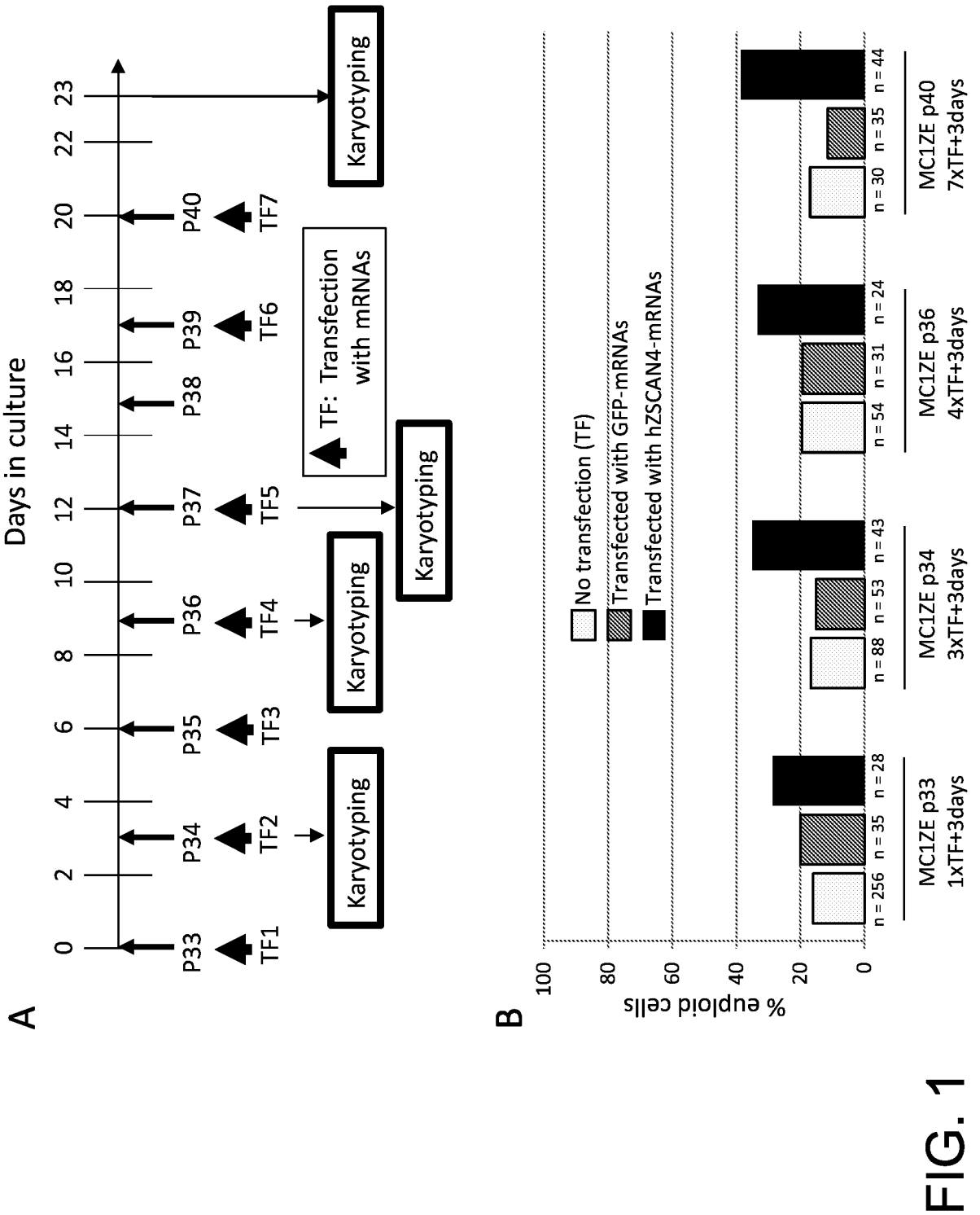

A
Days in culture
0 2 4 6 8 10 12 14 16 18 20 22 23
P33 P34 P35 P36 P37 P38 P39 P40
TF1 TF2 TF3 TF4 TF5 TF6 TF7
Karyotyping
Karyotyping
Karyotyping
Karyotyping
TF: Transfection with mRNAs
B
% euploid cells
100 80 60 40 20 0
No transfection (TF)
Transfected with GFP-mRNAs
Transfected with hZSCAN4-mRNAs
n = 256 n = 35 n = 28
n = 88 n = 53 n = 43
n = 54 n = 31 n = 24
n = 30 n = 35 n = 44
MC1ZE p33 1xTF+3days
MC1ZE p34 3xTF+3days
MC1ZE p36 4xTF+3days
MC1ZE p40 7xTF+3days

FIG. 1

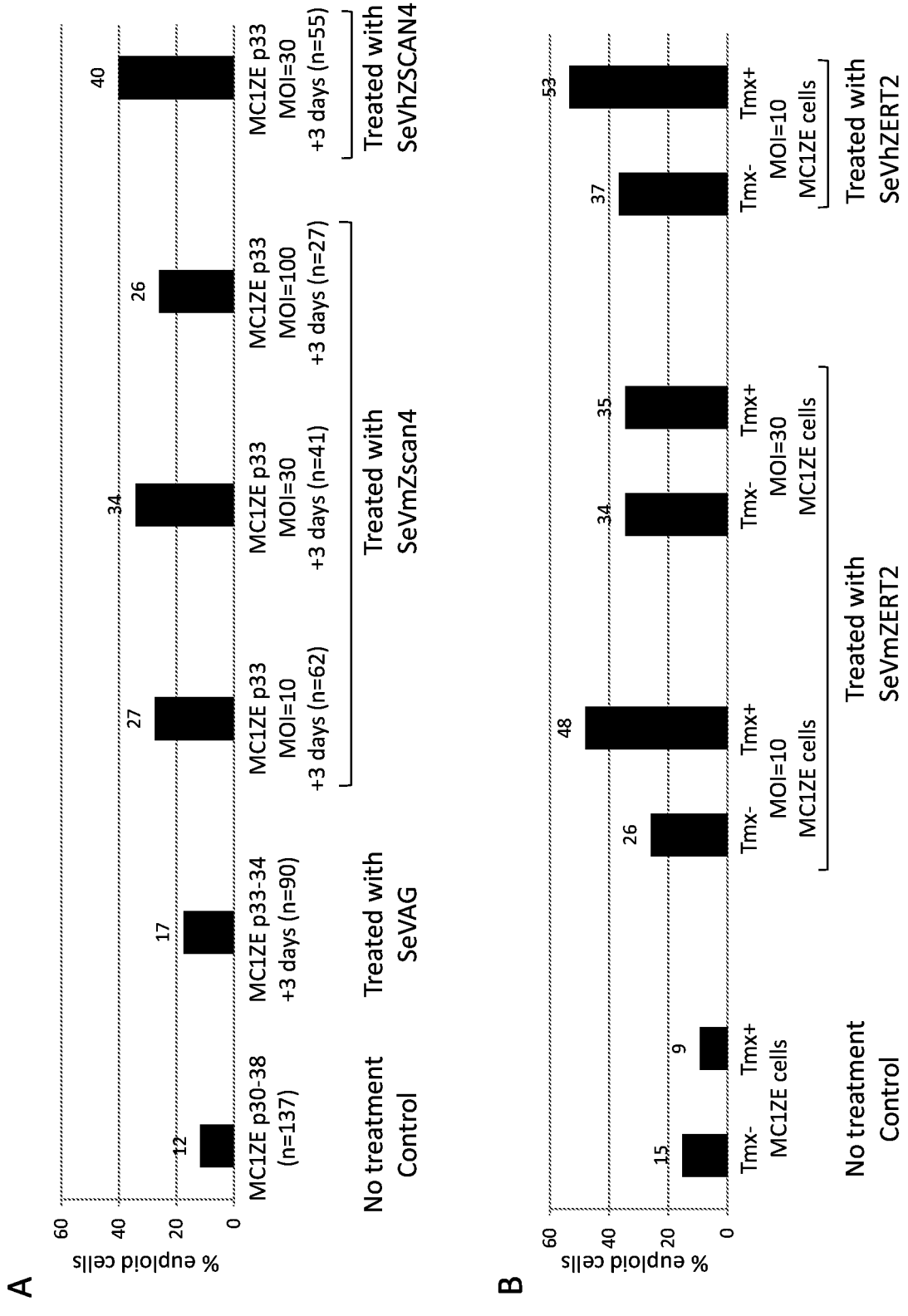

A
% euploid cells
0
20
40
60
12
17
27
34
26
40
MC1ZE p30-38 (n=137)
MC1ZE p33-34 +3 days (n=90)
MC1ZE p33 MOI=10 +3 days (n=62)
MC1ZE p33 MOI=30 +3 days (n=41)
MC1ZE p33 MOI=100 +3 days (n=27)
MC1ZE p33 MOI=30 +3 days (n=55)
No treatment Control
Treated with SeVAG
Treated with SeVmZscan4
Treated with SeVhZSCAN4
B
% euploid cells
0
20
40
60
15
9
48
26
34
35
37
53
Tmx- Tmx+ MC1ZE cells
Tmx- Tmx+ MOI=10 MC1ZE cells
Tmx- Tmx+ MOI=30 MC1ZE cells
Tmx- Tmx+ MOI=10 MC1ZE cells
No treatment Control
Treated with SeVmZERT2
Treated with SeVhZERT2

FIG. 2

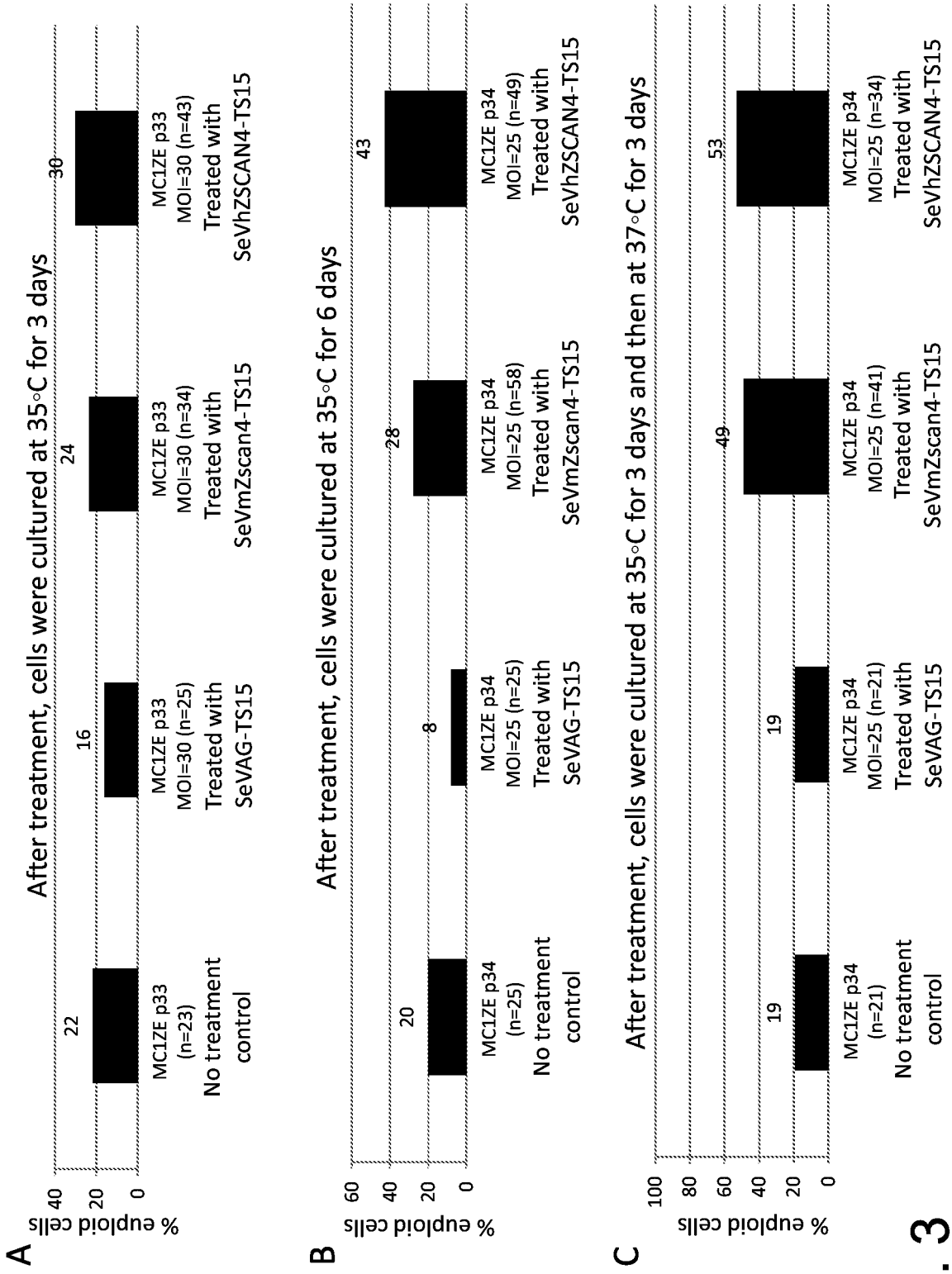

A
After treatment, cells were cultured at 35°C for 3 days
% euploid cells
0
20
40
22
16
24
30
MC1ZE p33 (n=23) No treatment control
MC1ZE p33 MOI=30 (n=25) Treated with SeVAG-TS15
MC1ZE p33 MOI=30 (n=34) Treated with SeVmZscan4-TS15
MC1ZE p33 MOI=30 (n=43) Treated with SeVhZSCAN4-TS15
B
After treatment, cells were cultured at 35°C for 6 days
% euploid cells
0
20
40
60
20
8
28
43
MC1ZE p34 (n=25) No treatment control
MC1ZE p34 MOI=25 (n=25) Treated with SeVAG-TS15
MC1ZE p34 MOI=25 (n=58) Treated with SeVmZscan4-TS15
MC1ZE p34 MOI=25 (n=49) Treated with SeVhZSCAN4-TS15
C
After treatment, cells were cultured at 35°C for 3 days and then at 37°C for 3 days
% euploid cells
0
20
40
60
80
100
19
19
49
53
MC1ZE p34 (n=21) No treatment control
MC1ZE p34 MOI=25 (n=21) Treated with SeVAG-TS15
MC1ZE p34 MOI=25 (n=41) Treated with SeVmZscan4-TS15
MC1ZE p34 MOI=25 (n=34) Treated with SeVhZSCAN4-TS15

FIG. 3

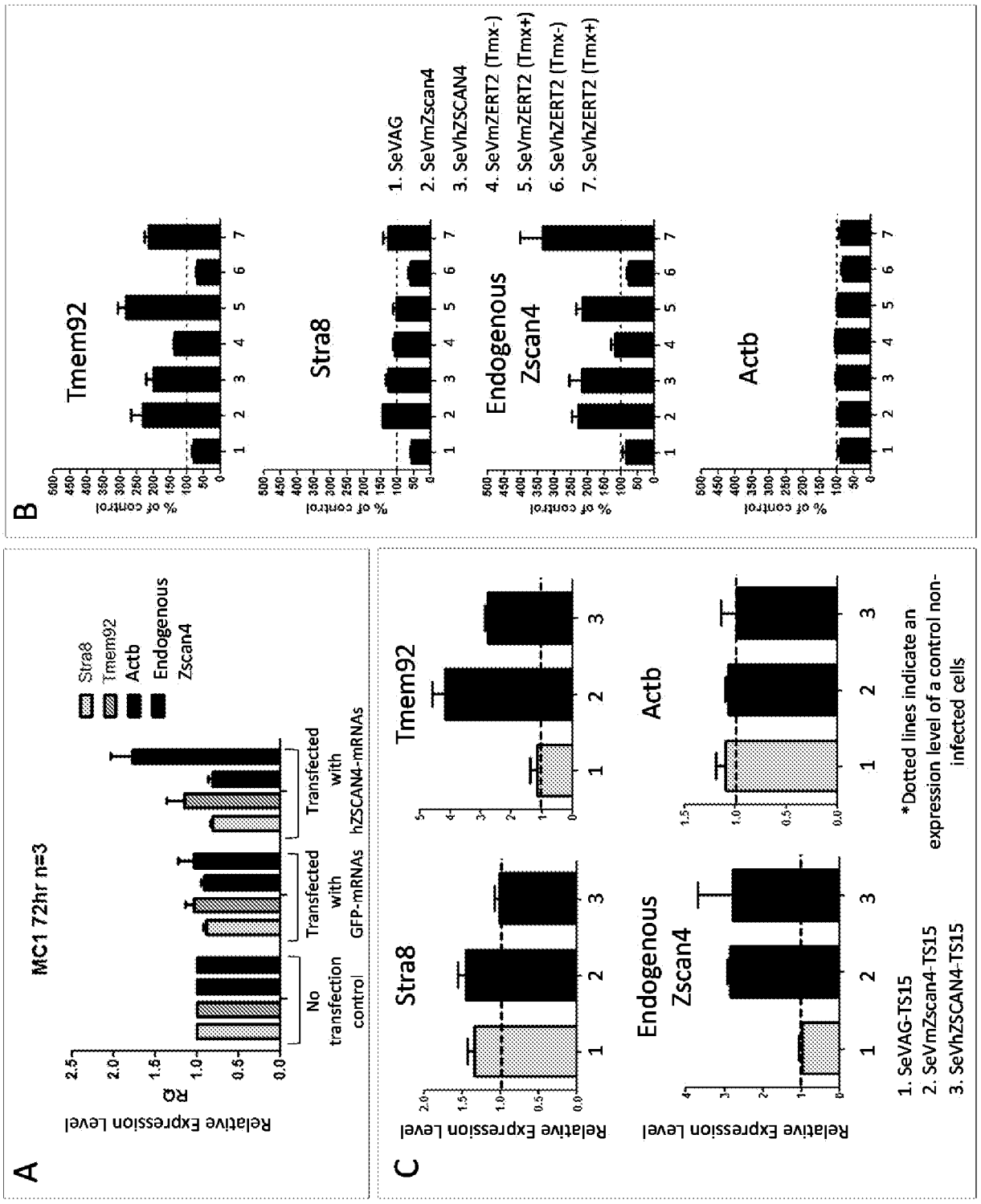

A
MC1 72hr n=3
Stra8
Tmem92
Actb
Endogenous Zscan4
RQ
Relative Expression Level
No transfection control
Transfected with GFP-mRNAs
Transfected with hZSCAN4-mRNAs
B
Tmem92
Stra8
Endogenous Zscan4
Actb
% of control
1. SeVAG
2. SeVmZscan4
3. SeVhZSCAN4
4. SeVmZERT2 (Tmx-)
5. SeVmZERT2 (Tmx+)
6. SeVhZERT2 (Tmx-)
7. SeVhZERT2 (Tmx+)
C
Stra8
Tmem92
Endogenous Zscan4
Actb
Relative Expression Level
1. SeVAG-TS15
2. SeVmZscan4-TS15
3. SeVhZSCAN4-TS15
*Dotted lines indicate an expression level of a control non-infected cells

FIG. 4

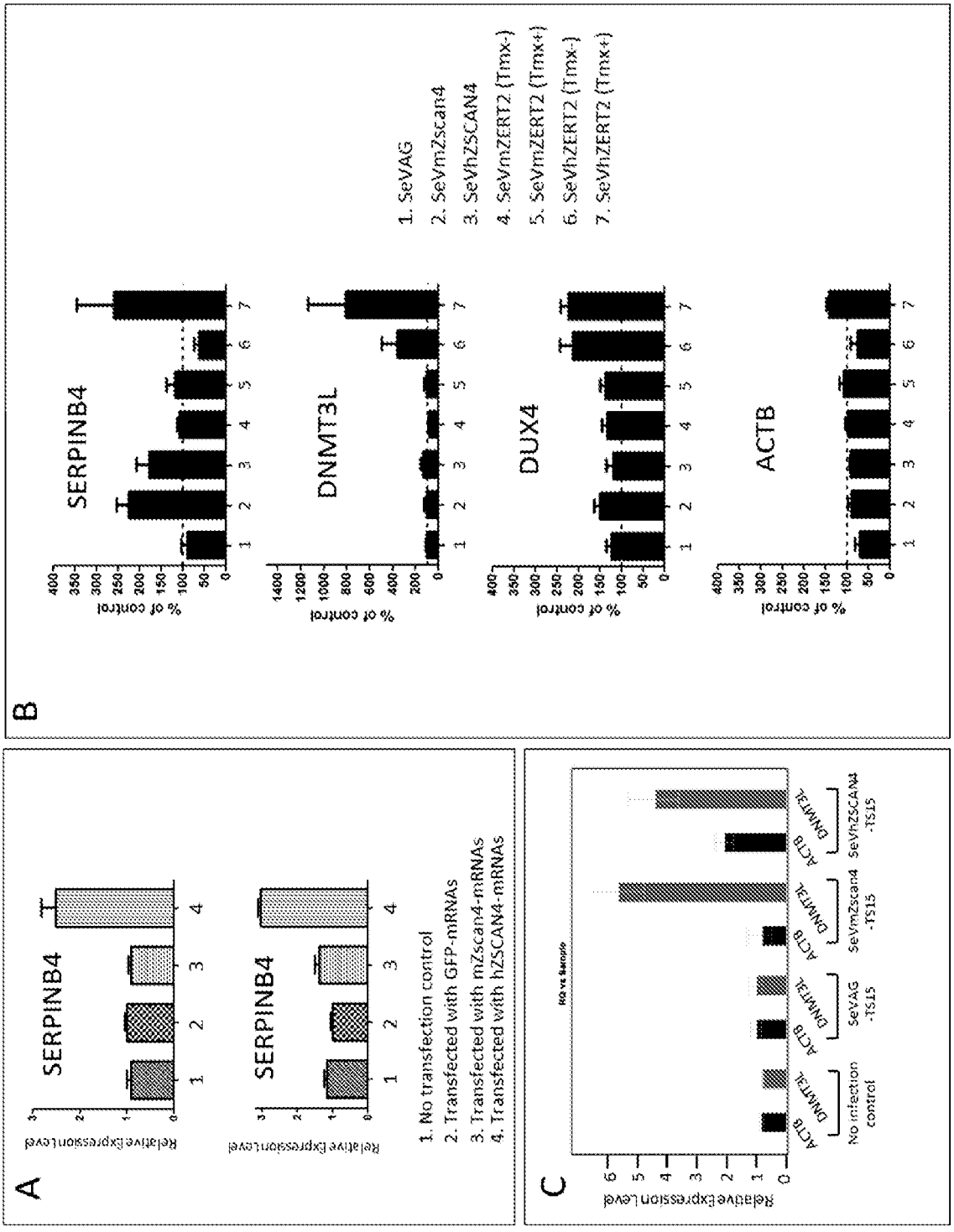

A
SERPINB4
Relative Expression Level
1 2 3 4
SERPINB4
Relative Expression Level
1 2 3 4
1. No transfection control
2. Transfected with GFP-mRNAs
3. Transfected with mZscan4-mRNAs
4. Transfected with hZSCAN4-mRNAs
B
SERPINB4
DNMT3L
DUX4
ACTB
% of control
1 2 3 4 5 6 7
1. SeVAG
2. SeVmZscan4
3. SeVhZSCAN4
4. SeVmZERT2 (Tmx-)
5. SeVmZERT2 (Tmx+)
6. SeVhZERT2 (Tmx-)
7. SeVhZERT2 (Tmx+)
C
Relative Expression Level
ACTB
DNMT3L
No infection control
SeVAG -TS15
SeVmZscan4 -TS15
SeVhZSCAN4 -TS15

FIG. 5

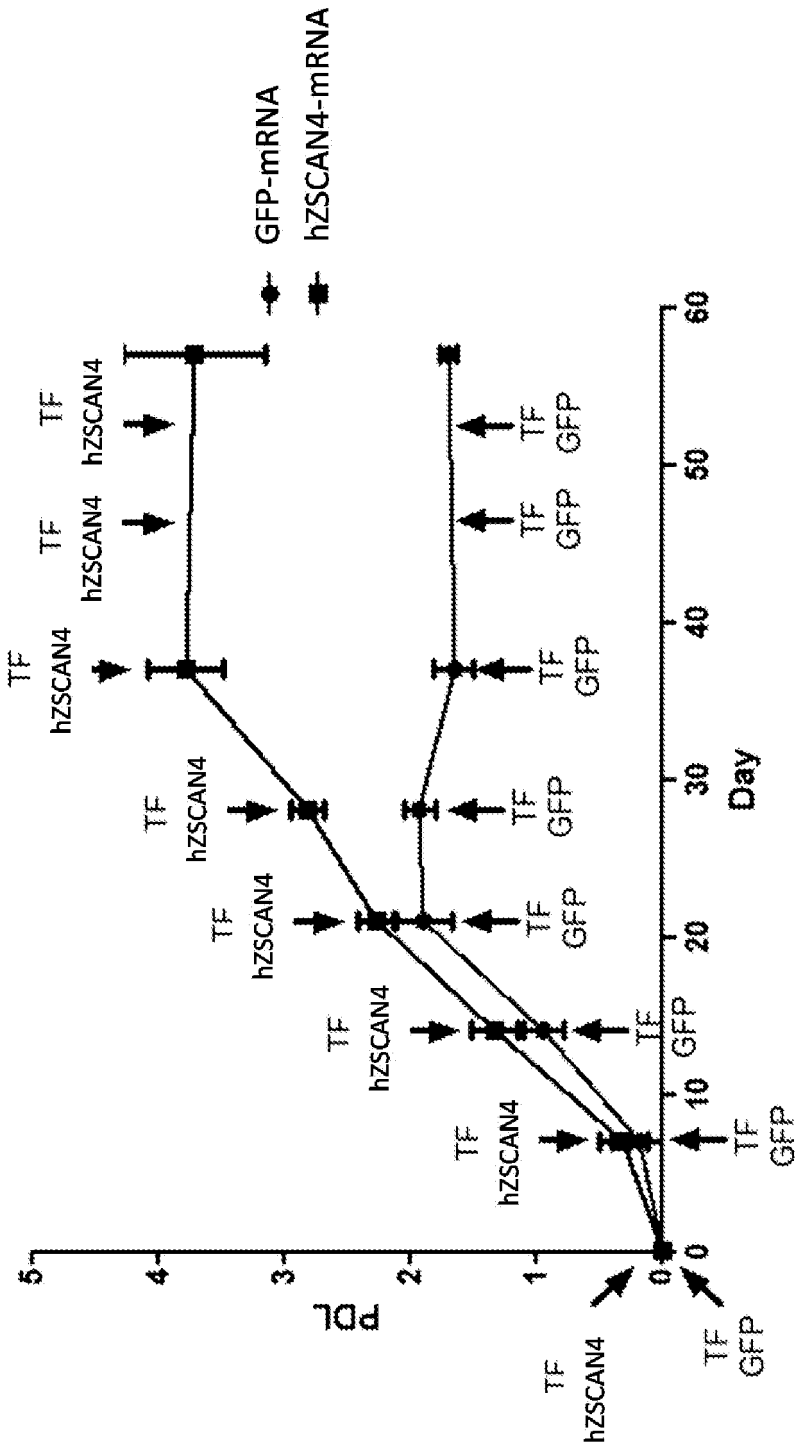

GFP-mRNA
hZSCAN4-mRNA
PDL
Day
0
1
2
3
4
5
0
10
20
30
40
50
60
TF
hZSCAN4
TF
GFP

FIG. 6

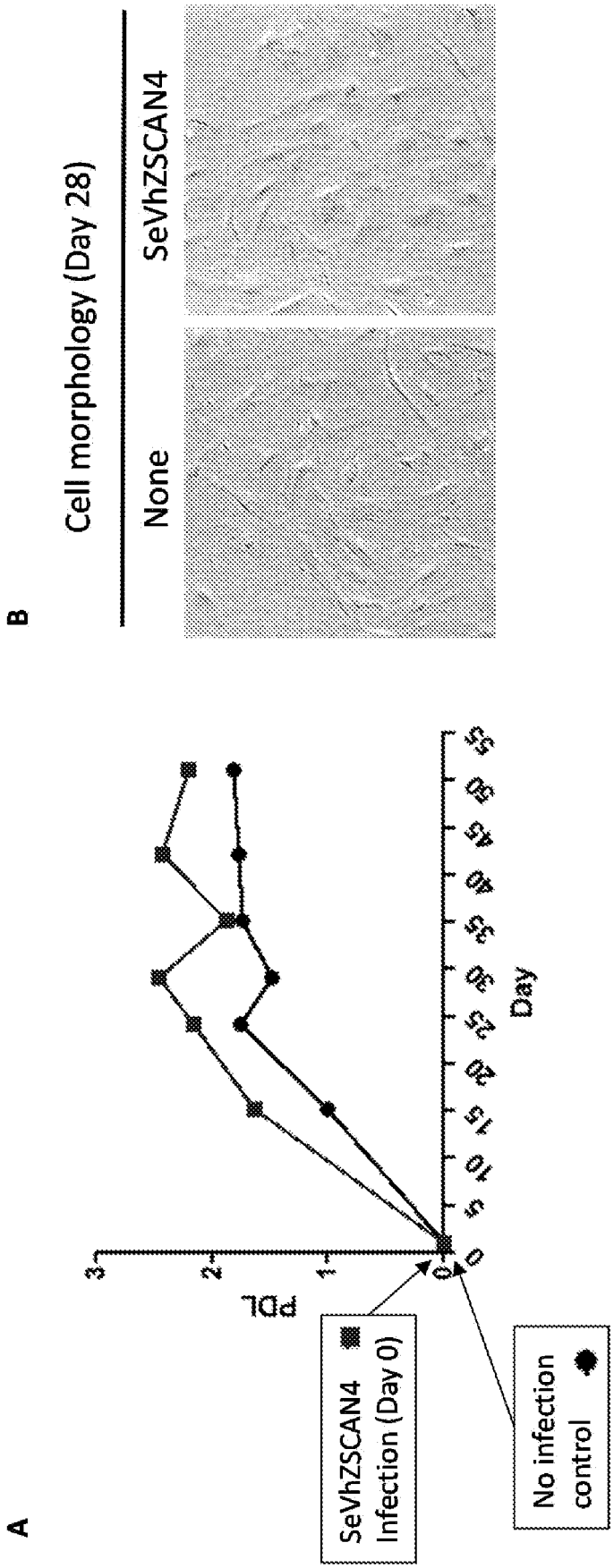

A
PDL
Day
SeVhZSCAN4 Infection (Day 0)
No infection control
B
Cell morphology (Day 28)
None
SeVhZSCAN4

FIG. 7

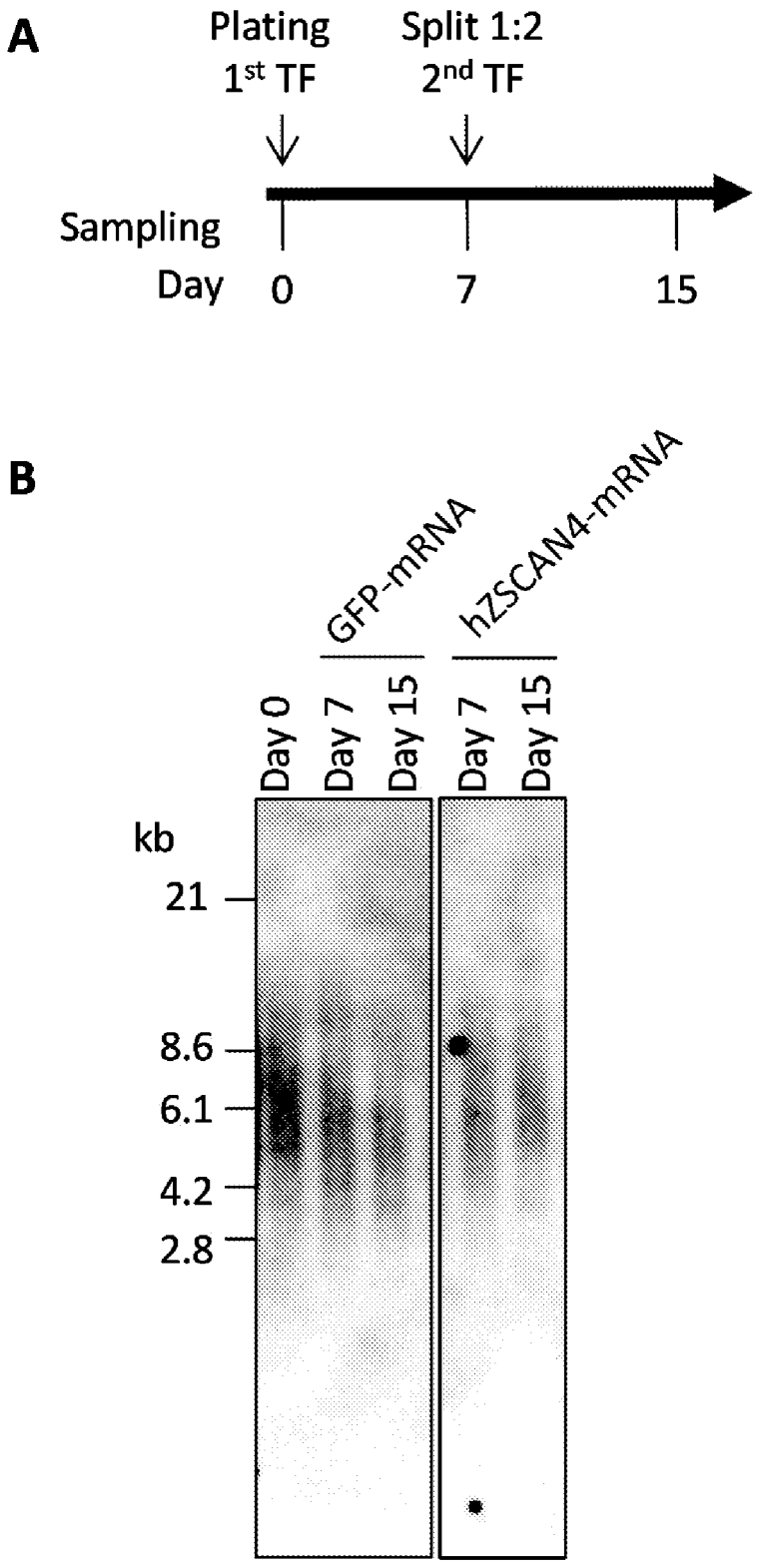

A
Plating
1st TF
Split 1:2
2nd TF
Sampling
Day
0
7
15
B
GFP-mRNA
hZSCAN4-mRNA
Day 0
Day 7
Day 15
Day 7
Day 15
kb
21
8.6
6.1
4.2
2.8

FIG. 8

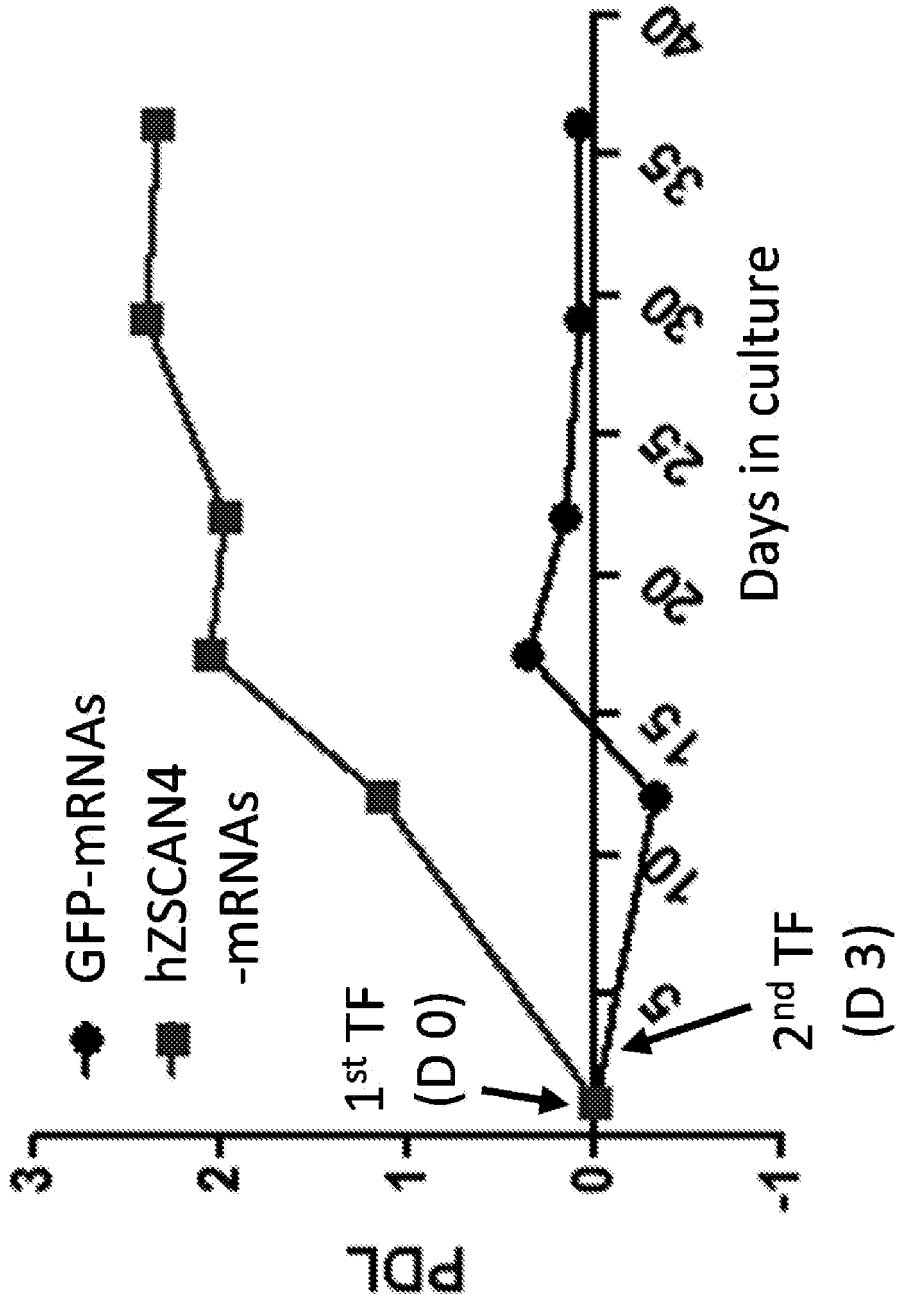

PDL
3
2
1
0
-1
0
5
10
15
20
25
30
35
40
Days in culture
1st TF
(D 0)
2nd TF
(D 3)
GFP-mRNAs
hZSCAN4
-mRNAs

FIG. 9

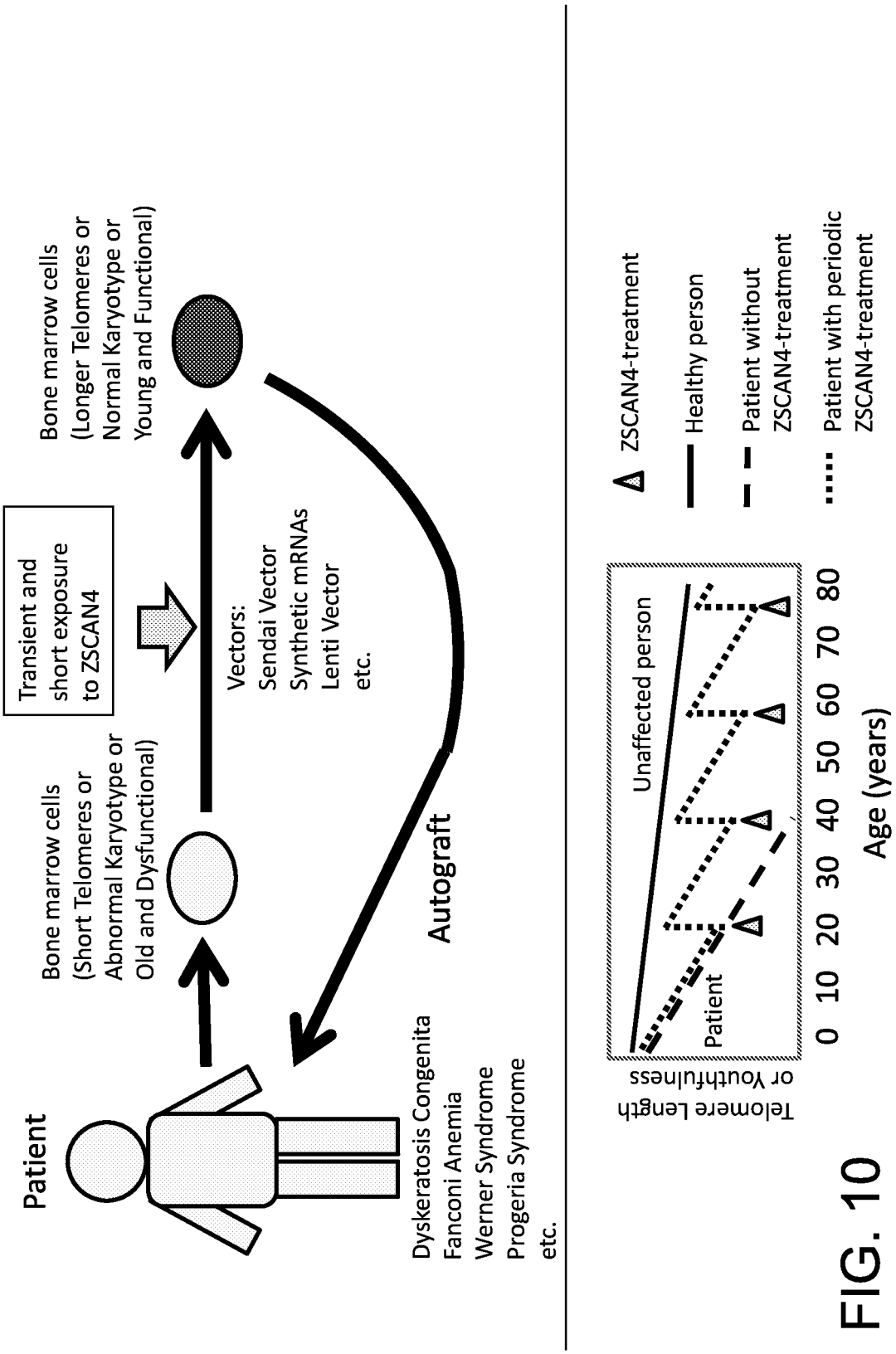

Patient
Bone marrow cells
(Short Telomeres or
Abnormal Karyotype or
Old and Dysfunctional)
Transient and
short exposure
to ZSCAN4
Vectors:
Sendai Vector
Synthetic mRNAs
Lenti Vector
etc.
Bone marrow cells
(Longer Telomeres or
Normal Karyotype or
Young and Functional)
Autograft
Dyskeratosis Congenita
Fanconi Anemia
Werner Syndrome
Progeria Syndrome
etc.
Telomere Length
or Youthfulness
Unaffected person
Patient
0 10 20 30 40 50 60 70 80
Age (years)
ZSCAN4-treatment
Healthy person
Patient without
ZSCAN4-treatment
Patient with periodic
ZSCAN4-treatment

FIG. 10

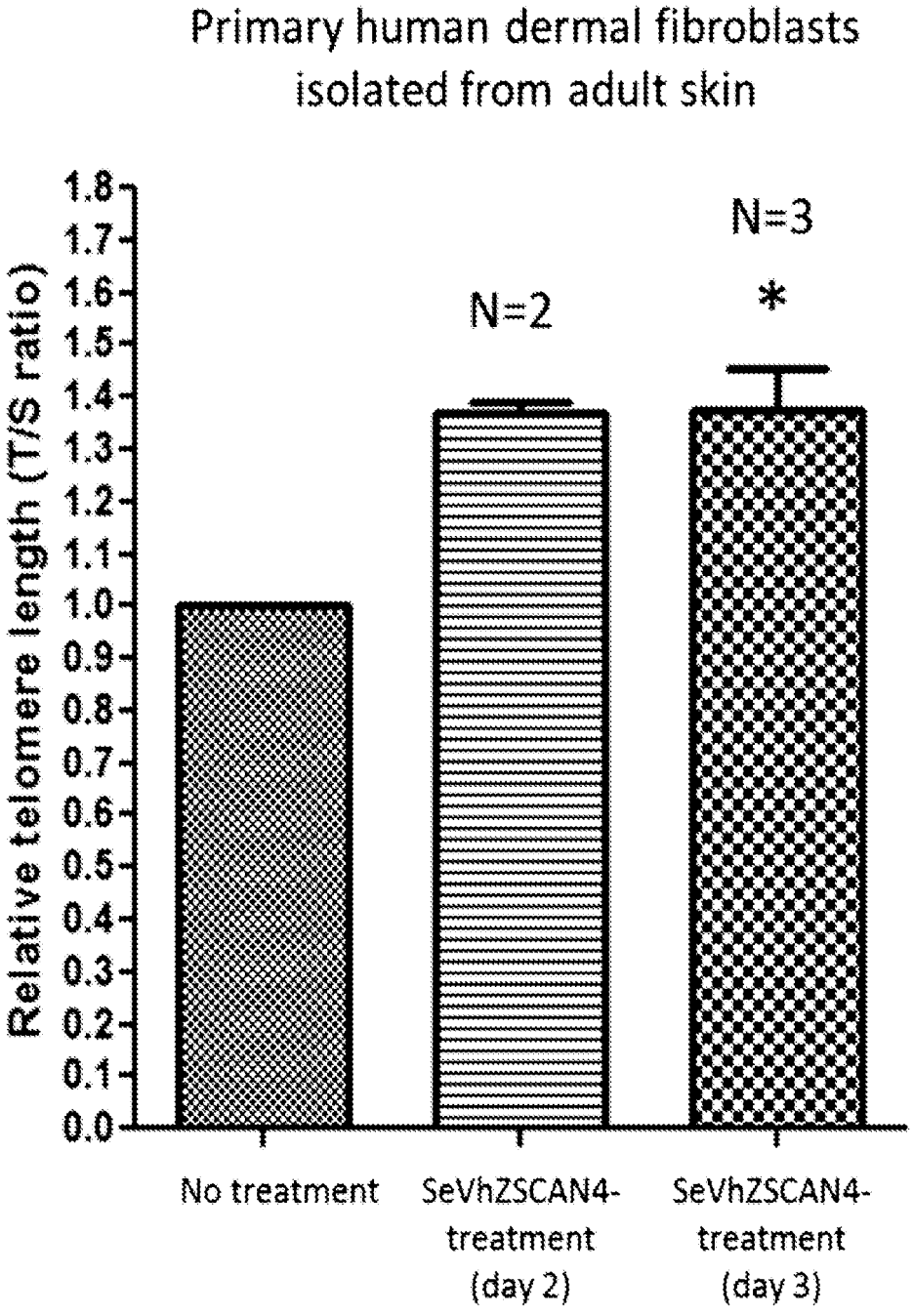

Primary human dermal fibroblasts
isolated from adult skin
Relative telomere length (T/S ratio)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
N=2
N=3
*
No treatment
SeVhZSCAN4-treatment (day 2)
SeVhZSCAN4-treatment (day 3)

FIG. 11

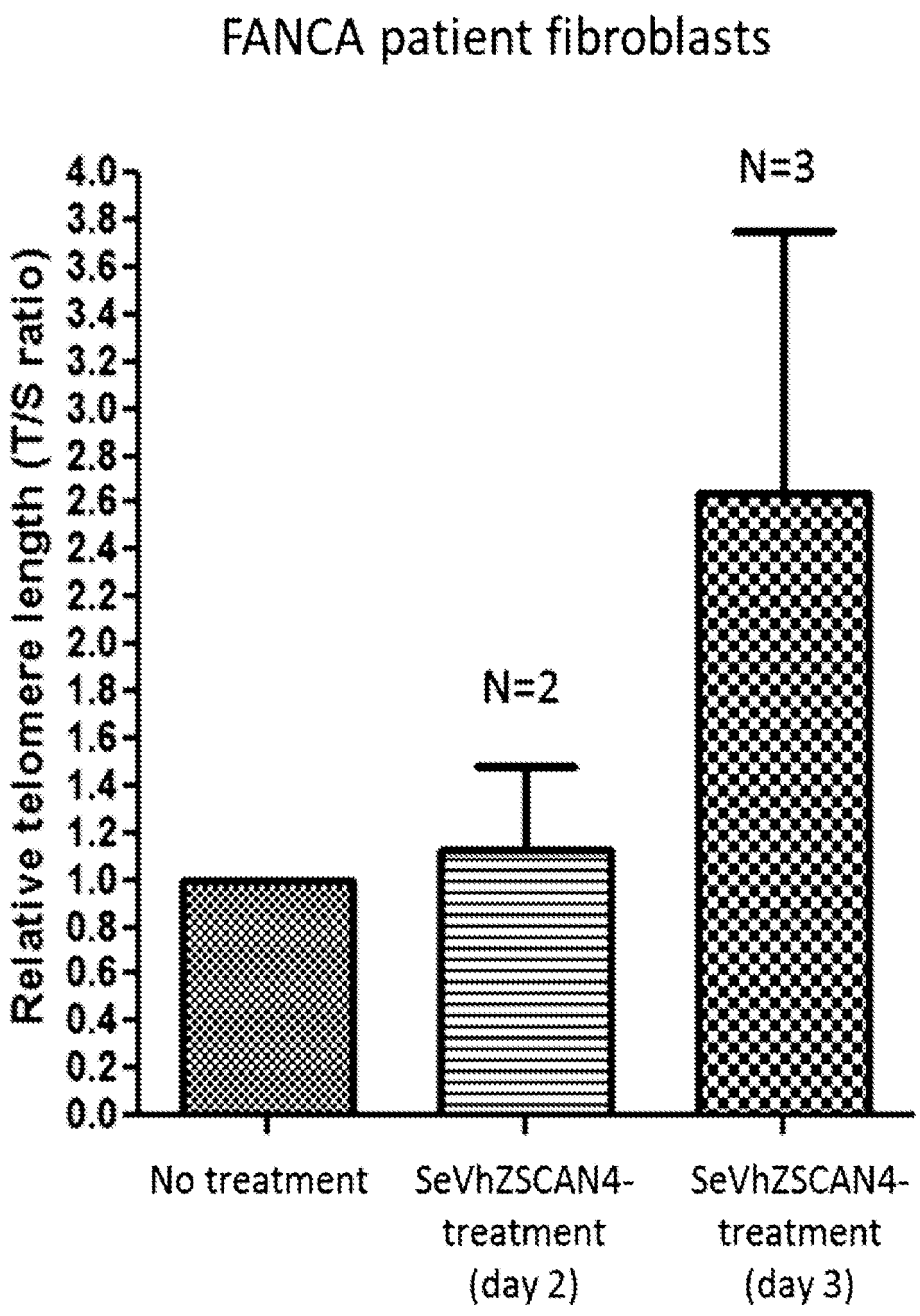

FANCA patient fibroblasts
Relative telomere length (T/S ratio)
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
N=3
N=2
No treatment
SeVhZSCAN4-treatment (day 2)
SeVhZSCAN4-treatment (day 3)

FIG. 12

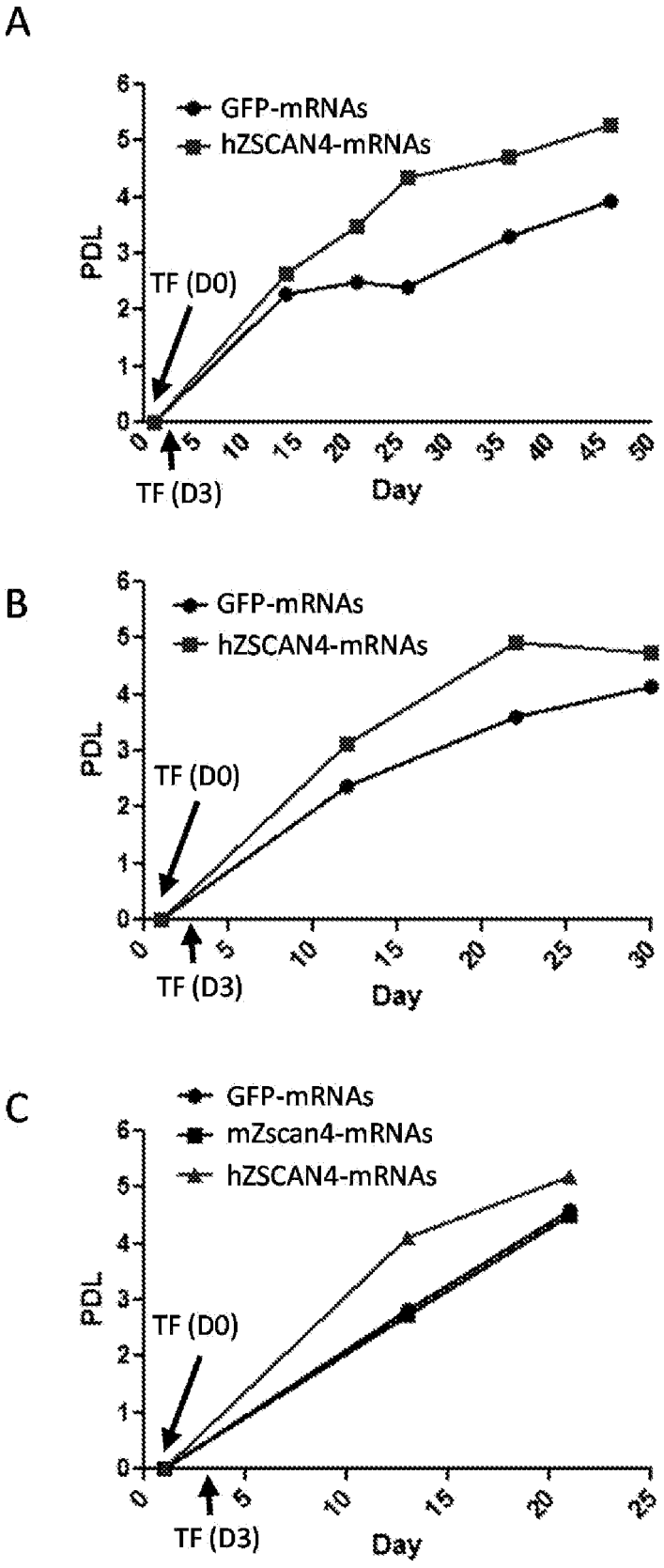
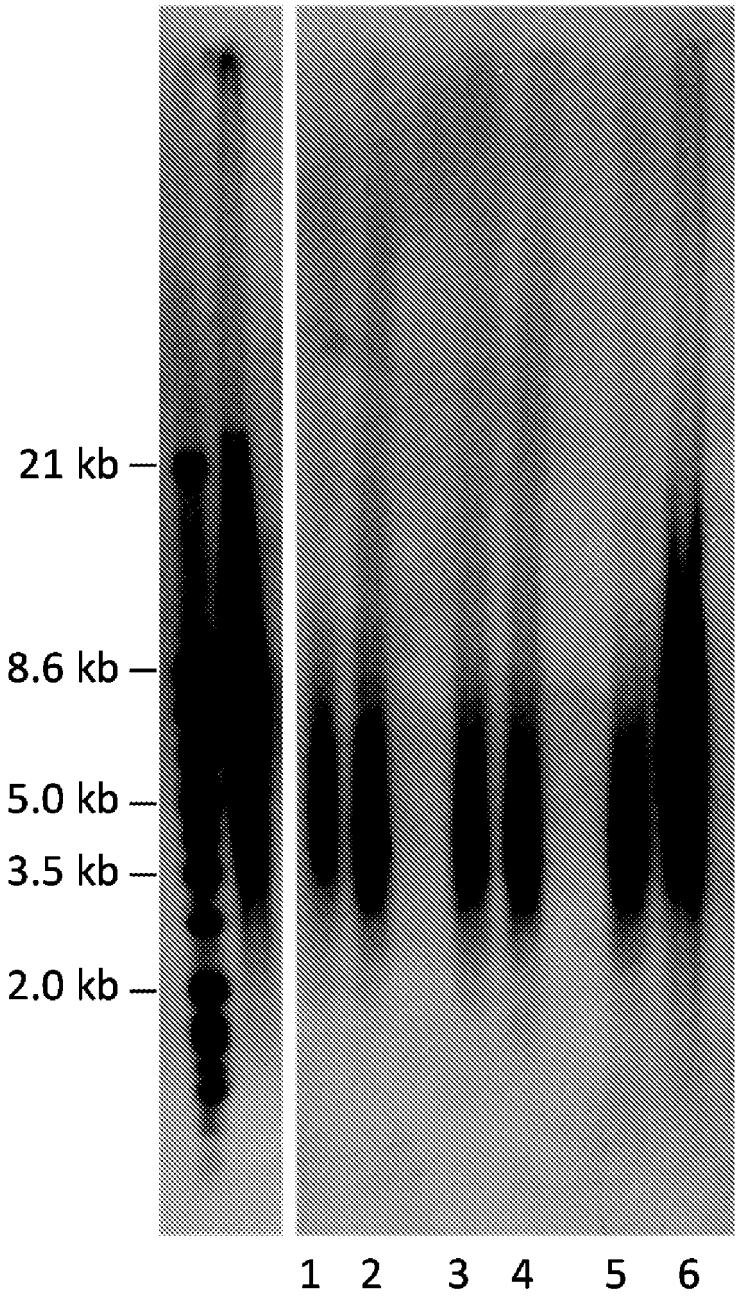

A
GFP-mRNAs
hZSCAN4-mRNAs
PDL
TF (D0)
TF (D3)
Day
B
GFP-mRNAs
hZSCAN4-mRNAs
PDL
TF (D0)
TF (D3)
Day
C
GFP-mRNAs
mZscan4-mRNAs
hZSCAN4-mRNAs
PDL
TF (D0)
TF (D3)
Day

FIG. 13



1. SeVAG-TS15 (P3, D14) -> 6.9 kb
2. SeVAG-TS15 (P7, D62) -> 6.7 kb
3. SeVmZscan4-TS15 (P3, D14) -> 6.8 kb
4. SeVmZscan4-TS15 (P7, D62) -> 6.7 kb
5. SeVhZSCAN4-TS15 (P3, D62) -> 6.7 kb
6. SeVhZSCAN4-TS15 (P7, D62) -> 7.8 kb

FIG. 14

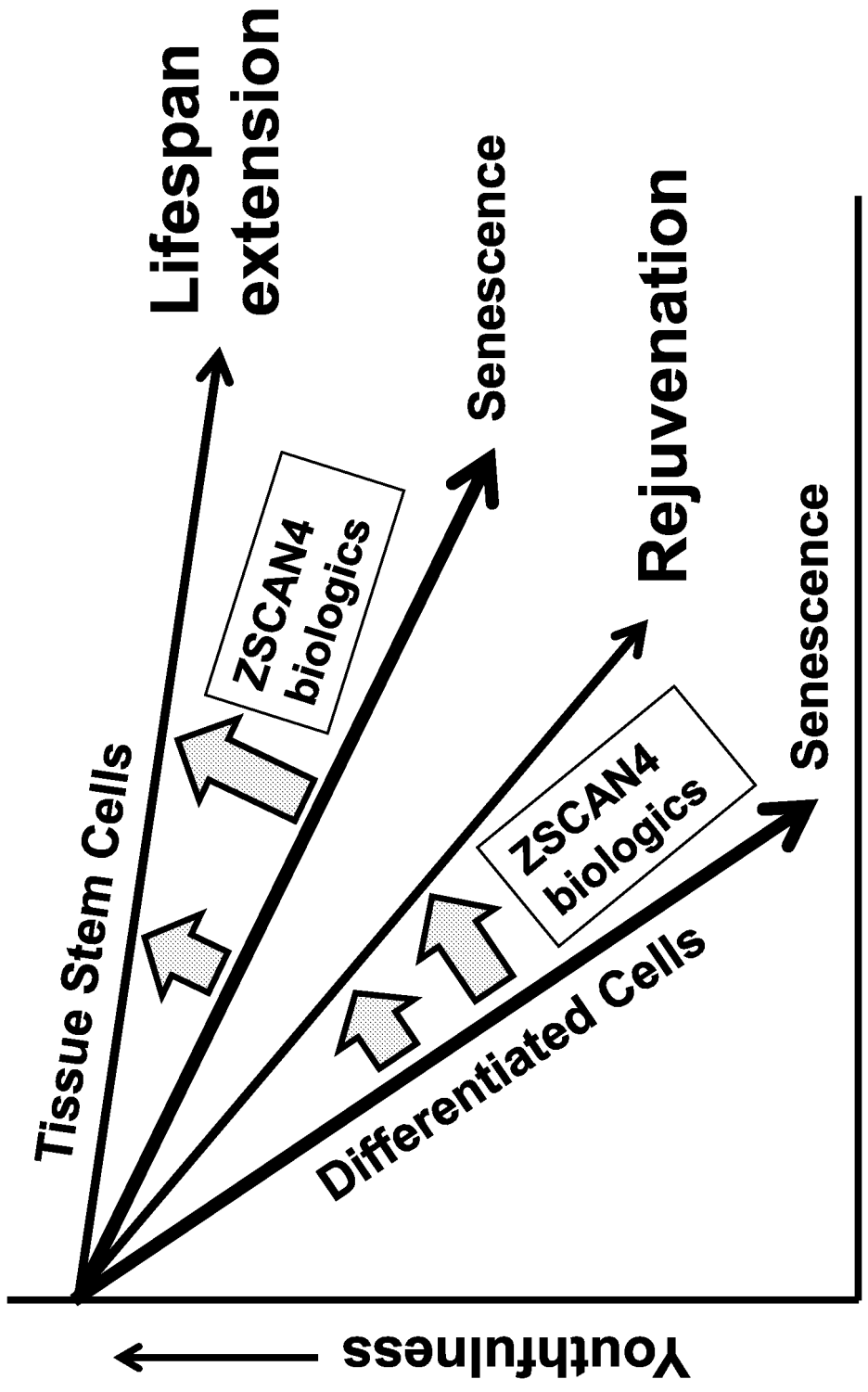

Youthfulness
Cell Divisions
Tissue Stem Cells
Differentiated Cells
Lifespan extension
Senescence
Rejuvenation
Senescence
ZSCAN4 biologics
ZSCAN4 biologics

FIG. 15

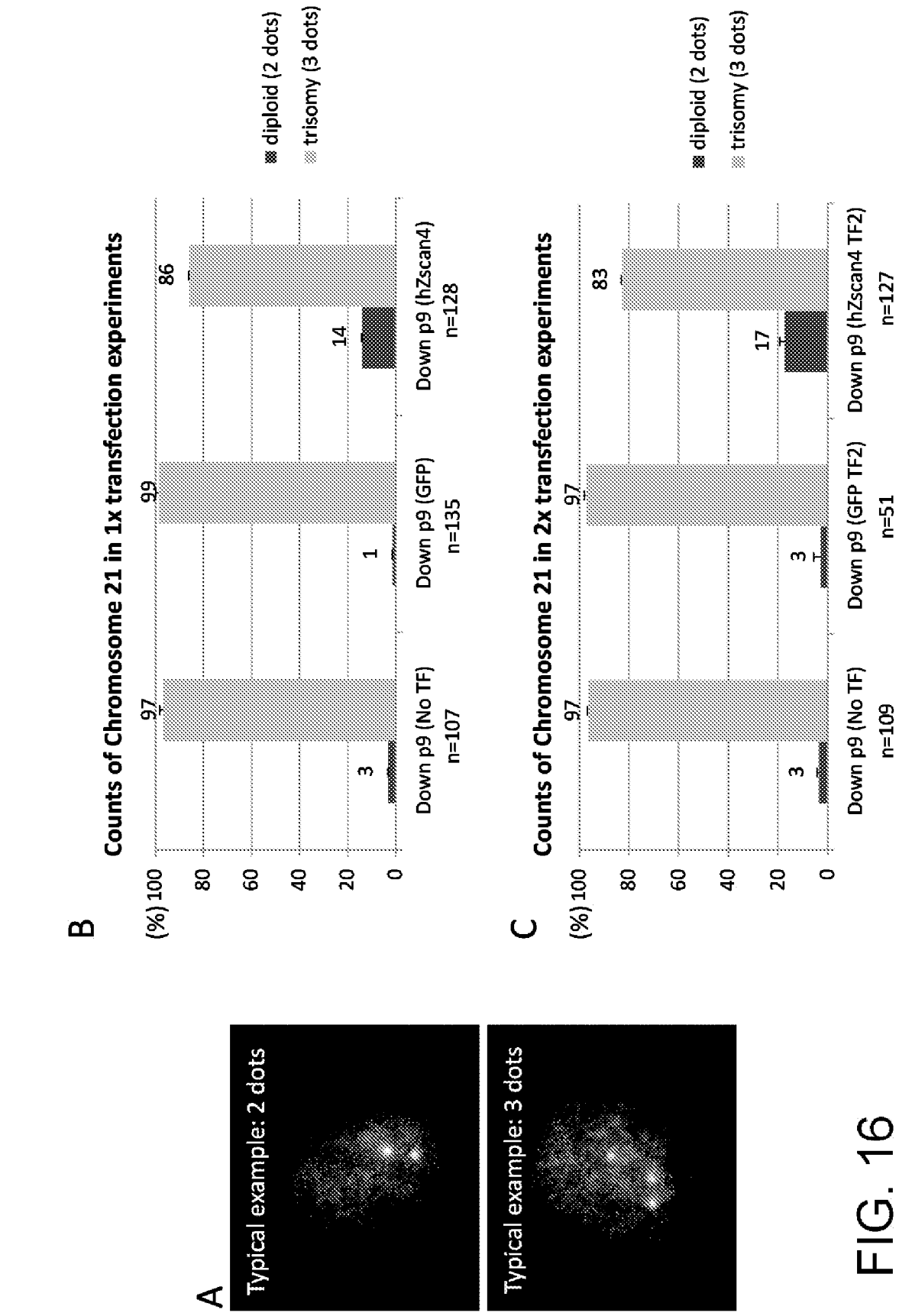

A
Typical example: 2 dots
Typical example: 3 dots
B
Counts of Chromosome 21 in 1x transfection experiments
(%) 100
80
60
40
20
0
97
3
99
1
14
86
diploid (2 dots)
trisomy (3 dots)
Down p9 (No TF) n=107
Down p9 (GFP) n=135
Down p9 (hZscan4) n=128
C
Counts of Chromosome 21 in 2x transfection experiments
(%) 100
80
60
40
20
0
97
3
97
3
17
83
diploid (2 dots)
trisomy (3 dots)
Down p9 (No TF) n=109
Down p9 (GFP TF2) n=51
Down p9 (hZscan4 TF2) n=127

FIG. 16

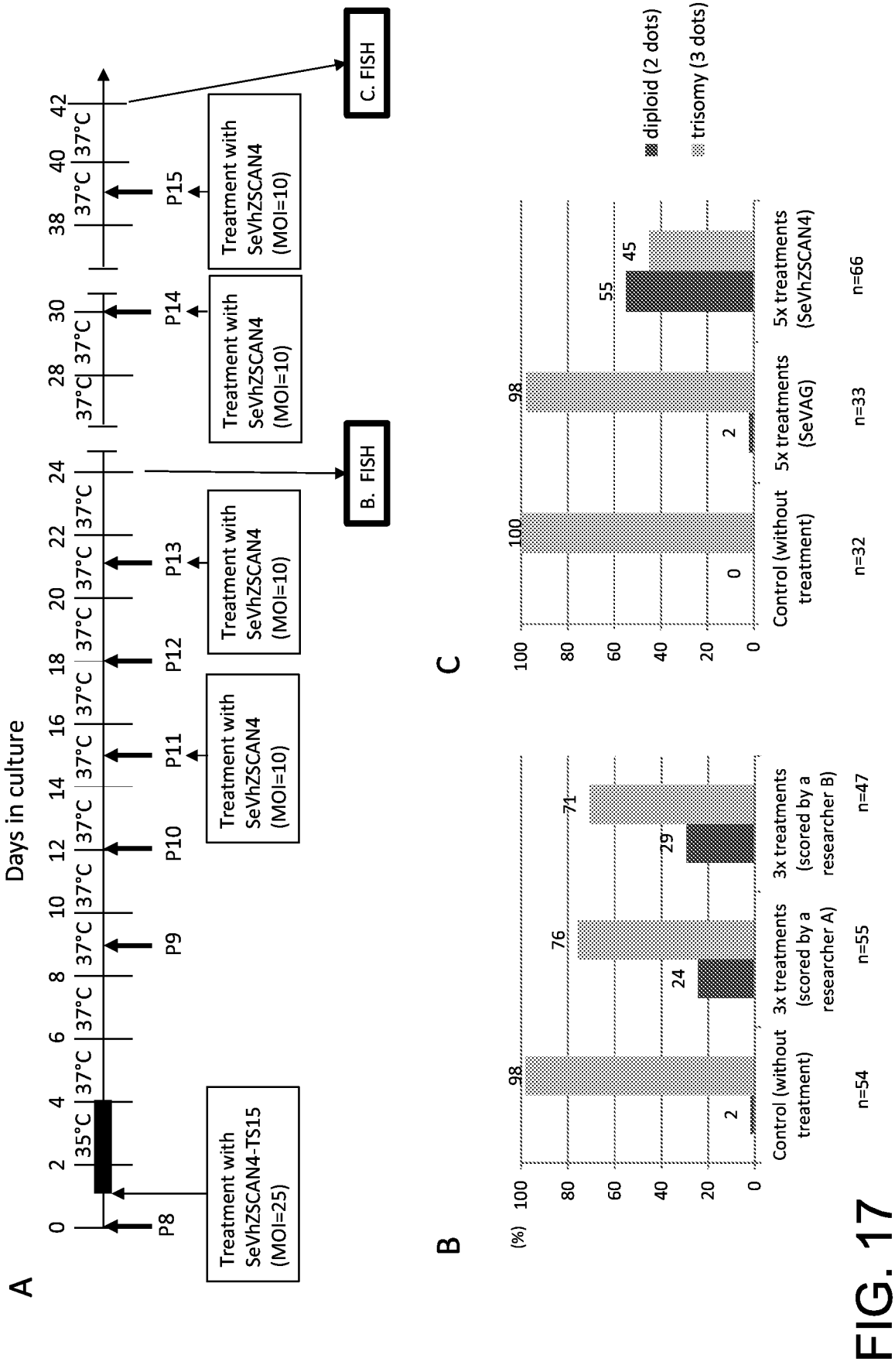

A
Days in culture
0 2 4 6 8 10 12 14 16 18 20 22 24 28 30 38 40 42
35°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C 37°C
P8 P9 P10 P11 P12 P13 P14 P15
Treatment with SeVhZSCAN4-TS15 (MOI=25)
Treatment with SeVhZSCAN4 (MOI=10)
Treatment with SeVhZSCAN4 (MOI=10)
Treatment with SeVhZSCAN4 (MOI=10)
Treatment with SeVhZSCAN4 (MOI=10)
Treatment with SeVhZSCAN4 (MOI=10)
B. FISH
C. FISH
B
(%) 100 80 60 40 20 0
98 2
76 24
71 29
Control (without treatment)
3x treatments (scored by a researcher A)
3x treatments (scored by a researcher B)
n=54
n=55
n=47
C
100 80 60 40 20 0
100 0
98 2
55 45
Control (without treatment)
5x treatments (SeVAG)
5x treatments (SeVhZSCAN4)
n=32
n=33
n=66
diploid (2 dots)
trisomy (3 dots)

FIG. 17

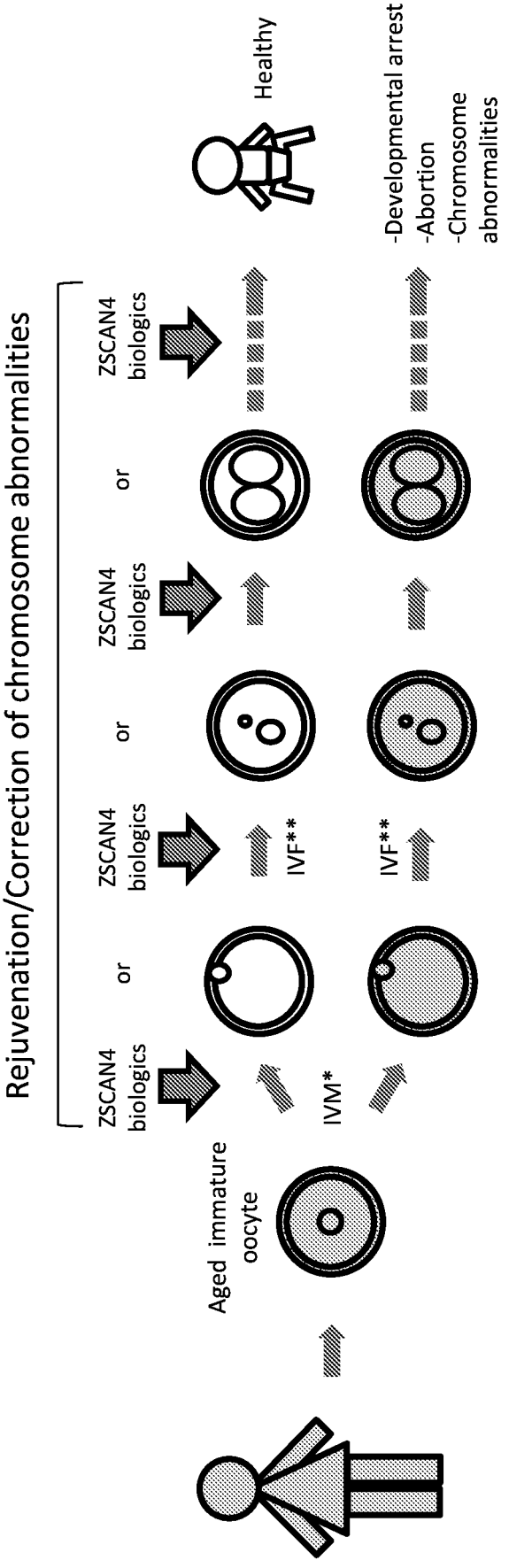

Rejuvenation/Correction of chromosome abnormalities
ZSCAN4 biologics
or
ZSCAN4 biologics
or
ZSCAN4 biologics
or
ZSCAN4 biologics
Aged immature oocyte
IVM*
IVF**
IVF**
Healthy
-Developmental arrest
-Abortion
-Chromosome abnormalities
*: In vitro Maturation
**: In vitro Fertilization

FIG. 18

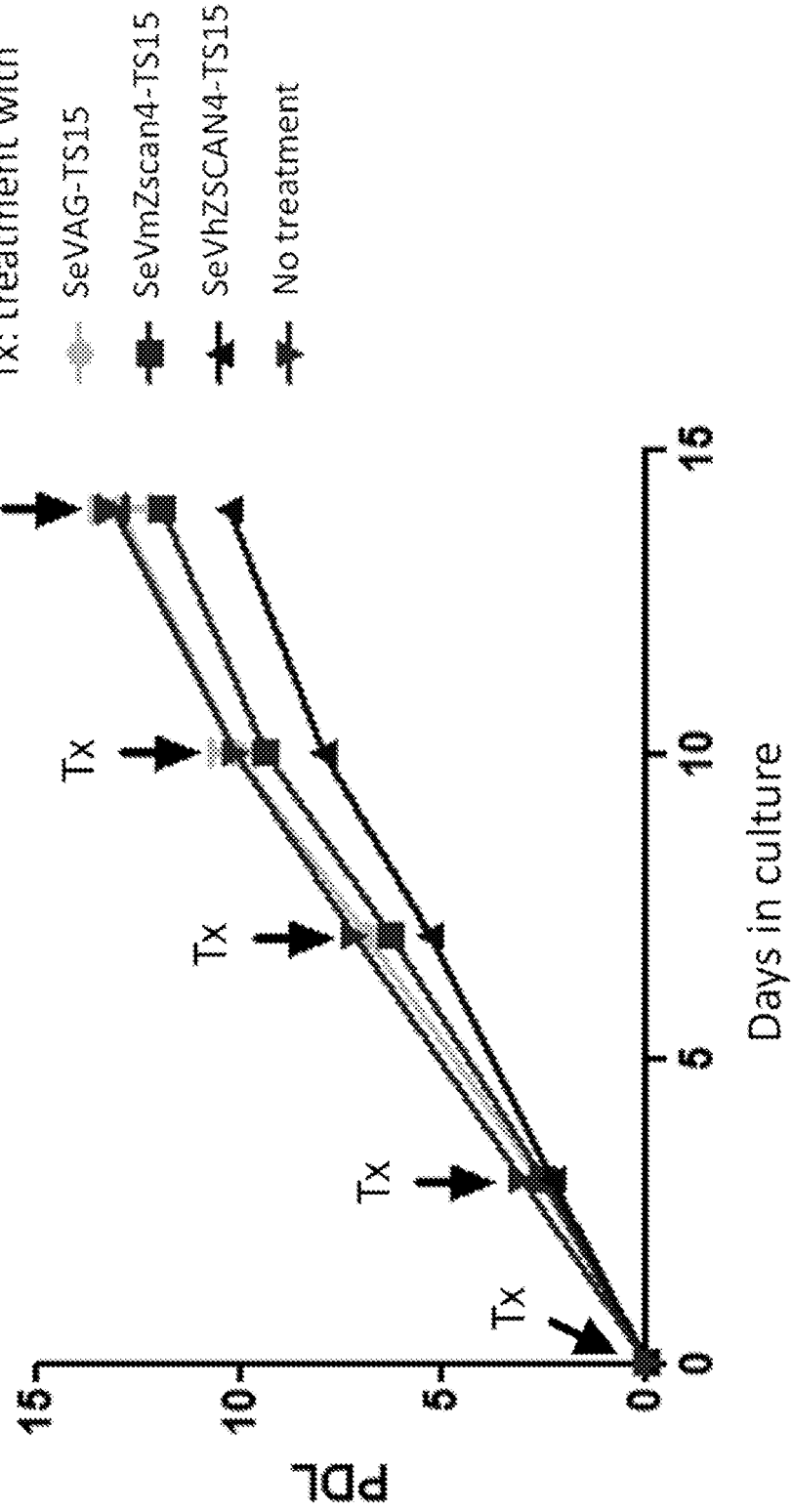

Tx: treatment with
SeVAG-TS15
SeVmZscan4-TS15
SeVhZSCAN4-TS15
No treatment
Tx
Tx
Tx
Tx
Tx
PDL
0
5
10
15
0
5
10
15
Days in culture

FIG. 19