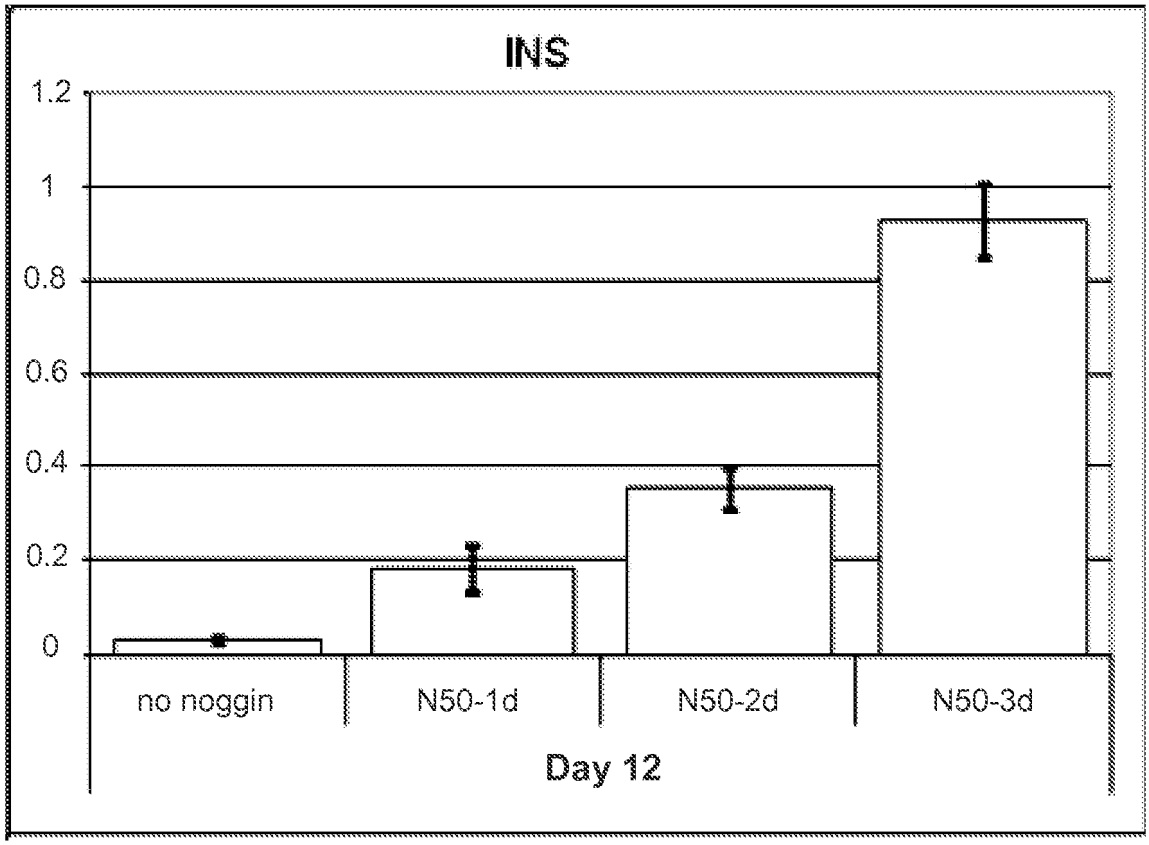


FIG. 31D

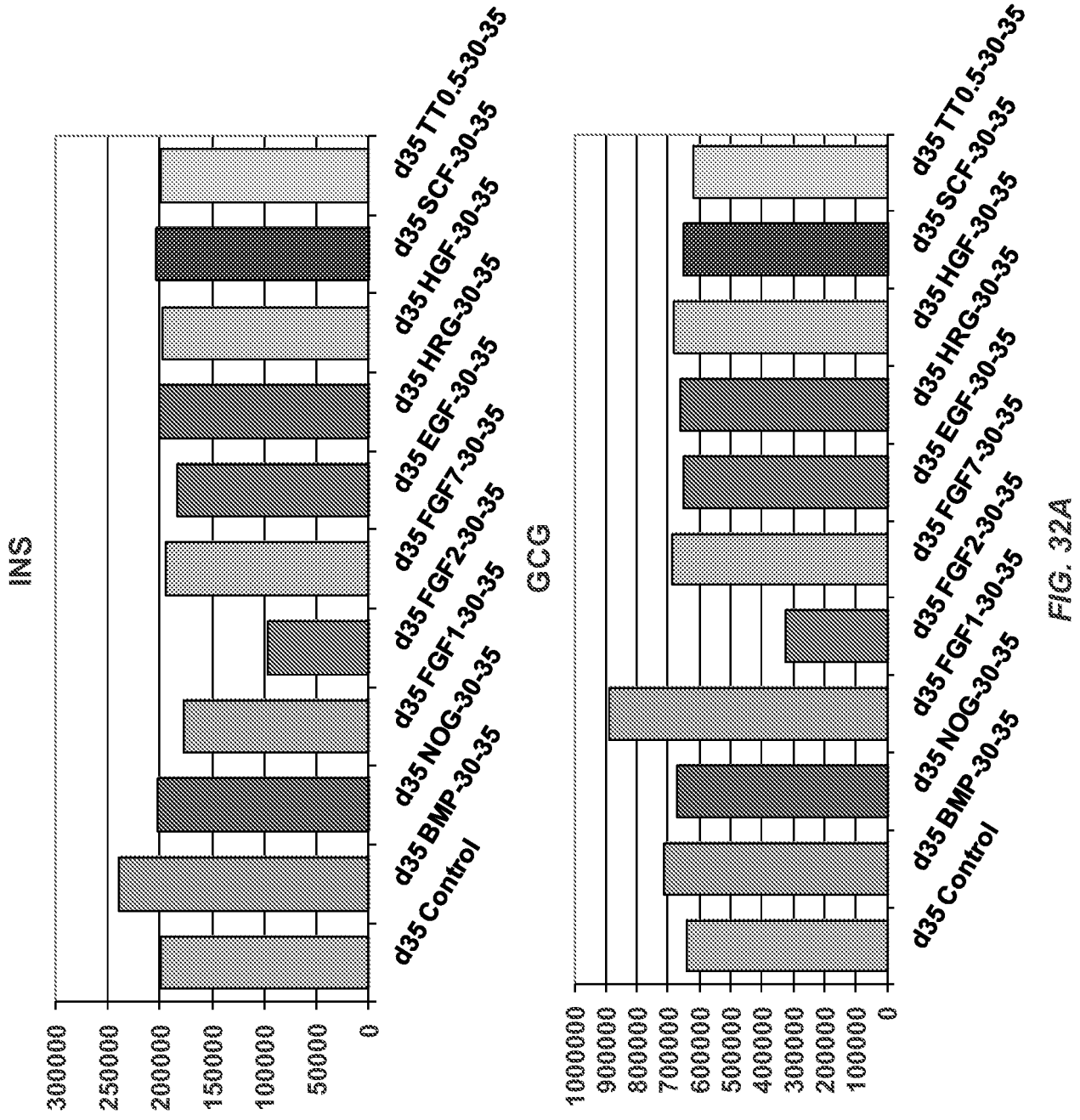

INS
300000
250000
200000
150000
100000
50000
0
d35 Control
d35 BMP-30-35
d35 NOG-30-35
d35 FGF1-30-35
d35 FGF2-30-35
d35 FGF7-30-35
d35 EGF-30-35
d35 HRG-30-35
d35 HGF-30-35
d35 SCF-30-35
d35 TT0.5-30-35
GCG
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
d35 Control
d35 BMP-30-35
d35 NOG-30-35
d35 FGF1-30-35
d35 FGF2-30-35
d35 FGF7-30-35
d35 EGF-30-35
d35 HRG-30-35
d35 HGF-30-35
d35 SCF-30-35
d35 TT0.5-30-35

FIG. 32A

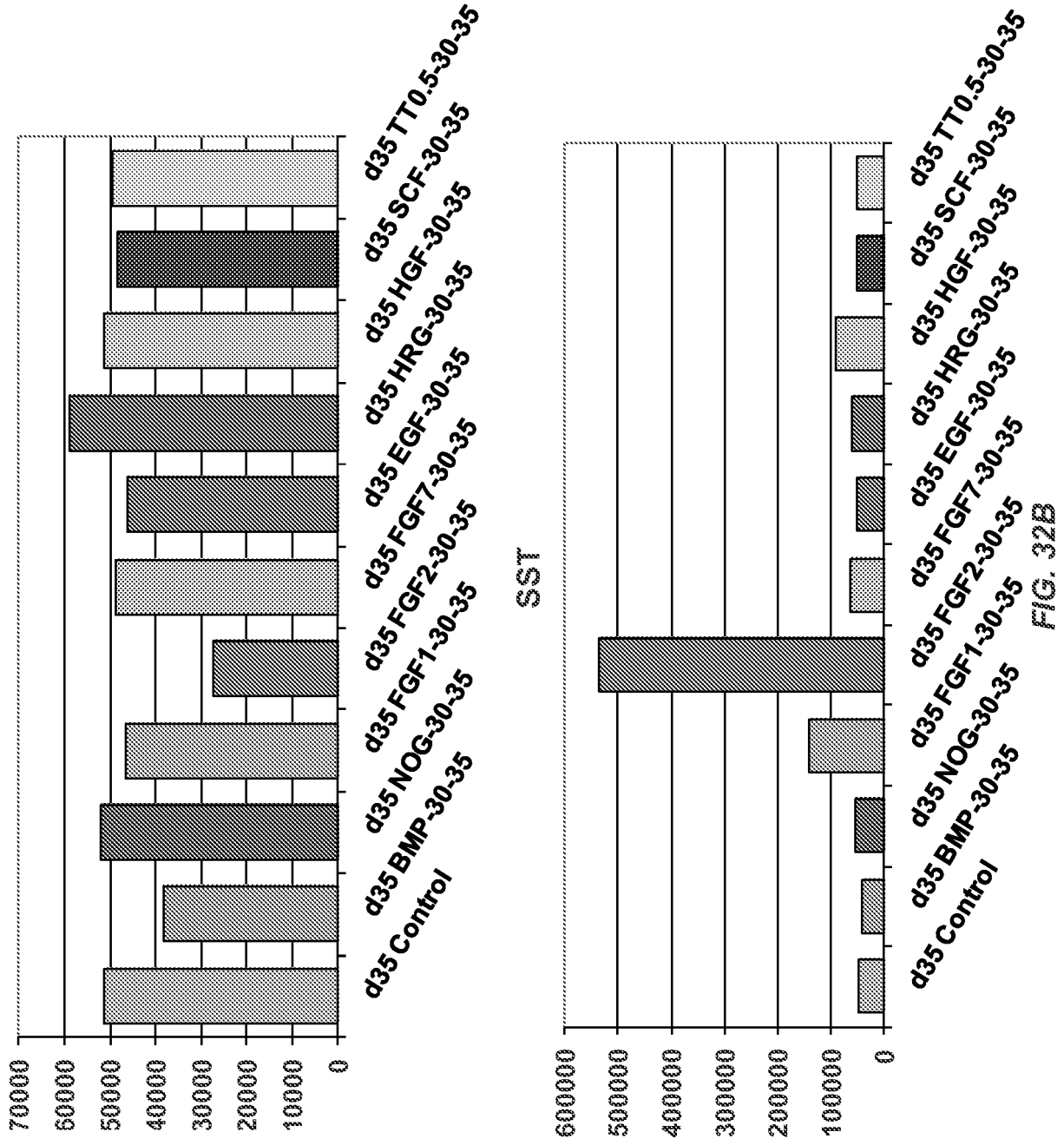

GHRL
70000
60000
50000
40000
30000
20000
10000
0
d35 Control
d35 BMP-30-35
d35 NOG-30-35
d35 FGF1-30-35
d35 FGF2-30-35
d35 FGF7-30-35
d35 EGF-30-35
d35 HRG-30-35
d35 HGF-30-35
d35 SCF-30-35
d35 TT0.5-30-35
SST
600000
500000
400000
300000
200000
100000
0
d35 Control
d35 BMP-30-35
d35 NOG-30-35
d35 FGF1-30-35
d35 FGF2-30-35
d35 FGF7-30-35
d35 EGF-30-35
d35 HRG-30-35
d35 HGF-30-35
d35 SCF-30-35
d35 TT0.5-30-35

FIG. 32B

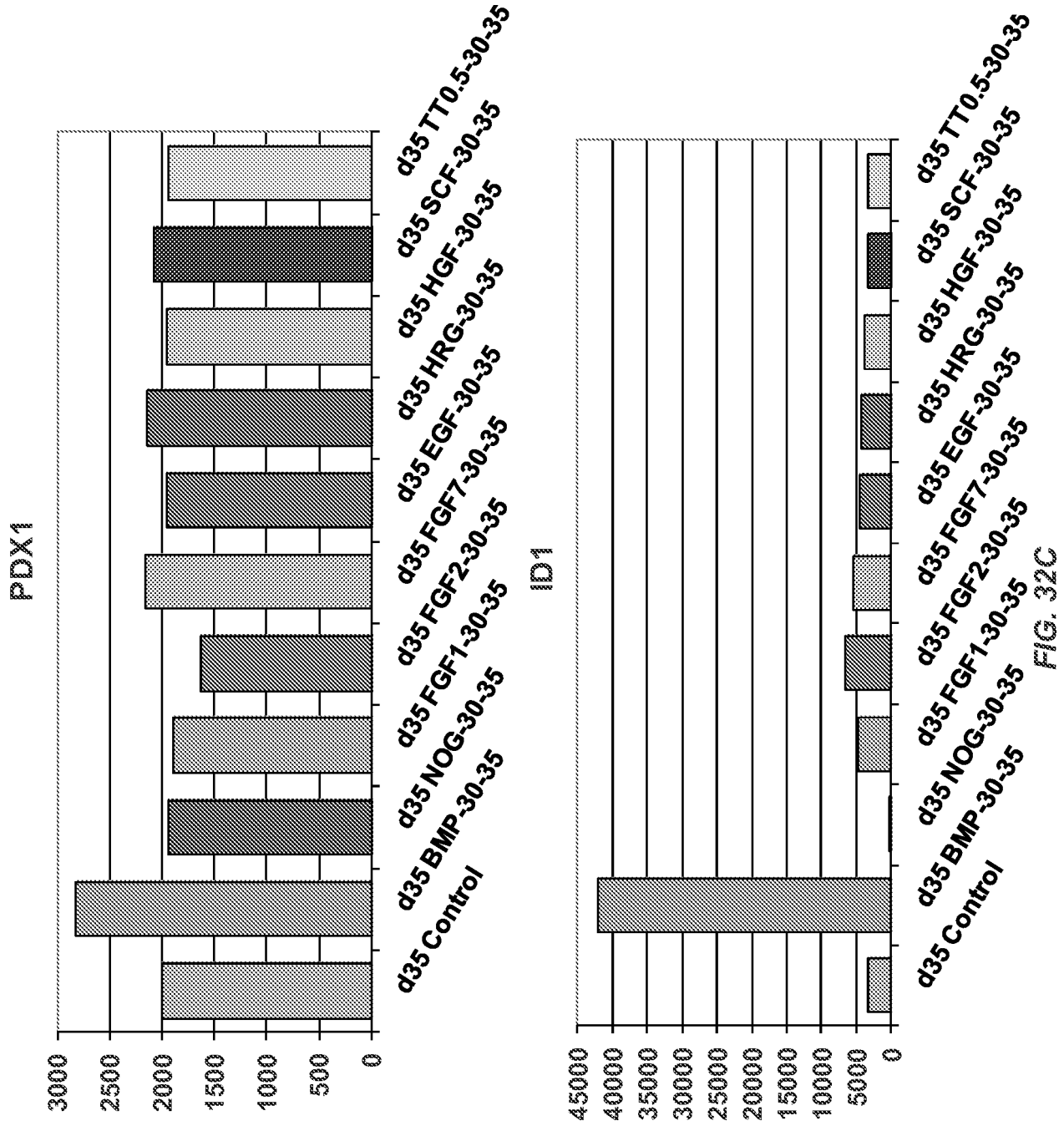

PDX1
3000
2500
2000
1500
1000
500
0
d35 Control
d35 BMP-30-35
d35 NOG-30-35
d35 FGF1-30-35
d35 FGF2-30-35
d35 FGF7-30-35
d35 EGF-30-35
d35 HRG-30-35
d35 HGF-30-35
d35 SCF-30-35
d35 TT0.5-30-35
ID1
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
d35 Control
d35 BMP-30-35
d35 NOG-30-35
d35 FGF1-30-35
d35 FGF2-30-35
d35 FGF7-30-35
d35 EGF-30-35
d35 HRG-30-35
d35 HGF-30-35
d35 SCF-30-35
d35 TT0.5-30-35

FIG. 32C

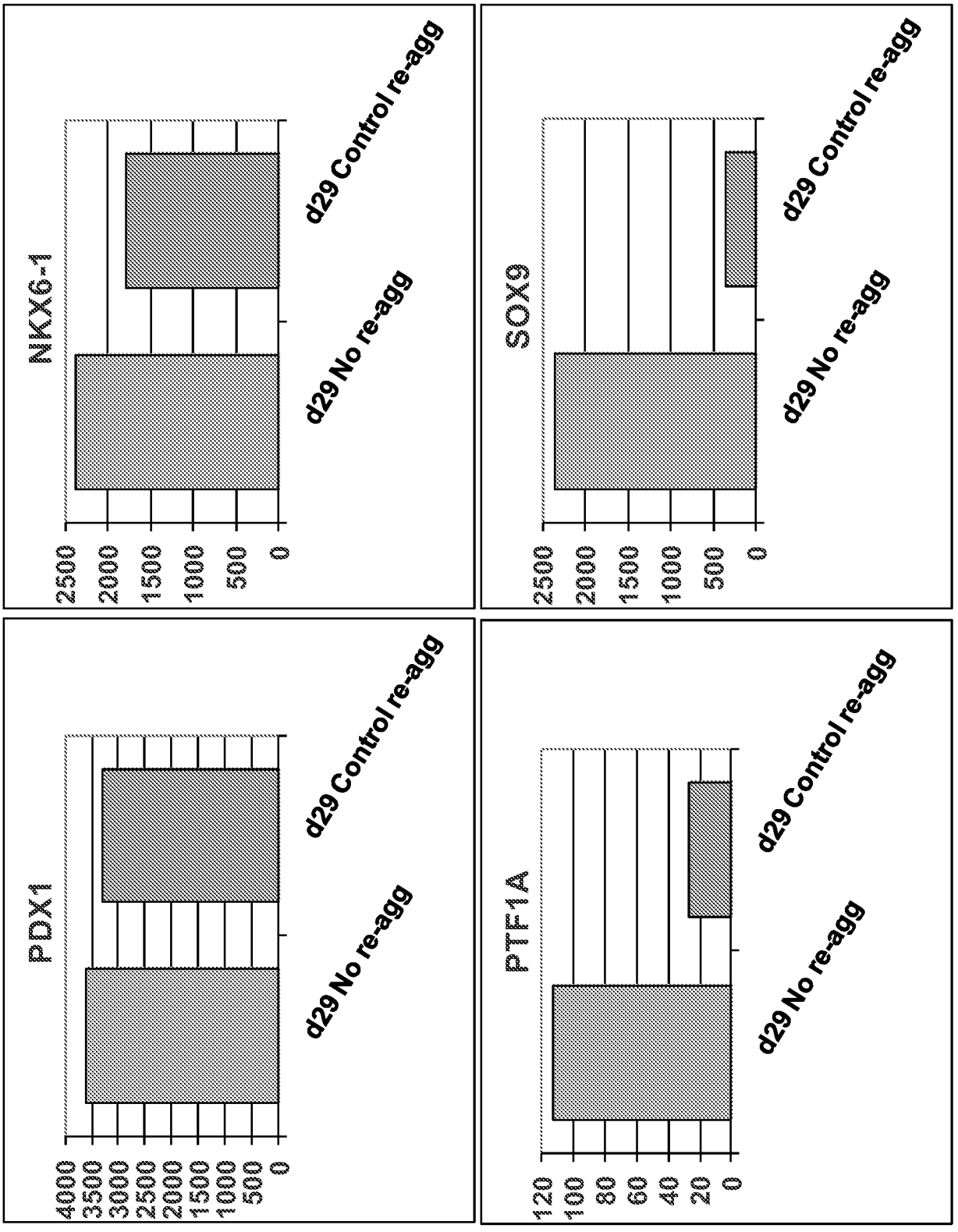

NKX6-1
2500
2000
1500
1000
500
0
d29 Control re-agg
d29 No re-agg
SOX9
2500
2000
1500
1000
500
0
d29 Control re-agg
d29 No re-agg
PDX1
4000
3500
3000
2500
2000
1500
1000
500
0
d29 Control re-agg
d29 No re-agg
PTF1A
120
100
80
60
40
20
0
d29 Control re-agg
d29 No re-agg

FIG. 33A

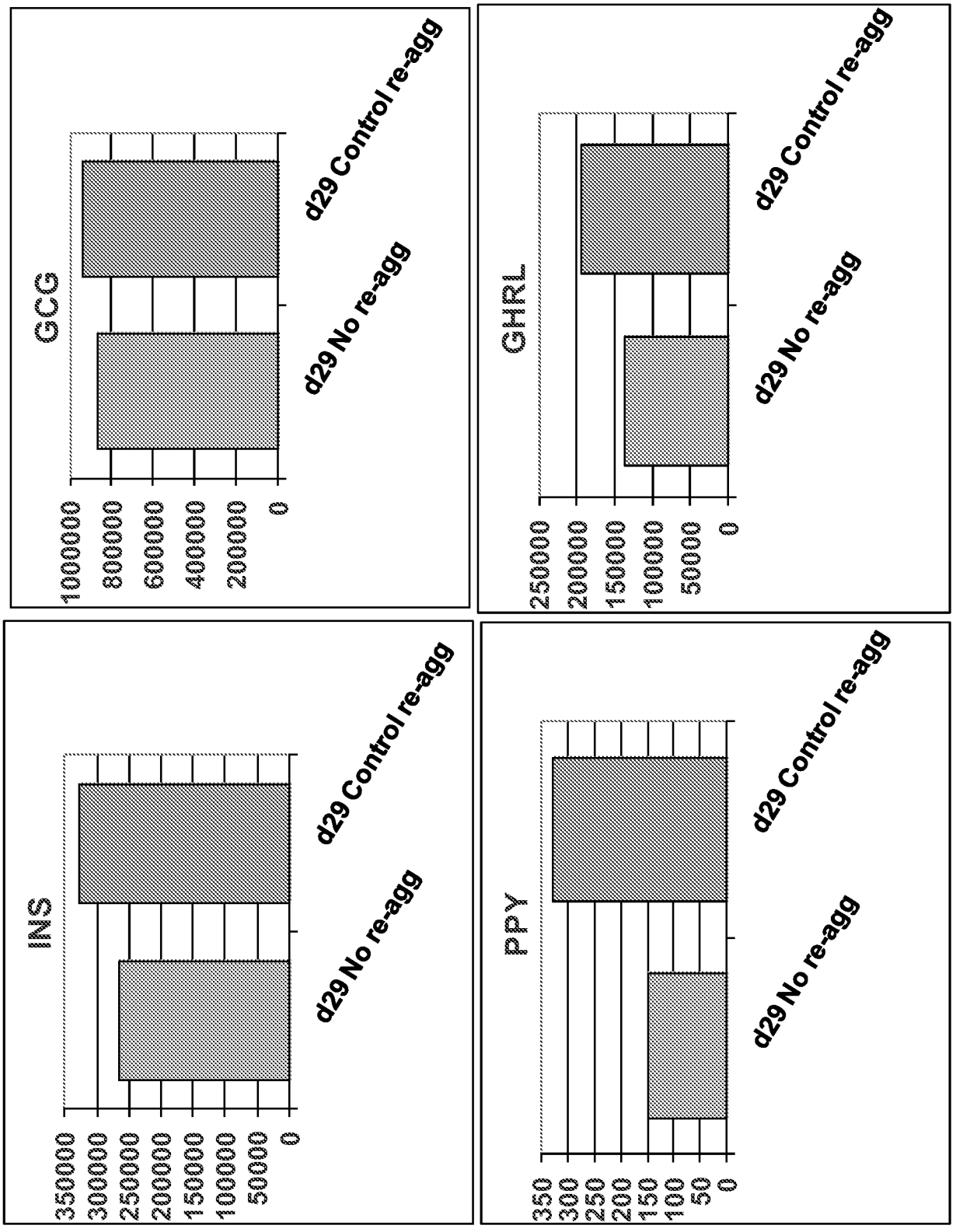

GCG
1000000
800000
600000
400000
200000
0
d29 Control re-agg
d29 No re-agg
GHRL
250000
200000
150000
100000
50000
0
d29 Control re-agg
d29 No re-agg
INS
350000
300000
250000
200000
150000
100000
50000
0
d29 Control re-agg
d29 No re-agg
PPY
350
300
250
200
150
100
50
0
d29 Control re-agg
d29 No re-agg

FIG. 33B

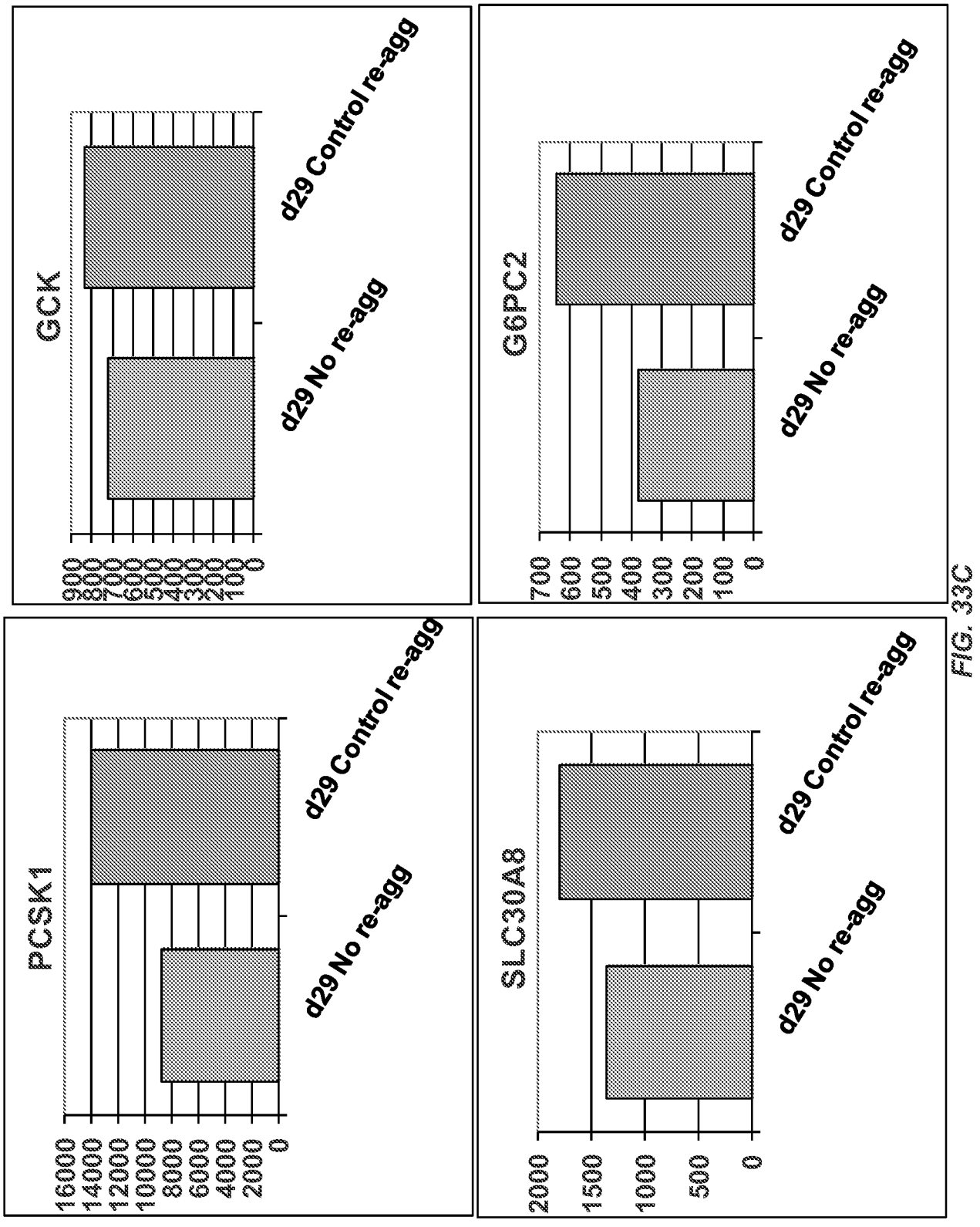

GCK
900
800
700
600
500
400
300
200
100
0
d29 Control re-agg
d29 No re-agg
G6PC2
700
600
500
400
300
200
100
0
d29 Control re-agg
d29 No re-agg
PCSK1
16000
14000
12000
10000
8000
6000
4000
2000
0
d29 Control re-agg
d29 No re-agg
SLC30A8
2000
1500
1000
500
0
d29 Control re-agg
d29 No re-agg

FIG. 33C

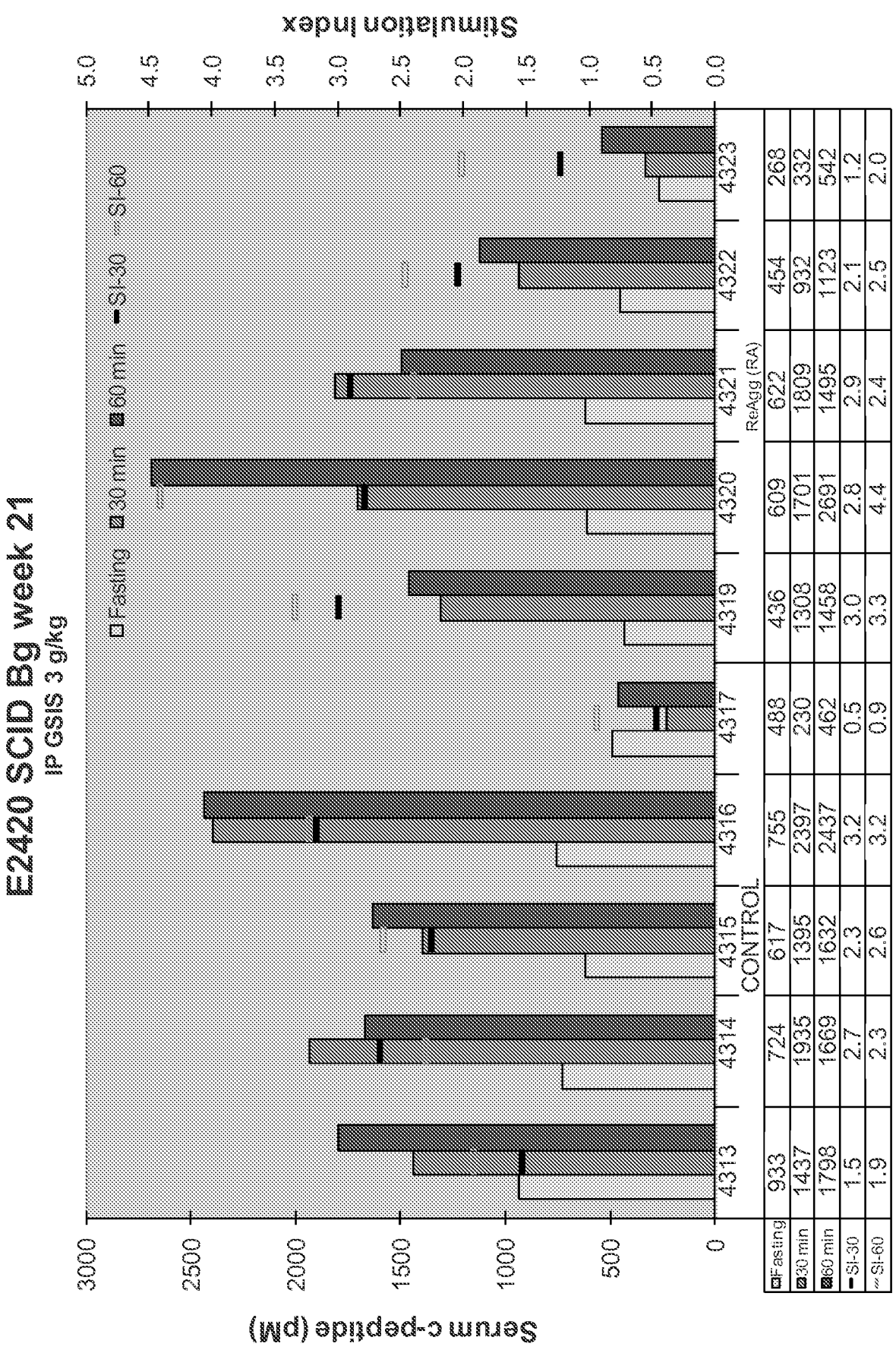

E2420 SCID Bg week 21
IP GSIS 3 g/kg
Fasting
30 min
60 min
SI-30
SI-60
Serum c-peptide (pM)
Stimulation Index
CONTROL
ReAgg (RA)
4313 4314 4315 4316 4317 4319 4320 4321 4322 4323
Fasting 933 724 617 755 488 436 609 622 454 268
30 min 1437 1935 1395 2397 230 1308 1701 1809 932 332
60 min 1798 1669 1632 2437 462 1458 2691 1495 1123 542
SI-30 1.5 2.7 2.3 3.2 0.5 3.0 2.8 2.9 2.1 1.2
SI-60 1.9 2.3 2.6 3.2 0.9 3.3 4.4 2.4 2.5 2.0

FIG. 34

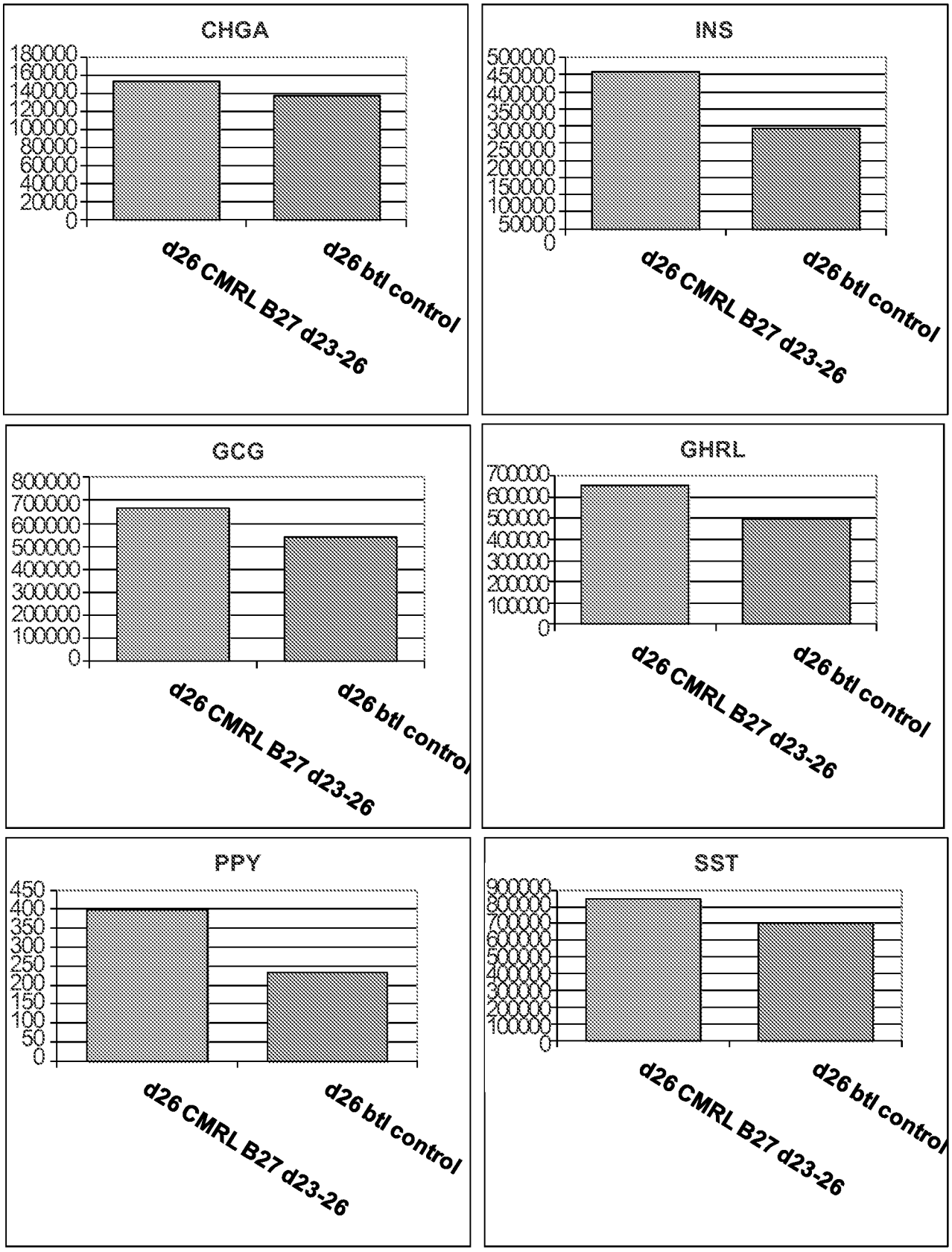

CHGA
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
d26 CMRL B27 d23-26
d26 btl control
INS
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
d26 CMRL B27 d23-26
d26 btl control
GCG
800000
700000
600000
500000
400000
300000
200000
100000
0
d26 CMRL B27 d23-26
d26 btl control
GHRL
700000
600000
500000
400000
300000
200000
100000
0
d26 CMRL B27 d23-26
d26 btl control
PPY
450
400
350
300
250
200
150
100
50
0
d26 CMRL B27 d23-26
d26 btl control
SST
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
d26 CMRL B27 d23-26
d26 btl control

FIG. 35A

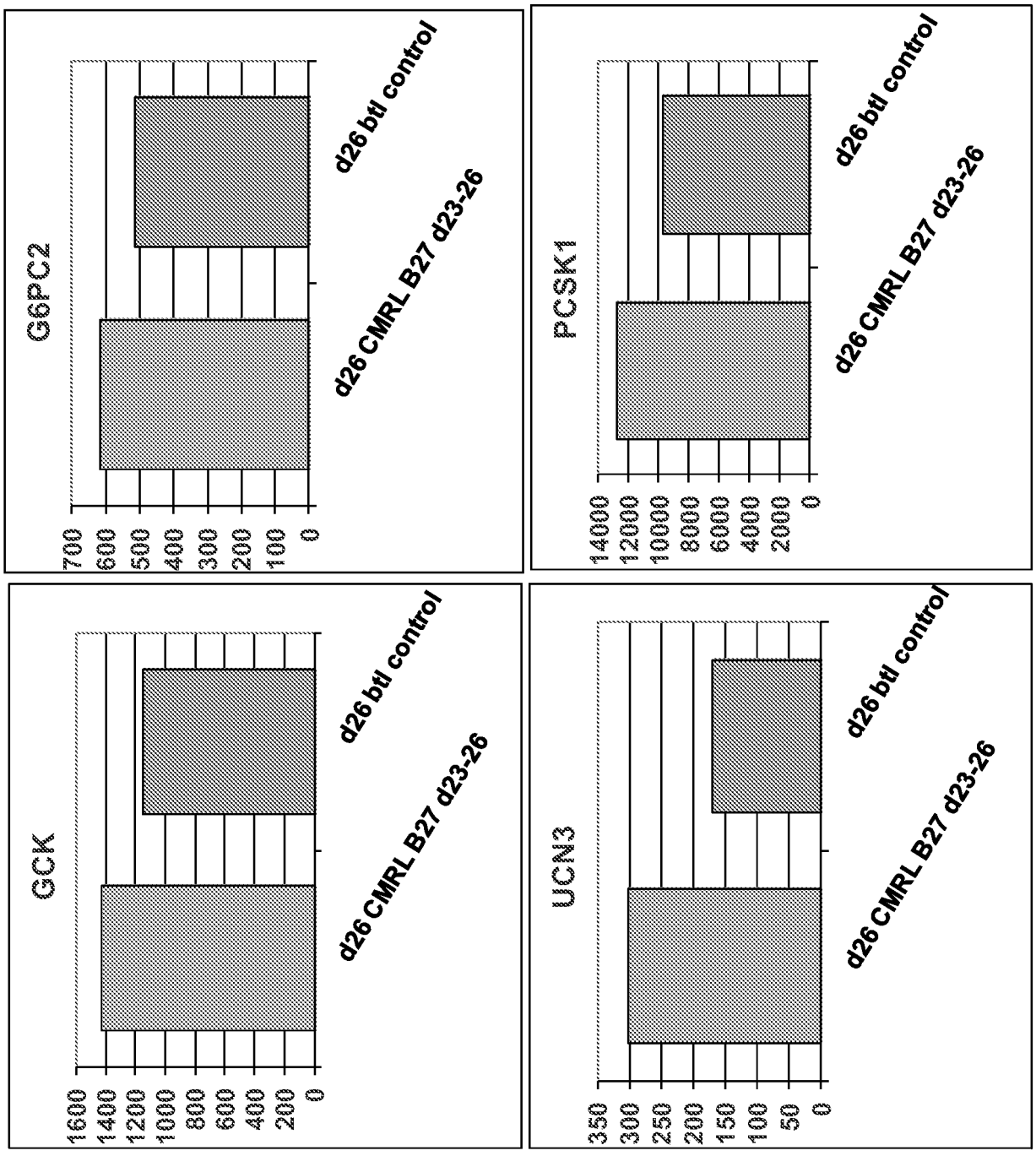

G6PC2
700
600
500
400
300
200
100
0
d26 btl control
d26 CMRL B27 d23-26
PCSK1
14000
12000
10000
8000
6000
4000
2000
0
d26 btl control
d26 CMRL B27 d23-26
GCK
1600
1400
1200
1000
800
600
400
200
0
d26 btl control
d26 CMRL B27 d23-26
UCN3
350
300
250
200
150
100
50
0
d26 btl control
d26 CMRL B27 d23-26

FIG. 35B

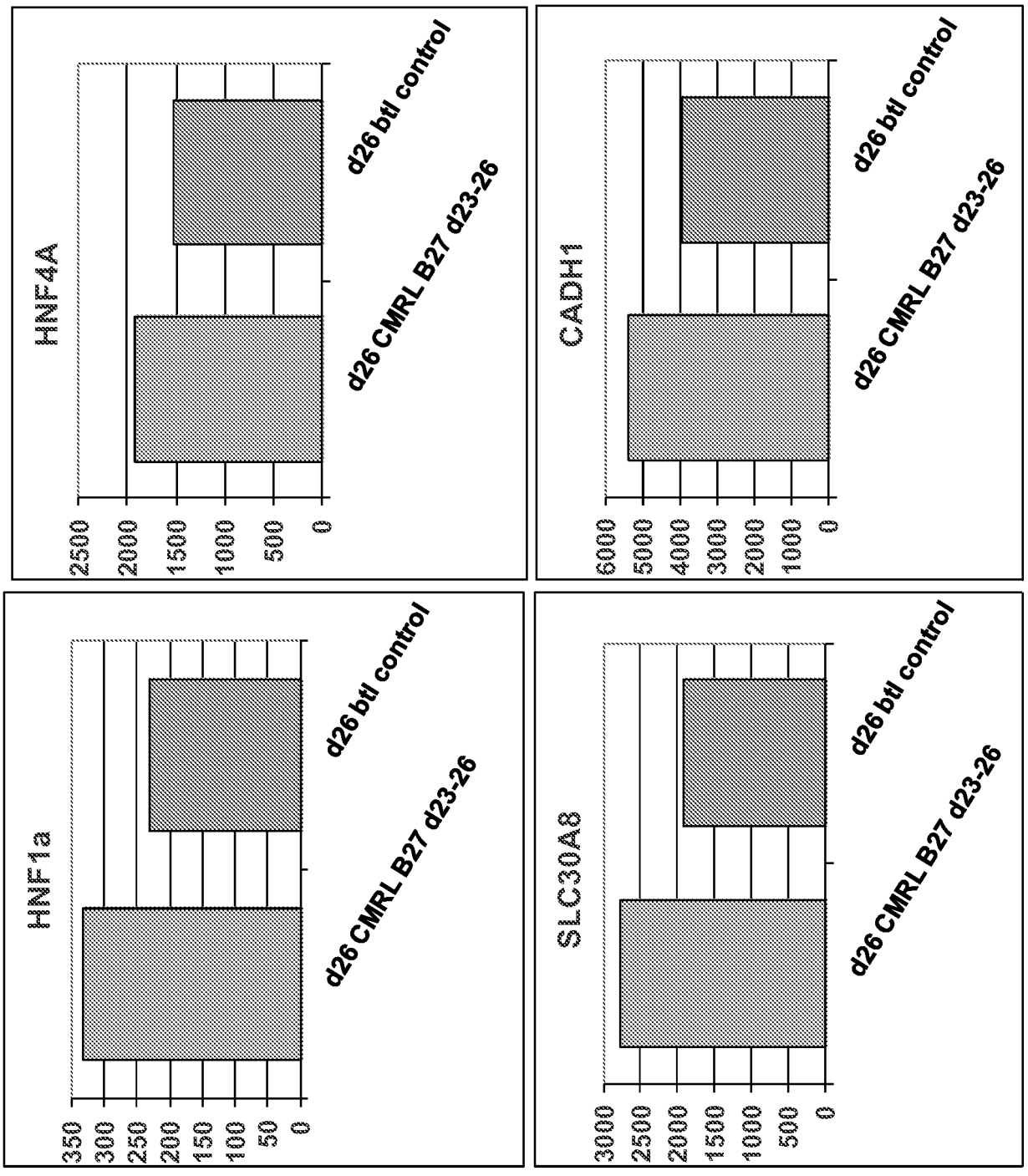

HNF4A
2500
2000
1500
1000
500
0
d26 btl control
d26 CMRL B27 d23-26
CADH1
6000
5000
4000
3000
2000
1000
0
d26 btl control
d26 CMRL B27 d23-26
HNF1a
350
300
250
200
150
100
50
0
d26 btl control
d26 CMRL B27 d23-26
SLC30A8
3000
2500
2000
1500
1000
500
0
d26 btl control
d26 CMRL B27 d23-26

FIG. 35C

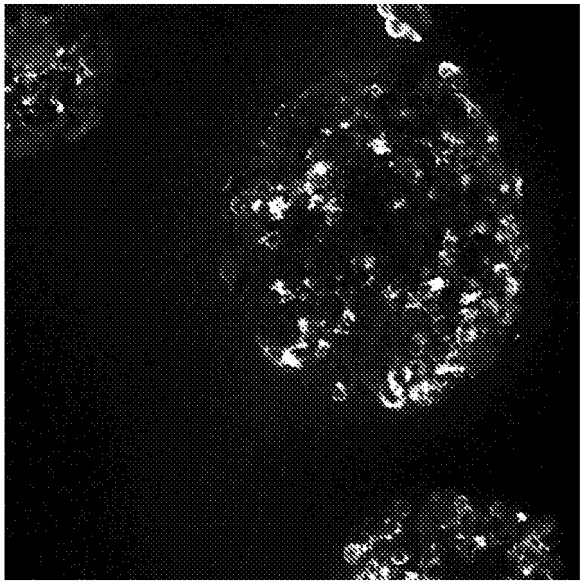


FIG. 36B

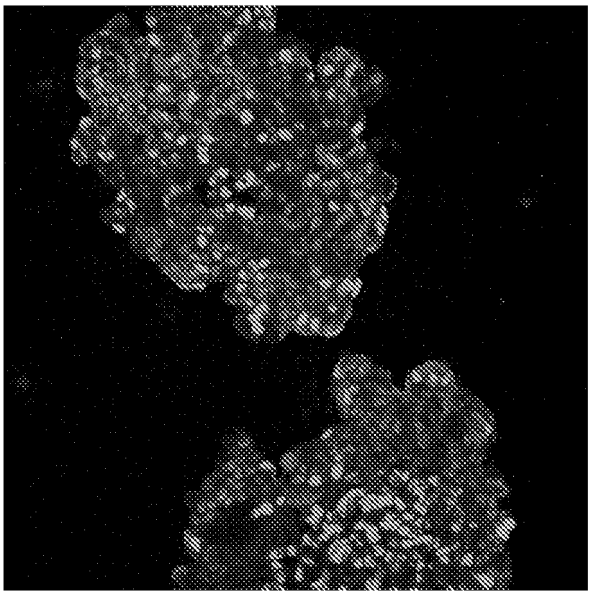


FIG. 36C

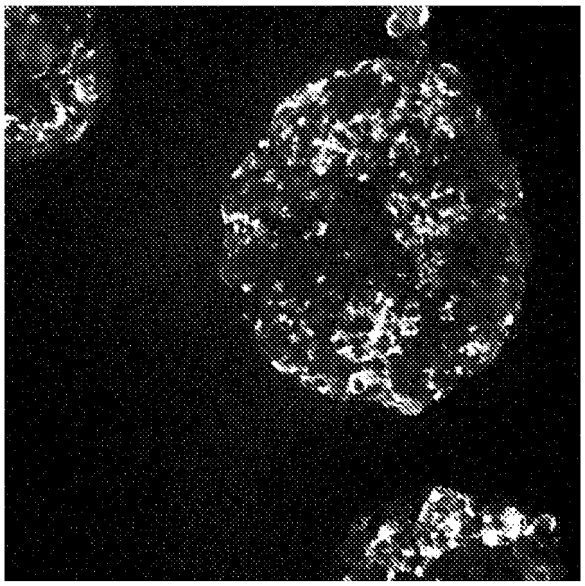


FIG. 36A

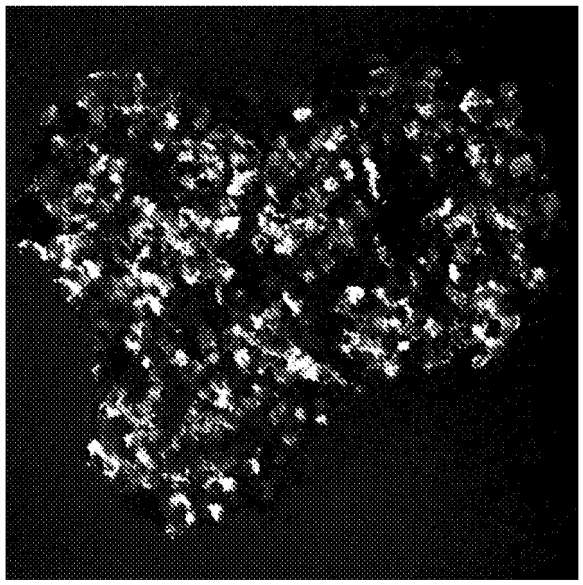


FIG. 37B

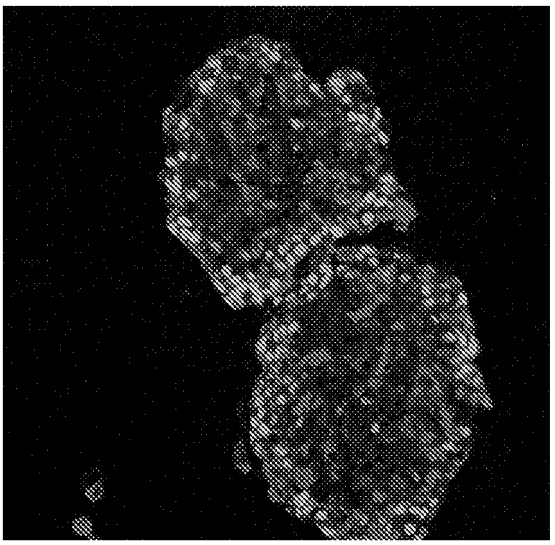


FIG. 37C

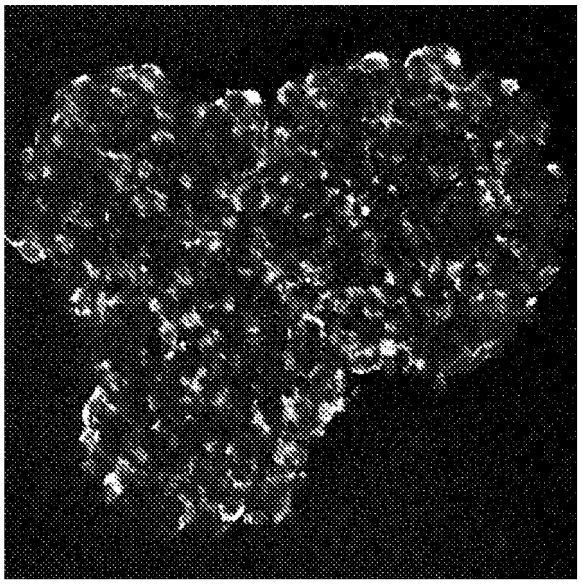


FIG. 37A

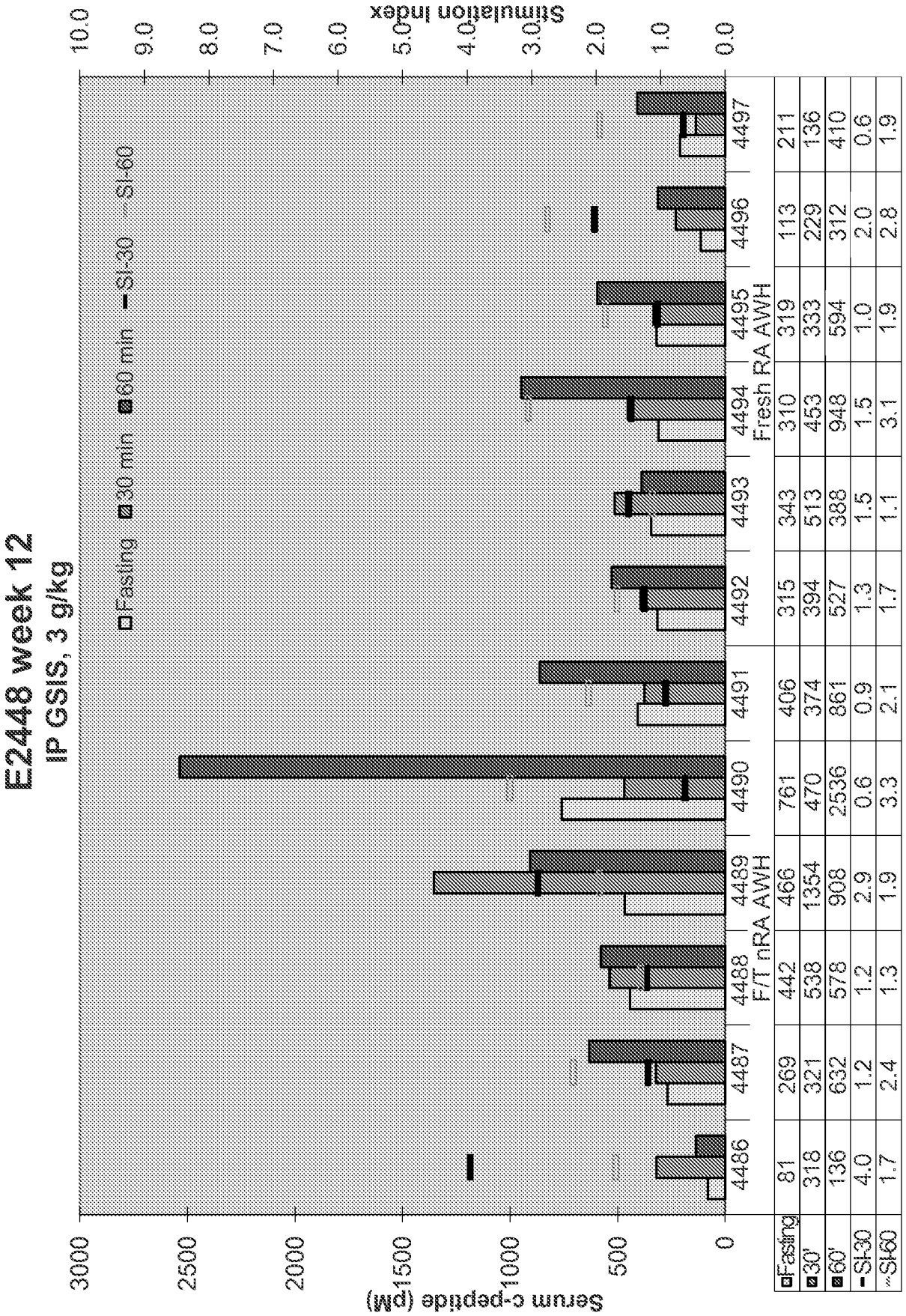

E2448 week 12
IP GSIS, 3 g/kg
Fasting
30 min
60 min
SI-30
SI-60
Serum c-peptide (pM)
Stimulation Index
F/T nRA AWH
Fresh RA AWH
4486 4487 4488 4489 4490 4491 4492 4493 4494 4495 4496 4497
Fasting 81 269 442 466 761 406 315 343 310 319 113 211
30' 318 321 538 1354 470 374 394 513 453 333 229 136
60' 136 632 578 908 2536 861 527 388 948 594 312 410
SI-30 4.0 1.2 1.2 2.9 0.6 0.9 1.3 1.5 1.5 1.0 2.0 0.6
SI-60 1.7 2.4 1.3 1.9 3.3 2.1 1.7 1.1 3.1 1.9 2.8 1.9

FIG. 38

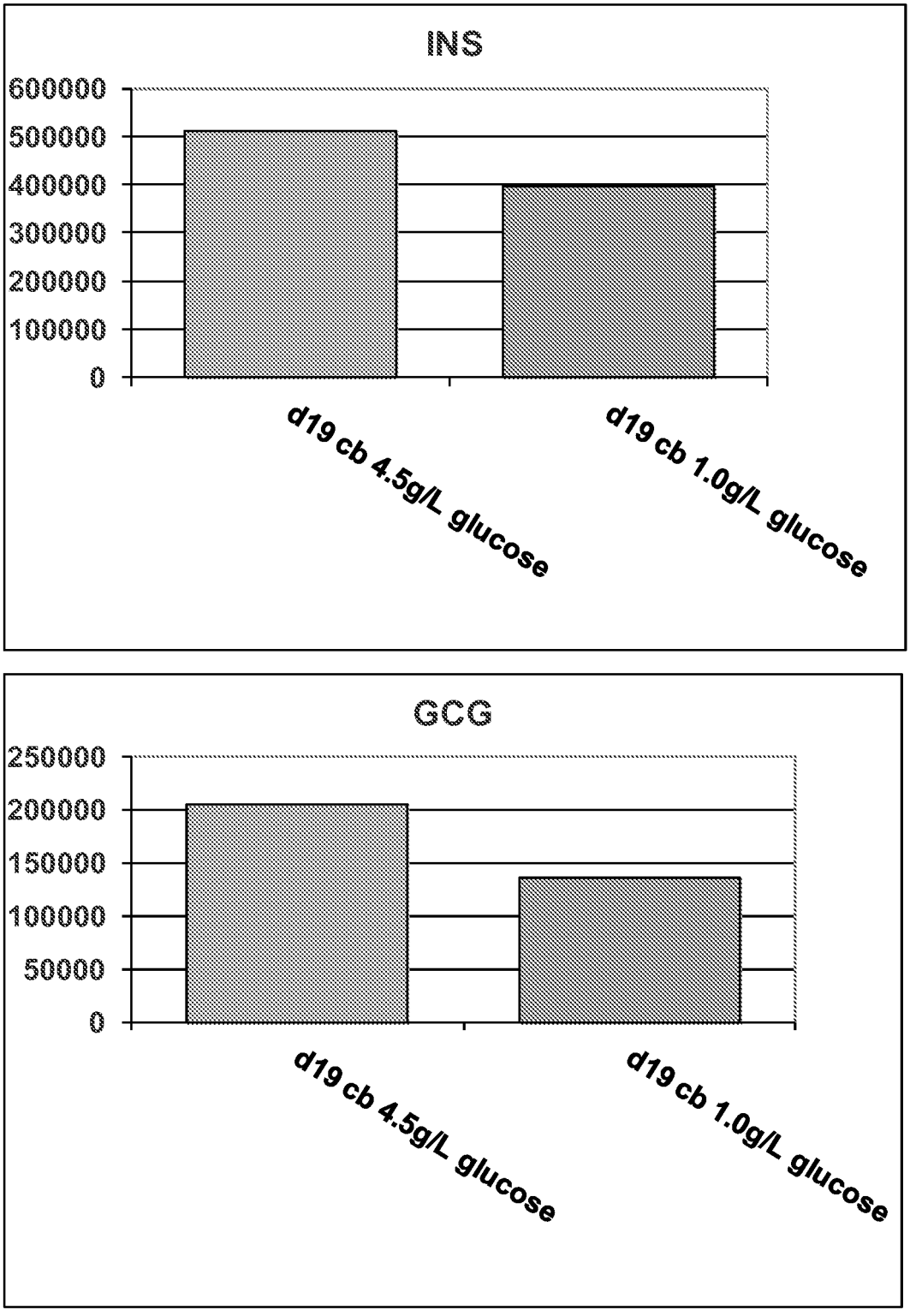
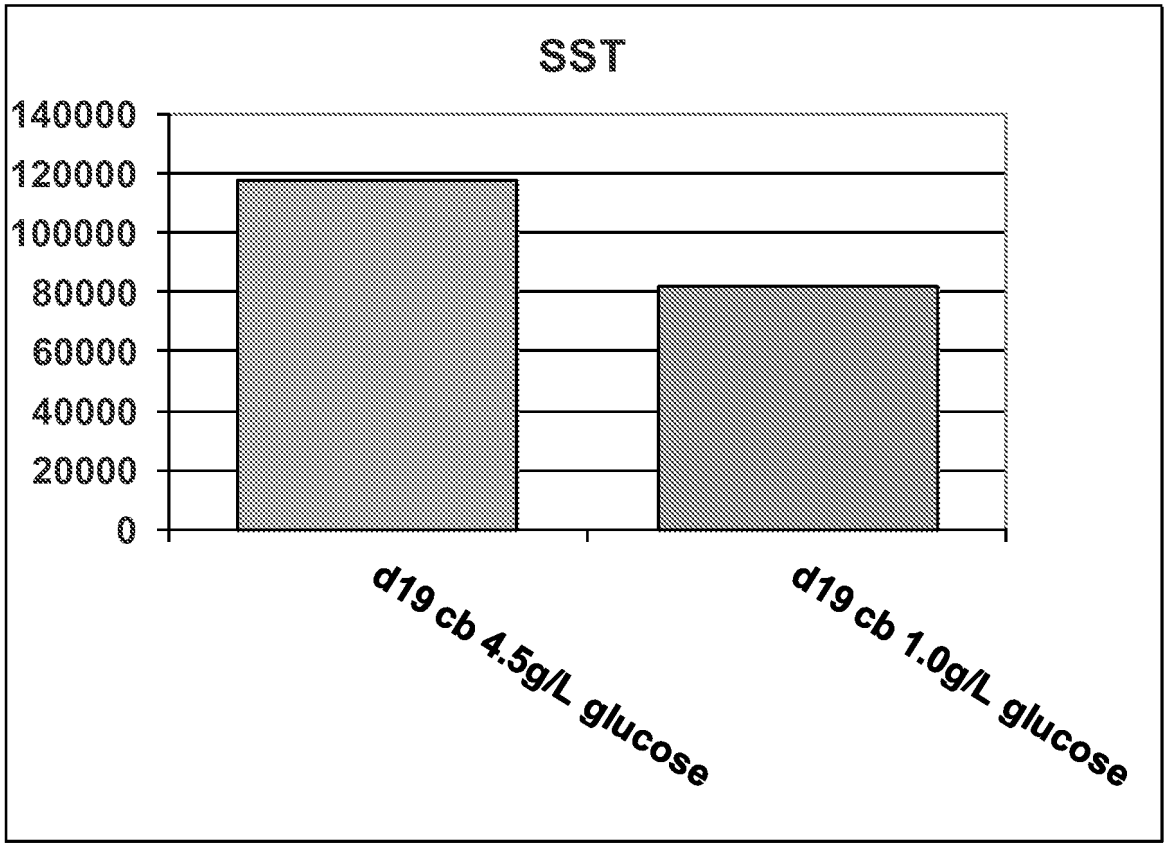

INS
600000
500000
400000
300000
200000
100000
0
d19 cb 4.5g/L glucose
d19 cb 1.0g/L glucose
GCG
250000
200000
150000
100000
50000
0
d19 cb 4.5g/L glucose
d19 cb 1.0g/L glucose

FIG. 39A


SST
140000
120000
100000
80000
60000
40000
20000
0
d19 cb 4.5g/L glucose
d19 cb 1.0g/L glucose

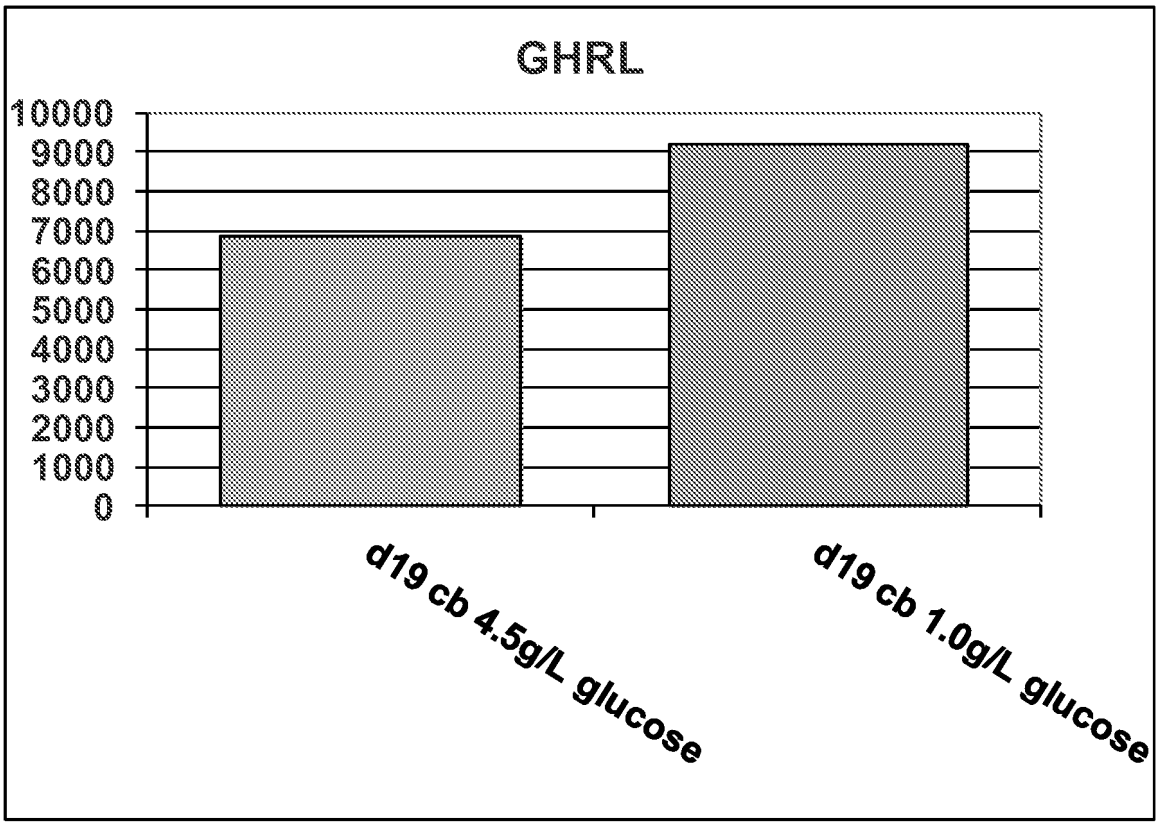

GHRL
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
d19 cb 4.5g/L glucose
d19 cb 1.0g/L glucose

FIG. 39B

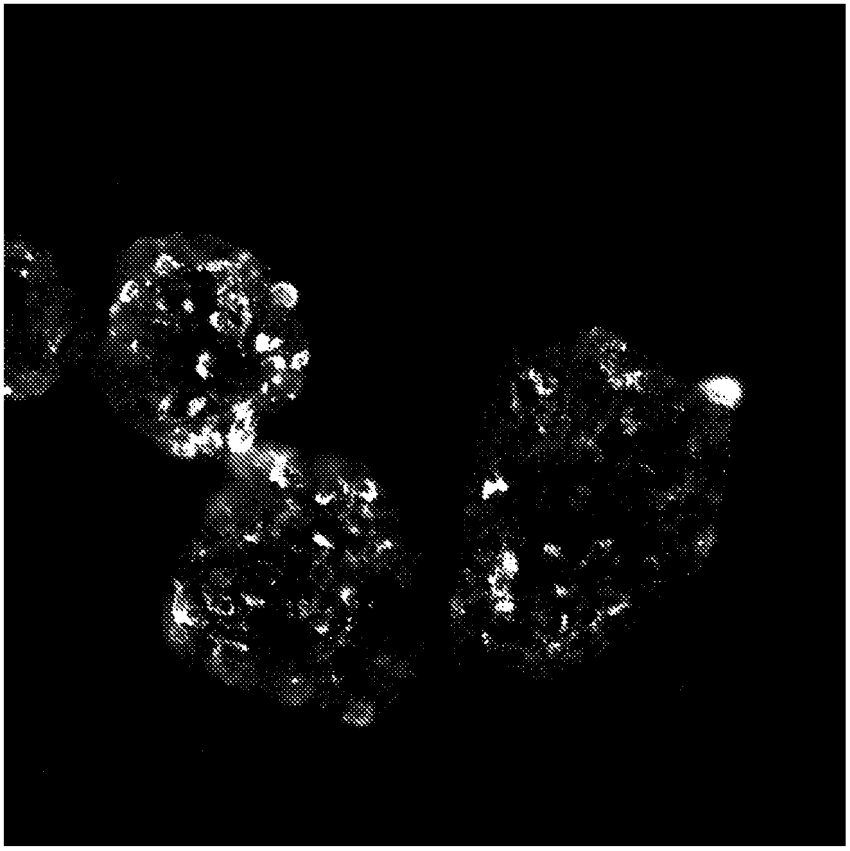


FIG. 40B

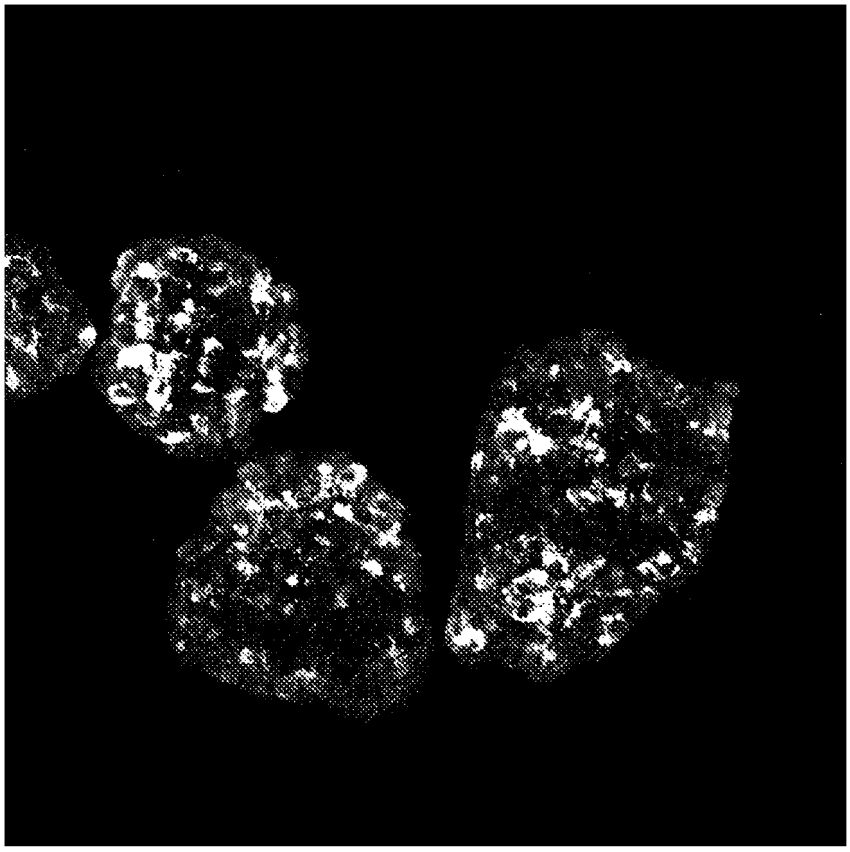


FIG. 40A

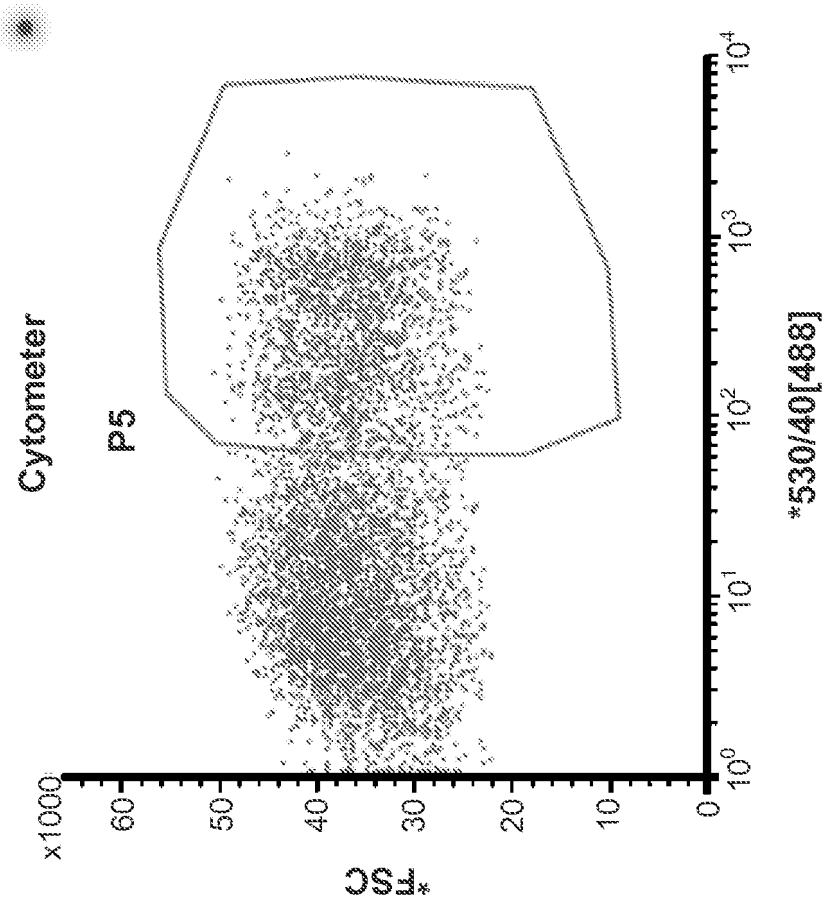

Cytometer
P5
*530/40[488]
*FSC
x1000
60
50
40
30
20
10
0
10^0
10^1
10^2
10^3
10^4

FIG. 41

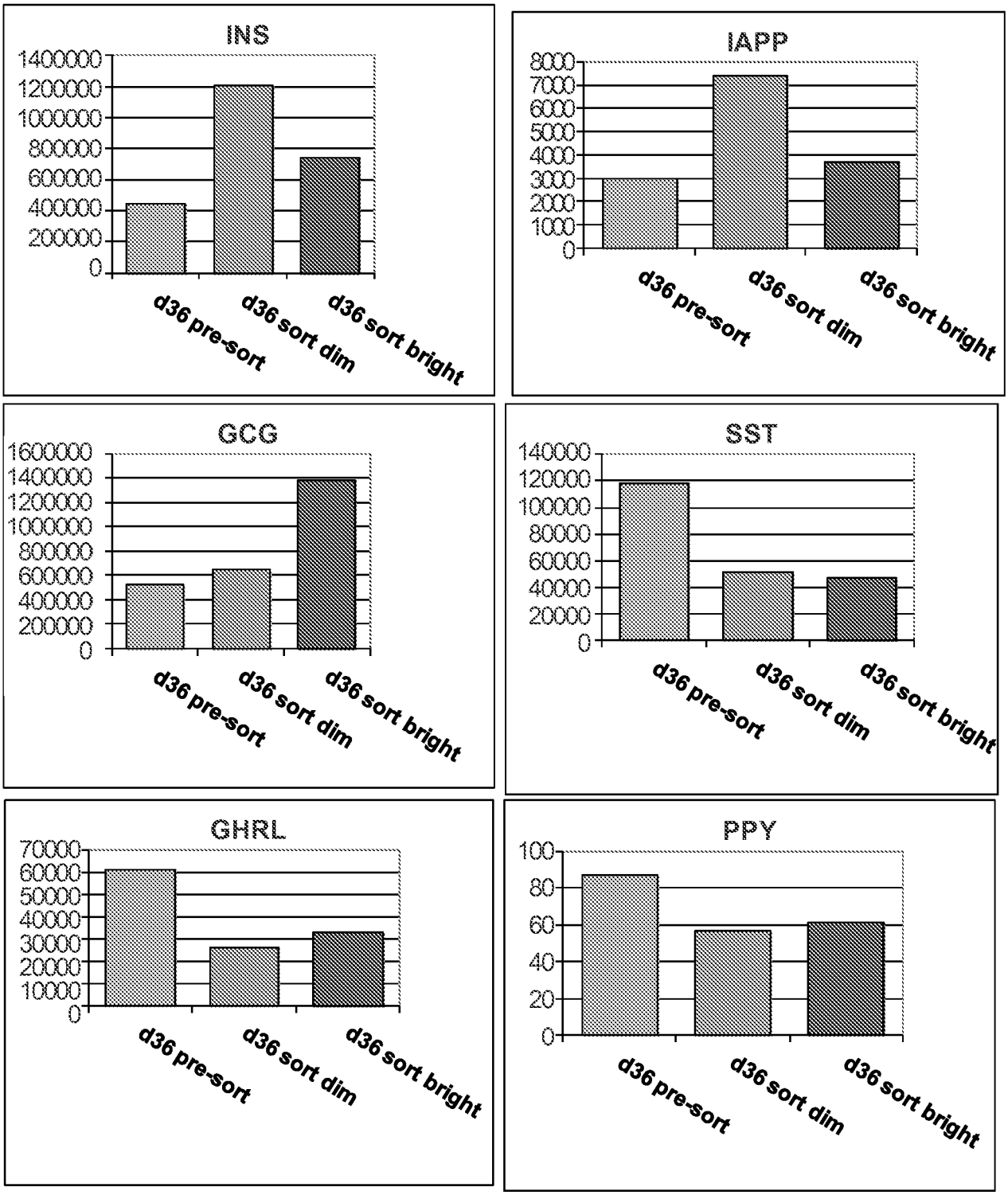

INS
1400000
1200000
1000000
800000
600000
400000
200000
0
d36 pre-sort
d36 sort dim
d36 sort bright
IAPP
8000
7000
6000
5000
4000
3000
2000
1000
0
d36 pre-sort
d36 sort dim
d36 sort bright
GCG
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
d36 pre-sort
d36 sort dim
d36 sort bright
SST
140000
120000
100000
80000
60000
40000
20000
0
d36 pre-sort
d36 sort dim
d36 sort bright
GHRL
70000
60000
50000
40000
30000
20000
10000
0
d36 pre-sort
d36 sort dim
d36 sort bright
PPY
100
80
60
40
20
0
d36 pre-sort
d36 sort dim
d36 sort bright

FIG. 42A

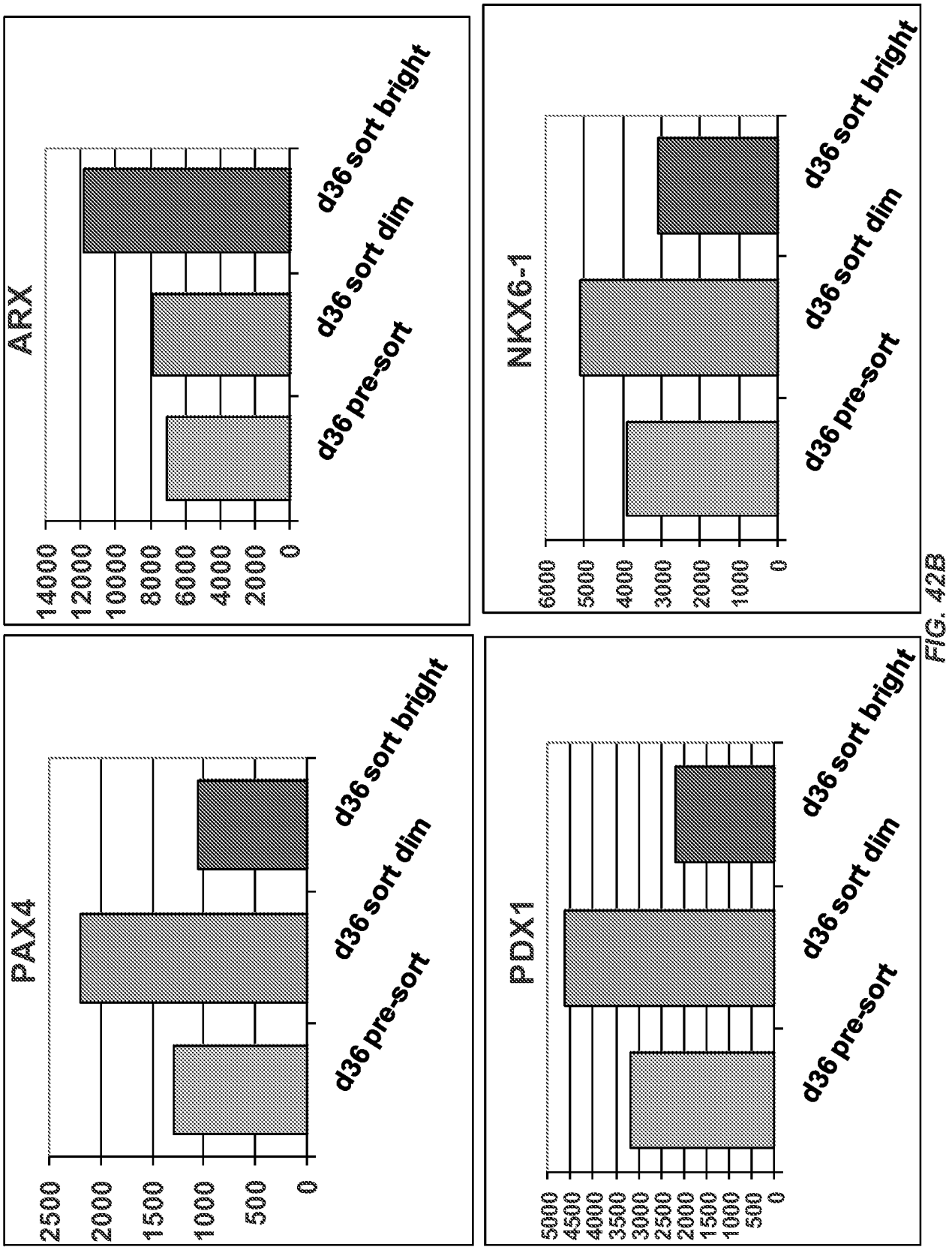

ARX
14000
12000
10000
8000
6000
4000
2000
0
d36 pre-sort
d36 sort dim
d36 sort bright
NKX6-1
6000
5000
4000
3000
2000
1000
0
d36 pre-sort
d36 sort dim
d36 sort bright
PAX4
2500
2000
1500
1000
500
0
d36 pre-sort
d36 sort dim
d36 sort bright
PDX1
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
d36 pre-sort
d36 sort dim
d36 sort bright

FIG. 42B

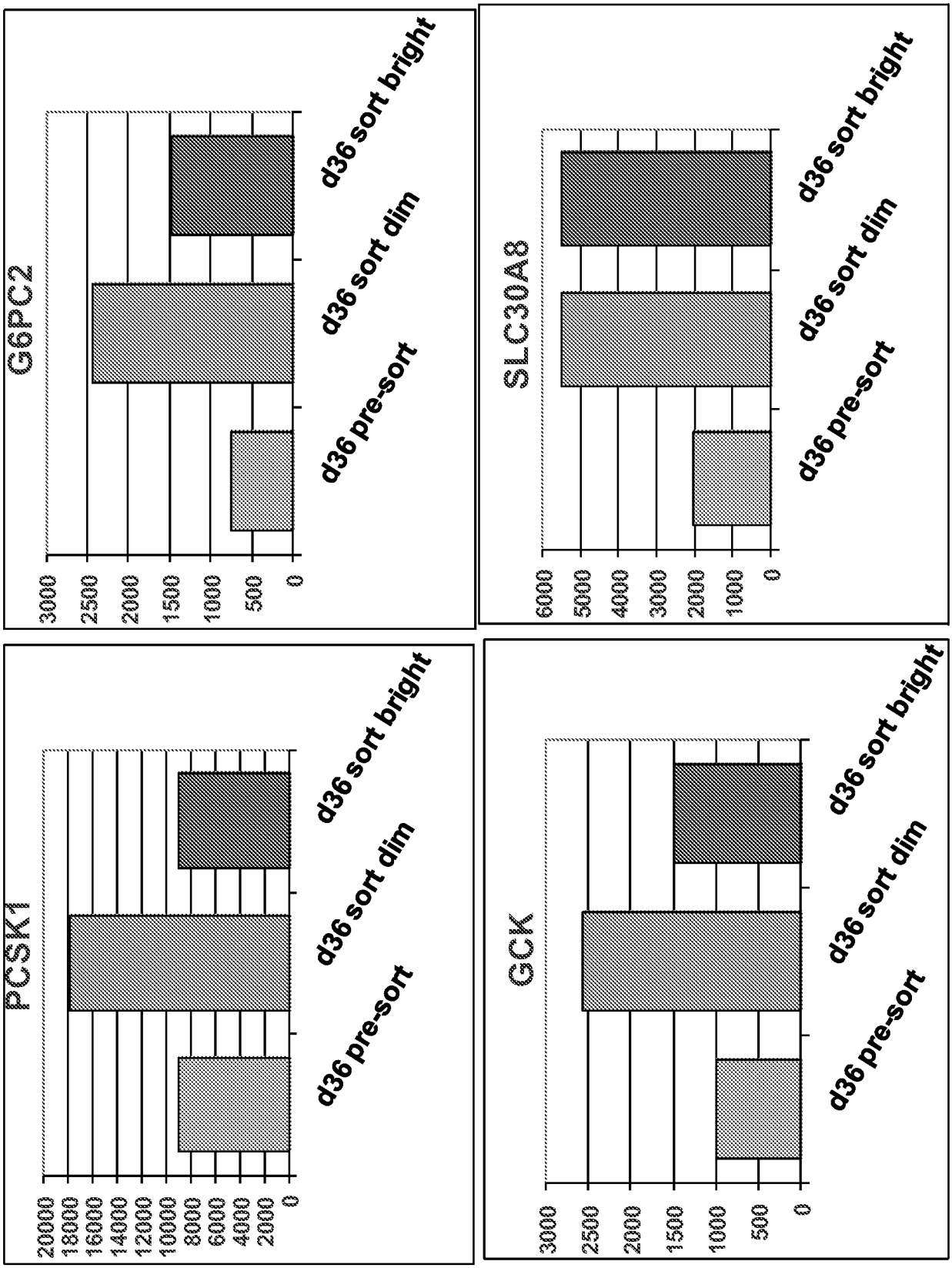

G6PC2
3000
2500
2000
1500
1000
500
0
d36 pre-sort
d36 sort dim
d36 sort bright
SLC30A8
6000
5000
4000
3000
2000
1000
0
d36 pre-sort
d36 sort dim
d36 sort bright
PCSK1
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
d36 pre-sort
d36 sort dim
d36 sort bright
GCK
3000
2500
2000
1500
1000
500
0
d36 pre-sort
d36 sort dim
d36 sort bright

FIG. 42C

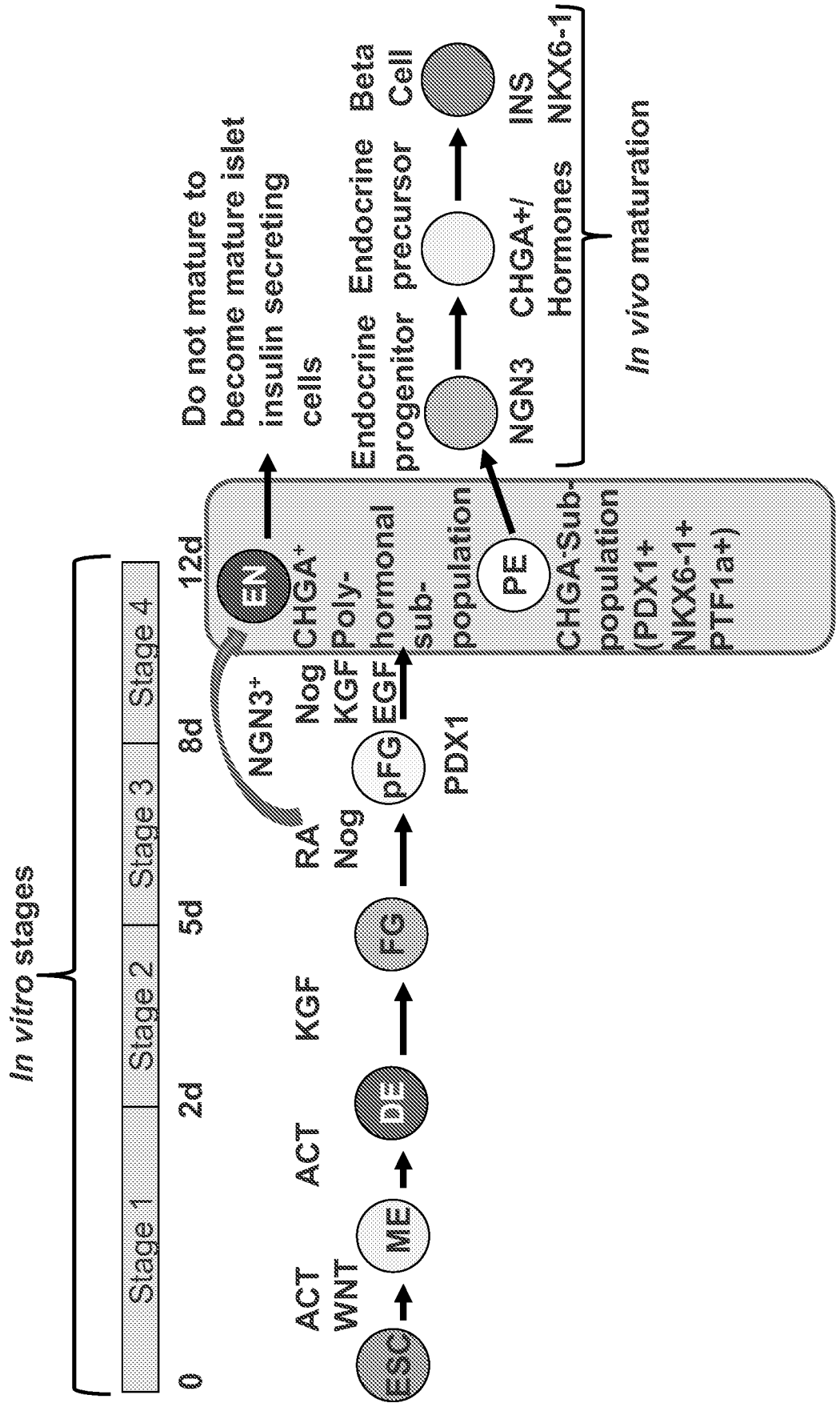

In vitro stages
Stage 1
Stage 2
Stage 3
Stage 4
0
2d
5d
8d
12d
ESC
ME
DE
FG
pFG
EN
PE
ACT
WNT
ACT
KGF
RA
Nog
Nog
KGF
EGF
NGN3+
PDX1
CHGA+
Poly-hormonal sub-population
CHGA-Sub-population (PDX1+ NKX6-1+ PTF1a+)
Do not mature to become mature islet insulin secreting cells
Endocrine progenitor
Endocrine precursor
Beta Cell
NGN3
CHGA+/ Hormones
INS
NKX6-1
In vivo maturation

FIG. 43

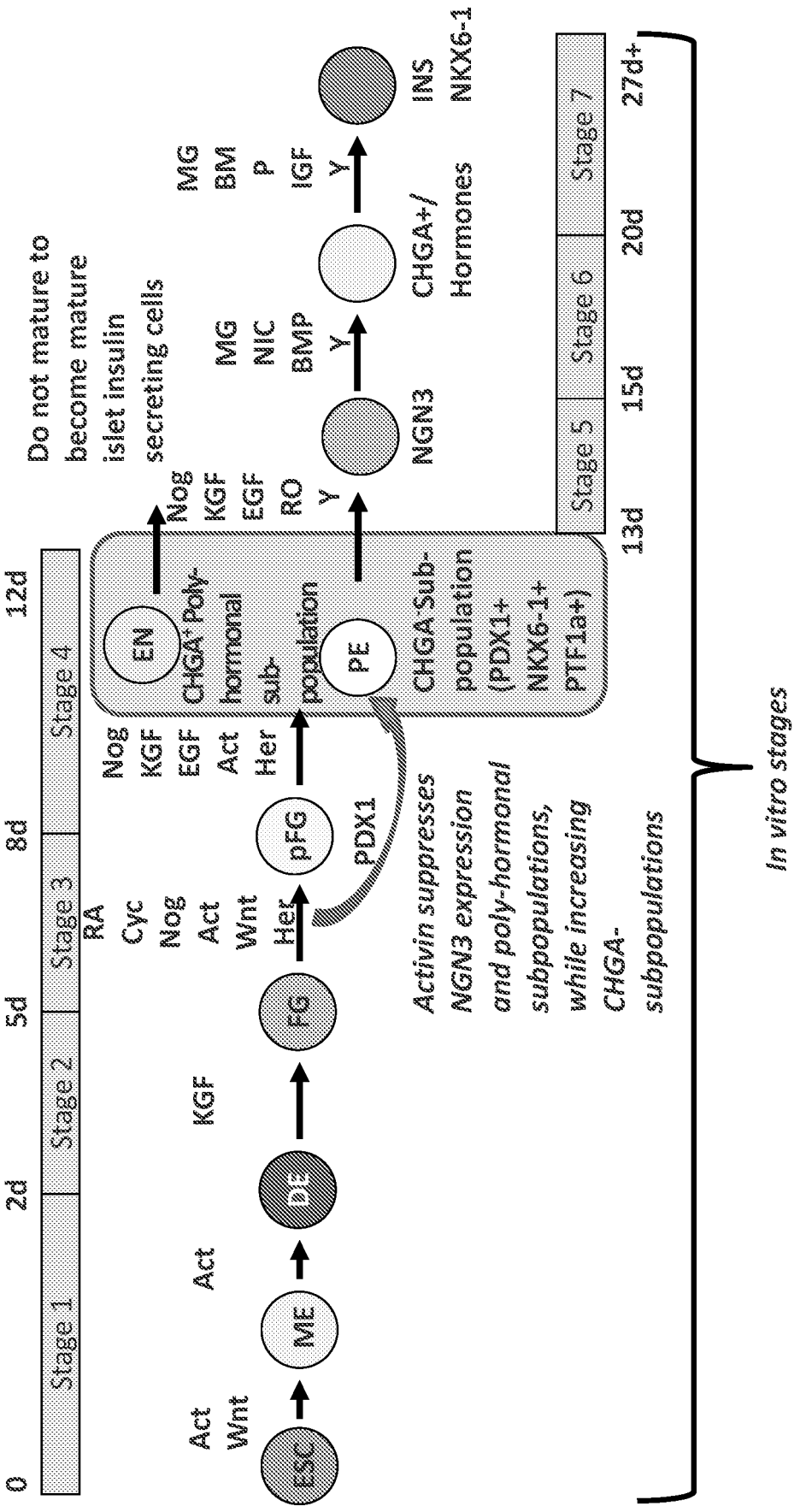

0
2d
5d
8d
12d
13d
15d
20d
27d+
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
ESC
ME
DE
FG
pFG
PE
EN
Act
Wnt
Act
KGF
RA
Cyc
Nog
Act
Wnt
Her
PDX1
Nog
KGF
EGF
Act
Her
Nog
KGF
EGF
RO
Y
NGN3
MG
NIC
BMP
Y
CHGA+/
Hormones
MG
BM
P
IGF
Y
INS
NKX6-1
CHGA+ Poly-hormonal sub-population
CHGA- Sub-population (PDX1+ NKX6-1+ PTF1a+)
Do not mature to become mature islet insulin secreting cells
Activin suppresses NGN3 expression and poly-hormonal subpopulations, while increasing CHGA- subpopulations
In vitro stages

FIG. 44

Stage 0
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
Undifferentiated pPSC Aggregates
Definitive Endoderm
Primitive Gut Tube
Posterior Foregut
Pancreatic Progenitor and Endocrine Precursor
Endocrine Precursor
Endocrine Cells
Hrg + Activin^lo
Activin^hi + Wnt
Activin^hi
KGF + TBI
TT + CYC + Nog + Act^hi Hrg Wnt
NKE + Act^lo Hrg
NKE + RO
BMP + Nic + Y
BMP + TTNPB + Nic + Y
DMEM/F12-XFKSR
RPMI + 0.2%FBS + ITS
DMEM + 1% B27
CMRL (or DMEM) + 1% B27
1 day
1 day
1 day
3 days
3 days
4+ days
2 days
3+ days
3+ days
pPSC
pPSC
ME
DE
PG
PF
PE
EP
pre-β
β-cell
OCT4
OCT4
BRA
SOX17
FOXA1
PDX1
NKX6.1
NGN3
INS
INS
NANOG
NANOG
FGF4
GSC
HNF1B
HNF6
PDX1
NKX2.2
NKX6.1
NKX6.1
SOX2
SOX2
WNT3
FOXA2
HNF4A
PROX1
PTF1A
CHGA
PDX1
PDX1
CDH1
CDH1
CDH2
CXCR4
SOX9
MAFB
MAFA

FIG. 45