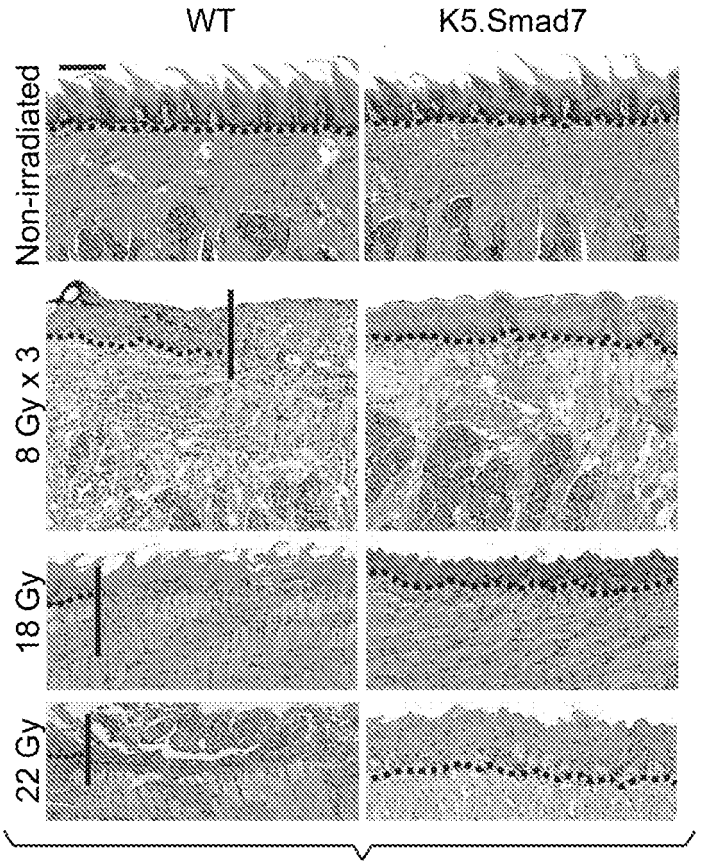

WT
K5.Smad7
Non-irradiated
8 Gy x 3
18 Gy
22 Gy

FIG. 1A

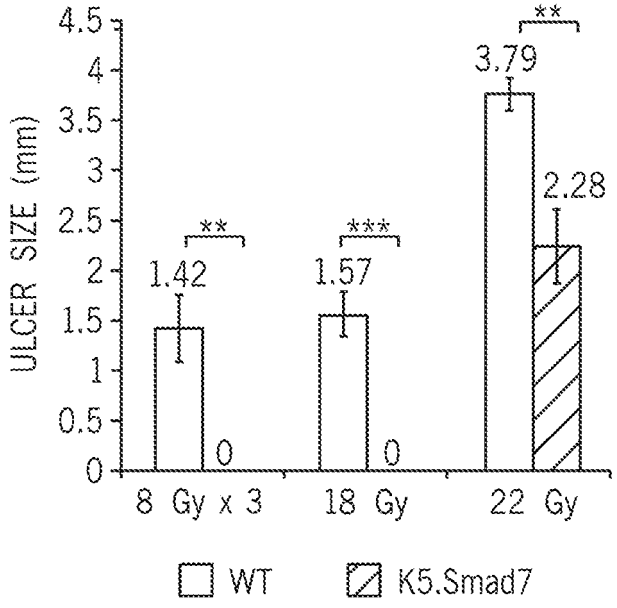

ULCER SIZE (mm)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
**
***
**
1.42
0
1.57
0
3.79
2.28
8 Gy x 3
18 Gy
22 Gy
WT
K5.Smad7

FIG. 1B

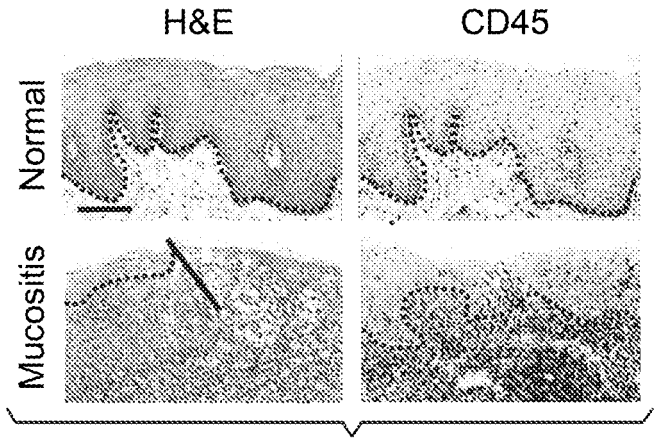

H&E
CD45
Normal
Mucositis

FIG. 1C

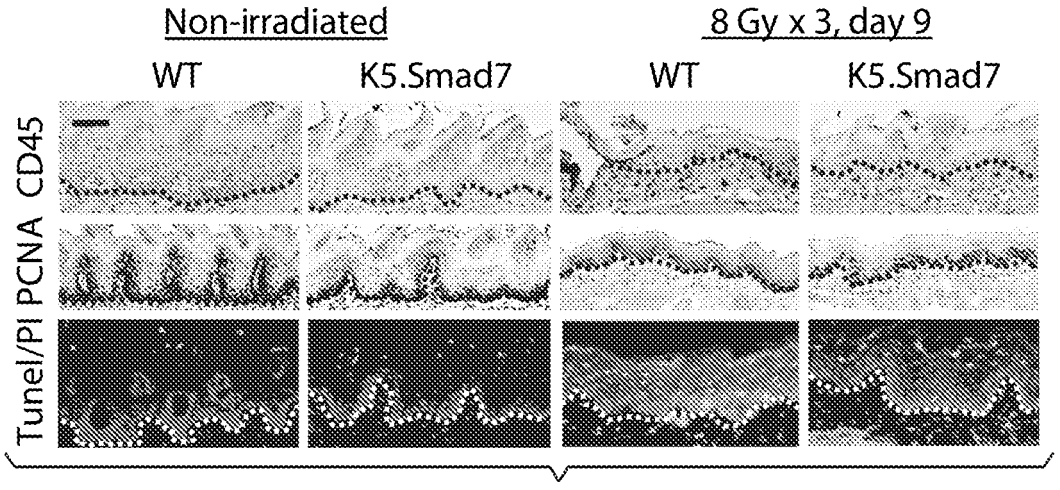

Non-irradiated
8 Gy x 3, day 9
WT
K5.Smad7
WT
K5.Smad7
CD45
PCNA
Tunel/PI

FIG. 1D

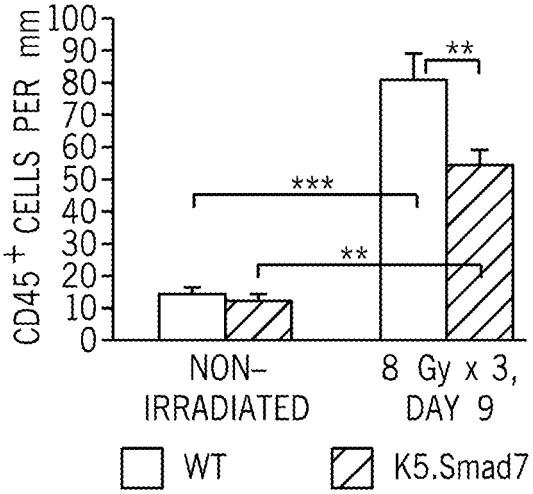


FIG. 1E

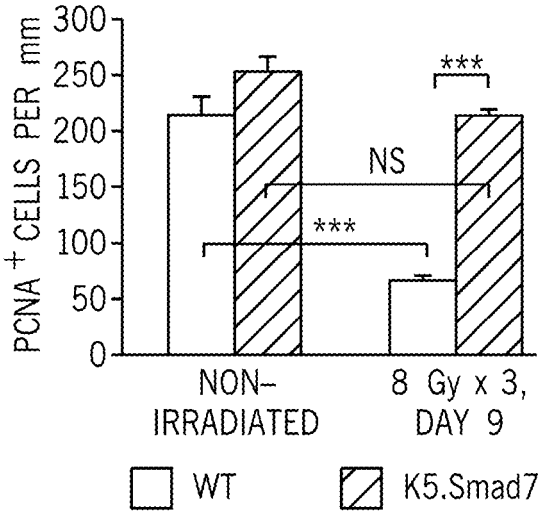


FIG. 1F

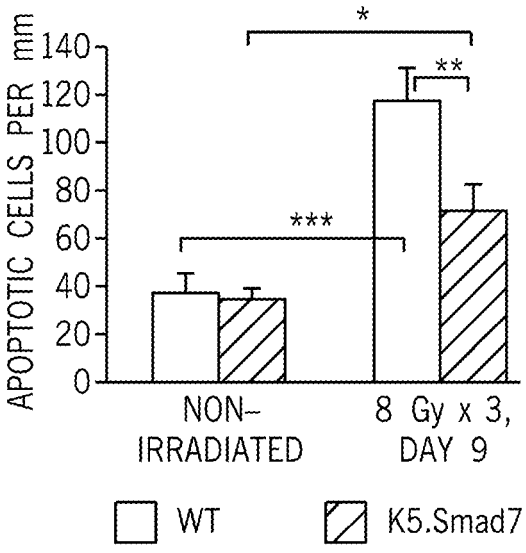


FIG. 1G

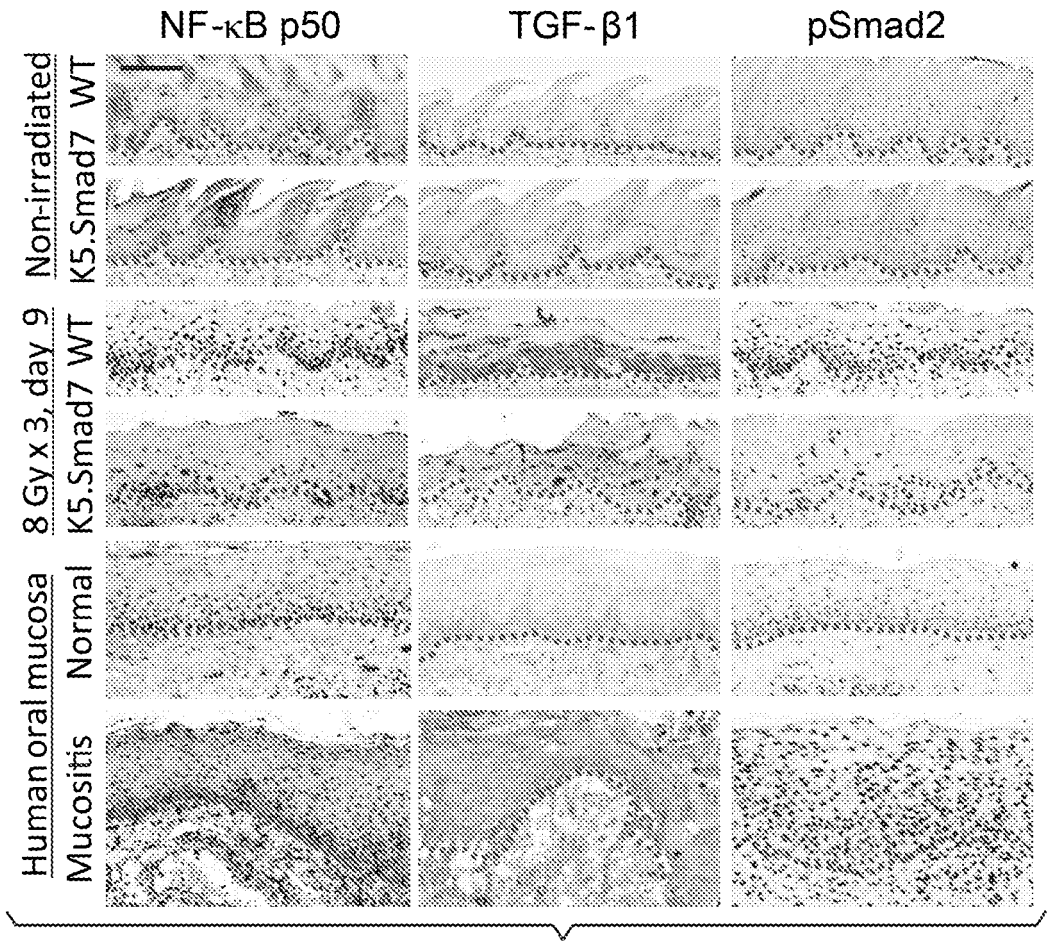

NF-κB p50
TGF-β1
pSmad2
Non-irradiated
WT
K5.Smad7
8 Gy x 3, day 9
WT
K5.Smad7
Human oral mucosa
Normal
Mucositis

FIG. 2A

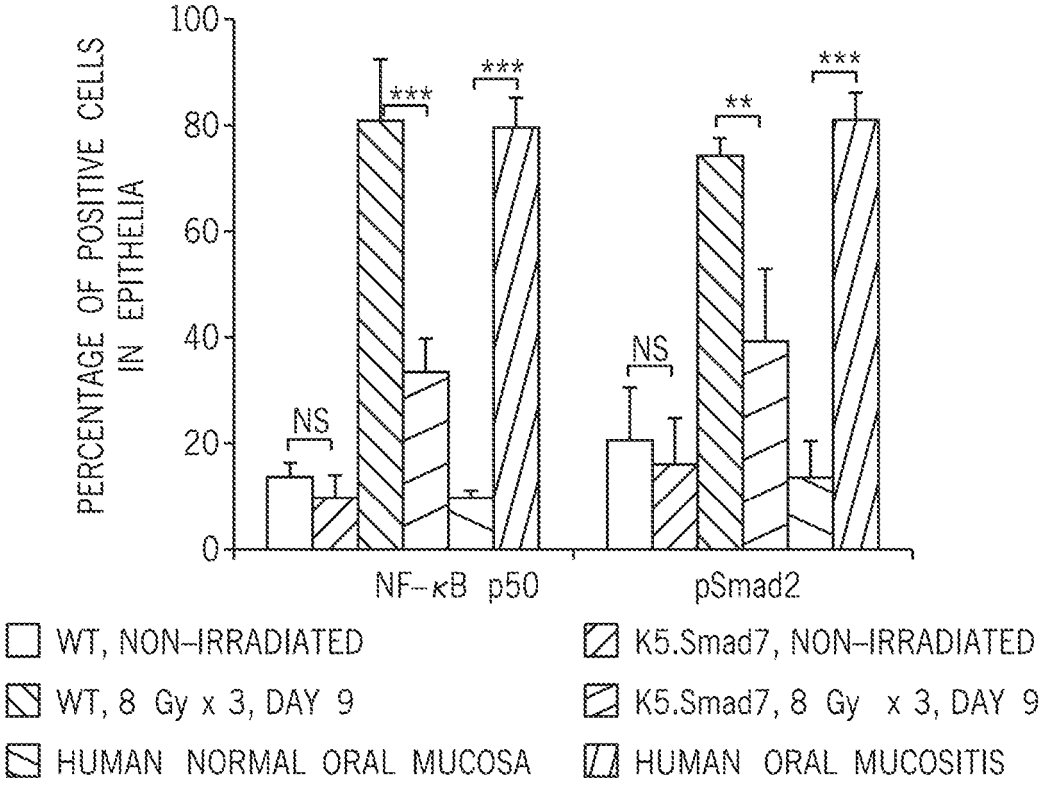

PERCENTAGE OF POSITIVE CELLS IN EPITHELIA
100
80
60
40
20
0
NS
***
***
NS
**
***
NF-κB p50
pSmad2
WT, NON-IRRADIATED
K5.Smad7, NON-IRRADIATED
WT, 8 Gy x 3, DAY 9
K5.Smad7, 8 Gy x 3, DAY 9
HUMAN NORMAL ORAL MUCOSA
HUMAN ORAL MUCOSITIS

FIG. 2B

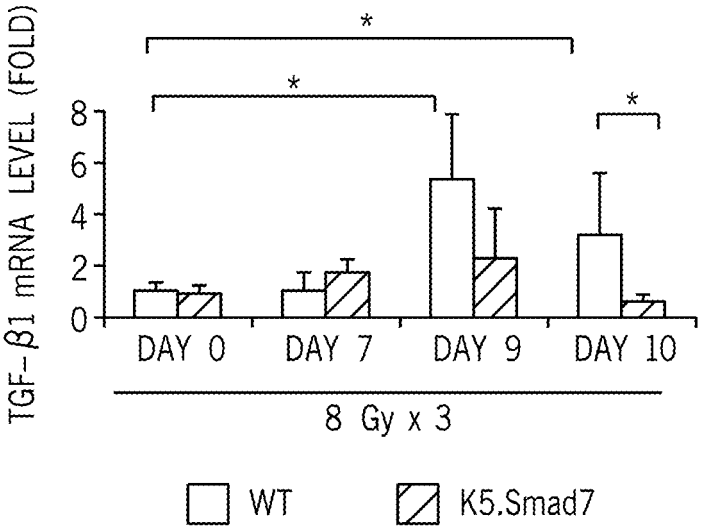

TGF-β1 mRNA LEVEL (FOLD)
0
2
4
6
8
*
*
*
DAY 0
DAY 7
DAY 9
DAY 10
8 Gy x 3
WT
K5.Smad7

FIG. 2C

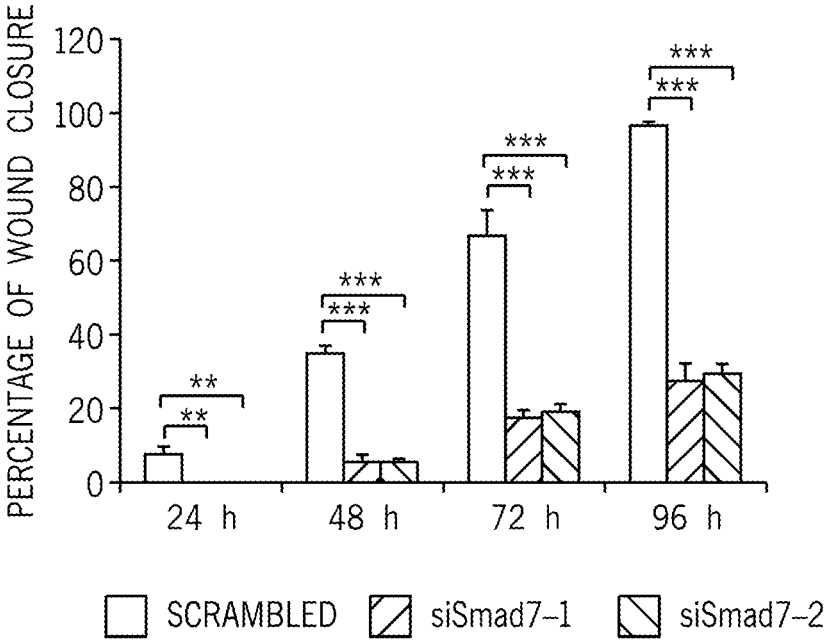

PERCENTAGE OF WOUND CLOSURE
0
20
40
60
80
100
120
**
**
***
***
***
***
***
***
24 h
48 h
72 h
96 h
SCRAMBLED
siSmad7-1
siSmad7-2

FIG. 2D

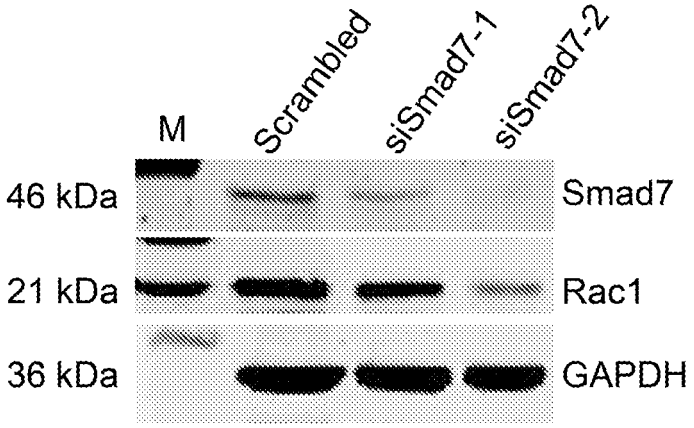


FIG. 2E

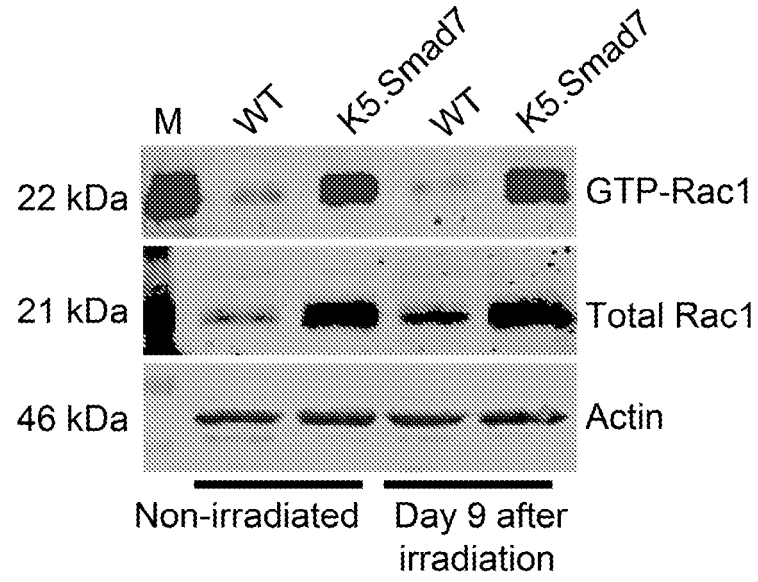


FIG. 2F

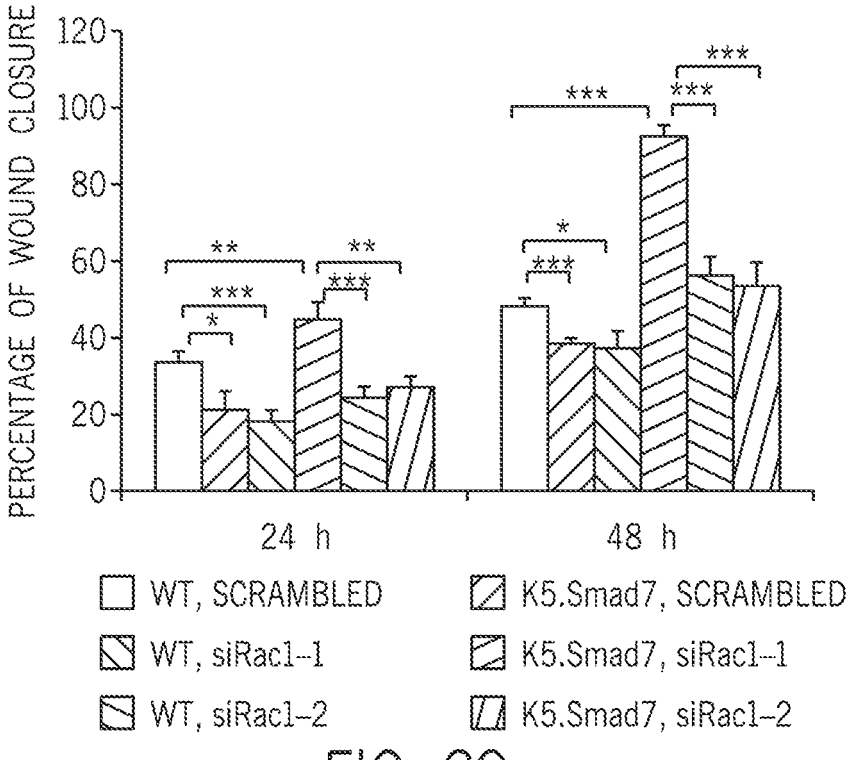


FIG. 2G

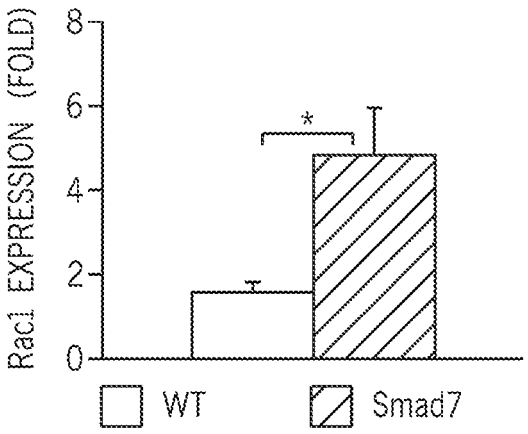


FIG. 3A

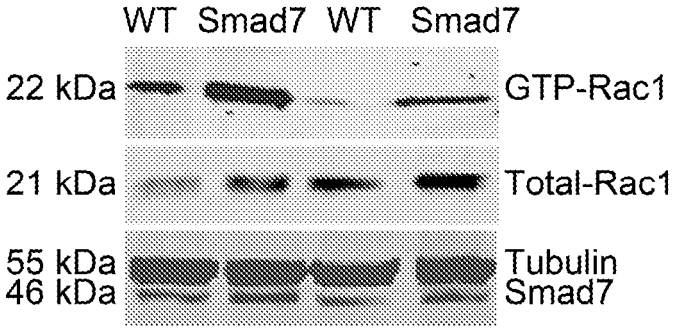


FIG. 3B

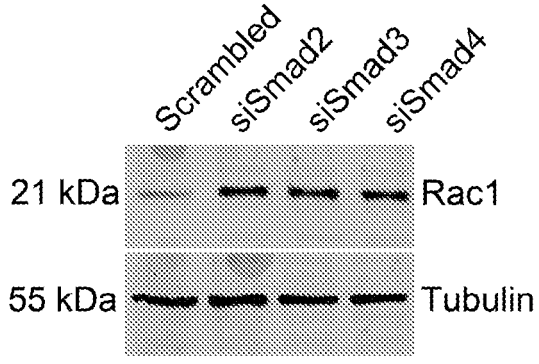


FIG. 3C

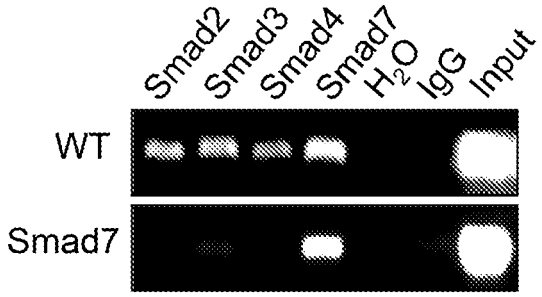


FIG. 3D

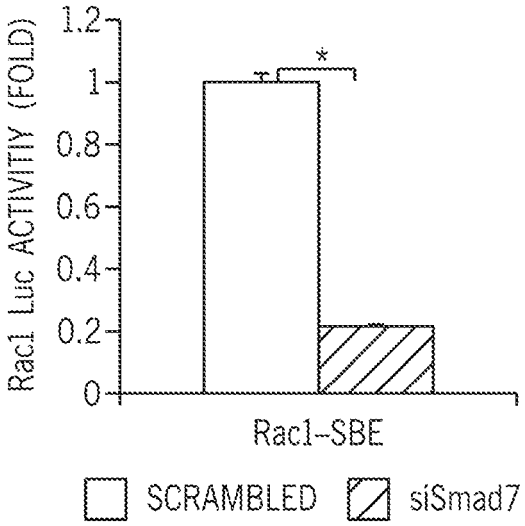


FIG. 3E

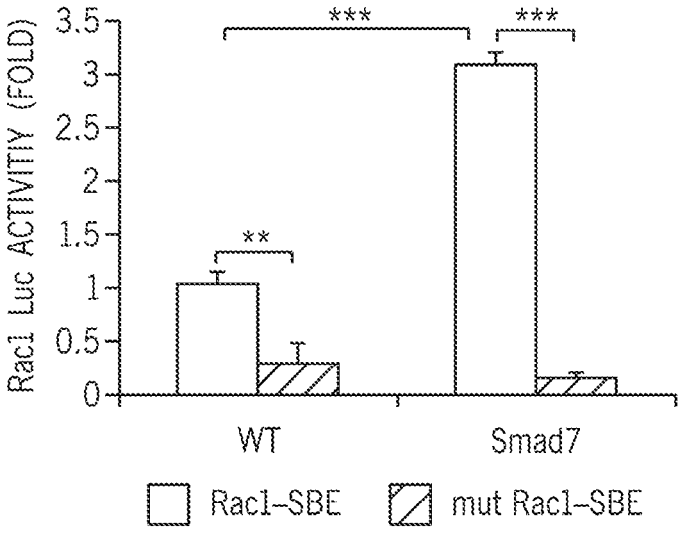


FIG. 3F

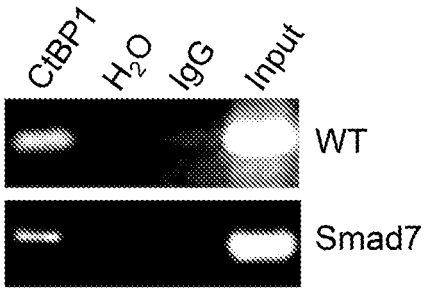

CtBP1
H_2O
IgG
Input
WT
Smad7

FIG. 3G

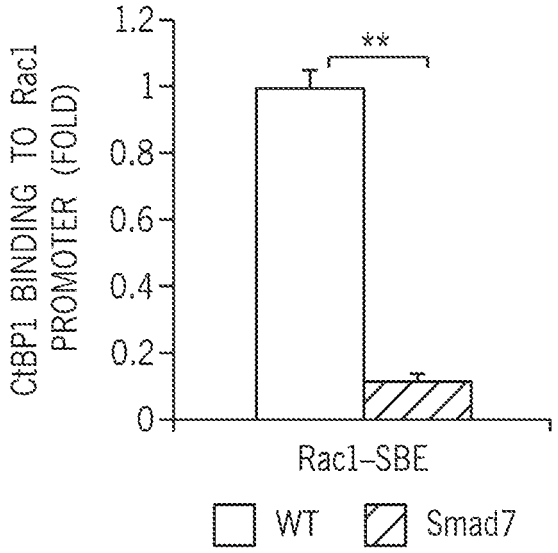

CtBP1 BINDING TO Rac1 PROMOTER (FOLD)
1.2
1
0.8
0.6
0.4
0.2
0
**
Rac1-SBE
WT
Smad7

FIG. 3H

FIG. 4A

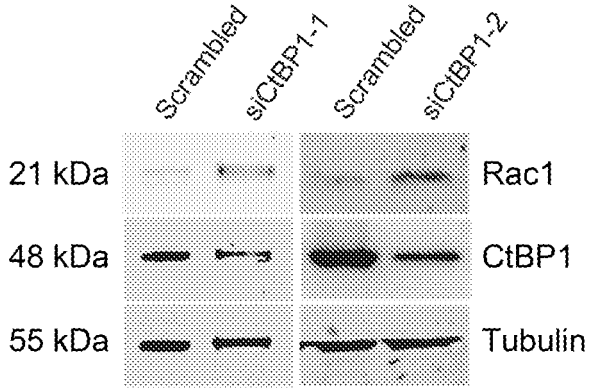


FIG. 4B

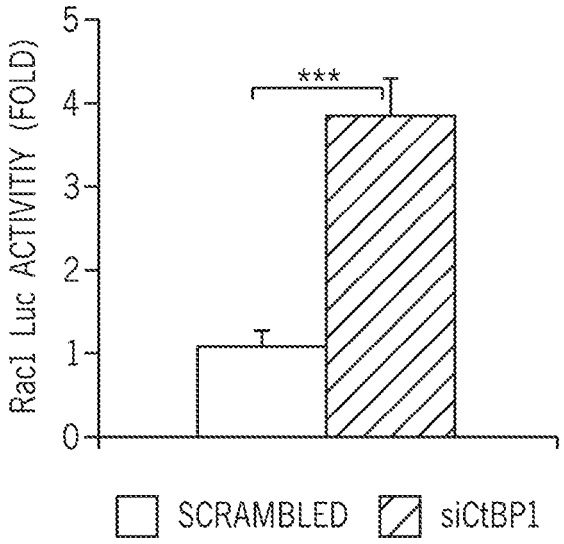
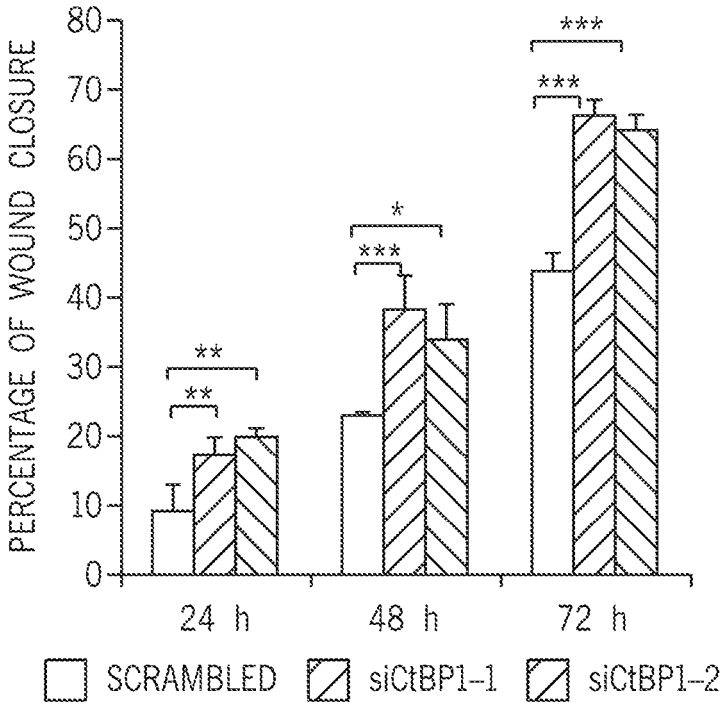


FIG. 4C



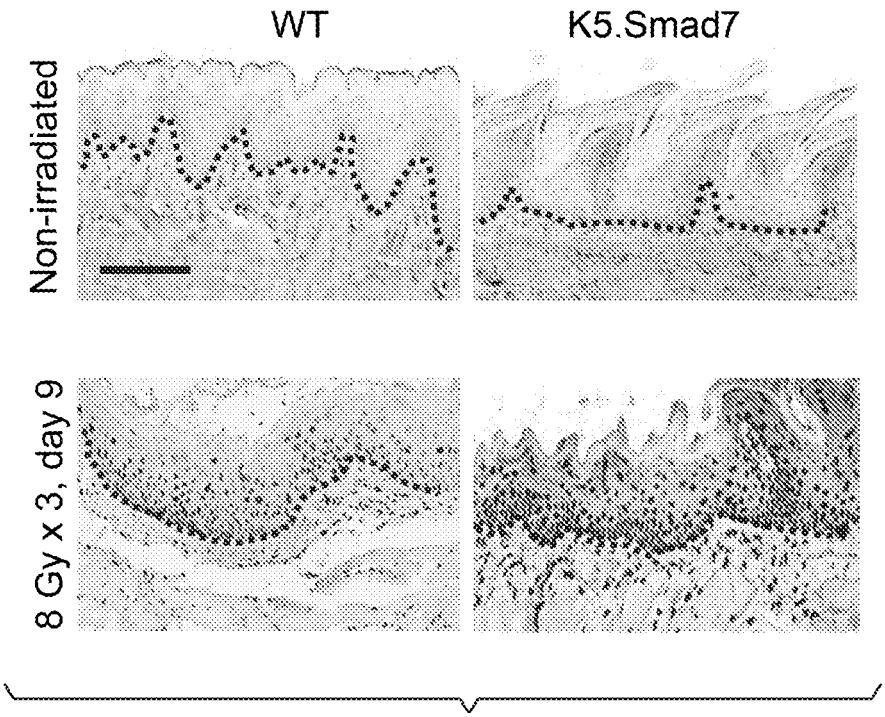

WT
K5.Smad7
Non-irradiated
8 Gy x 3, day 9

FIG. 4D

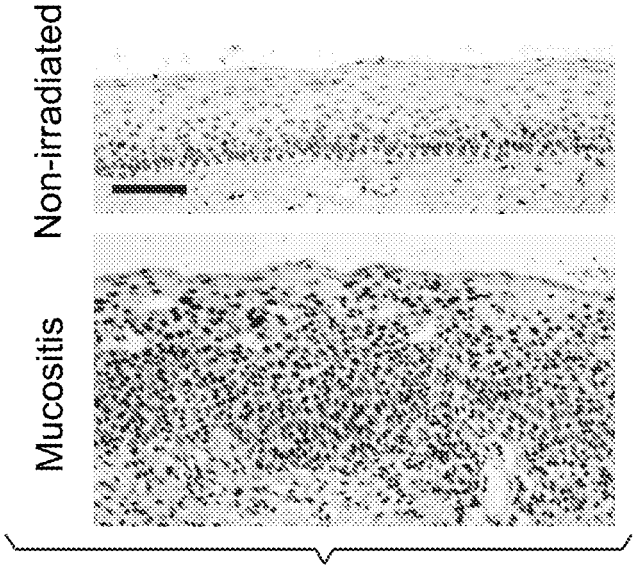

Non-irradiated
Mucositis

FIG. 4E

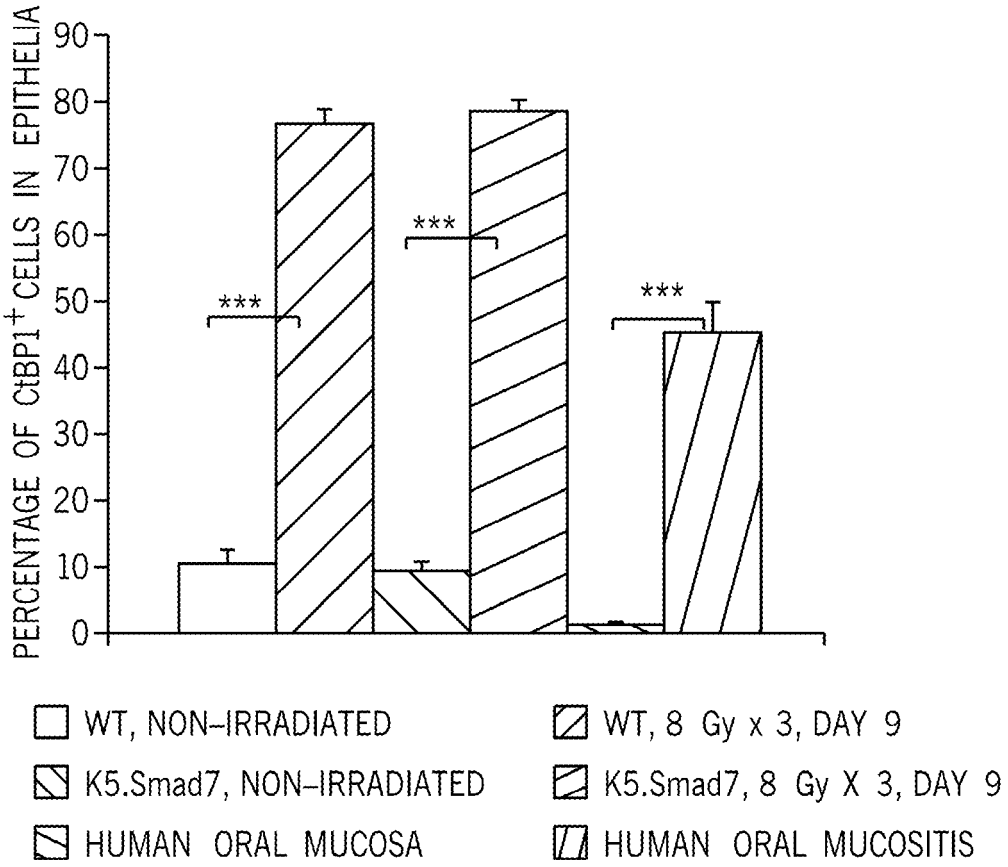

PERCENTAGE OF CtBP1+ CELLS IN EPITHELIA
90
80
70
60
50
40
30
20
10
0
***
***
***
WT, NON-IRRADIATED
K5.Smad7, NON-IRRADIATED
HUMAN ORAL MUCOSA
WT, 8 Gy x 3, DAY 9
K5.Smad7, 8 Gy X 3, DAY 9
HUMAN ORAL MUCOSITIS

FIG. 4F

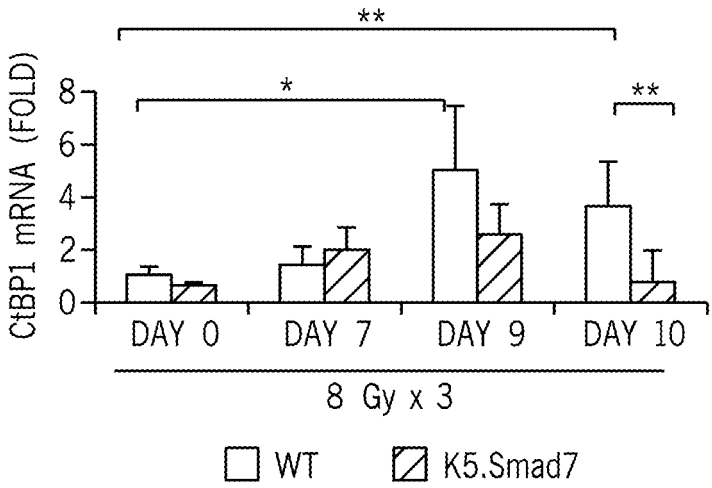

CtBP1 mRNA (FOLD)
8
6
4
2
0
**
*
**
DAY 0
DAY 7
DAY 9
DAY 10
8 Gy x 3
WT
K5.Smad7

FIG. 4G

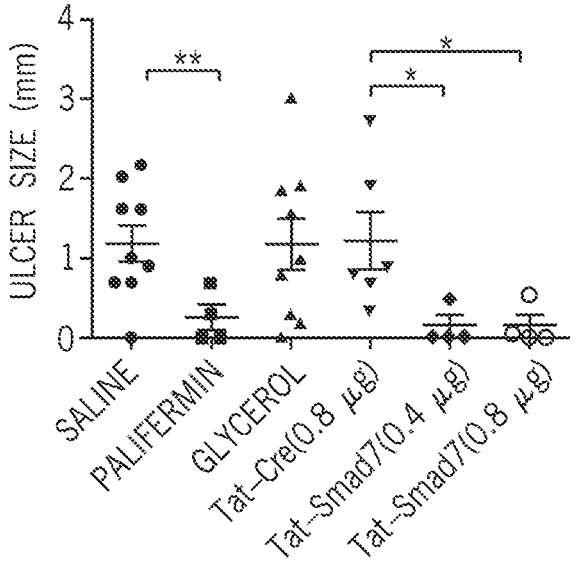

ULCER SIZE (mm)
0
1
2
3
4
**
*
*
SALINE
PALIFERMIN
GLYCEROL
Tat-Cre(0.8 μg)
Tat-Smad7(0.4 μg)
Tat-Smad7(0.8 μg)

FIG. 5A

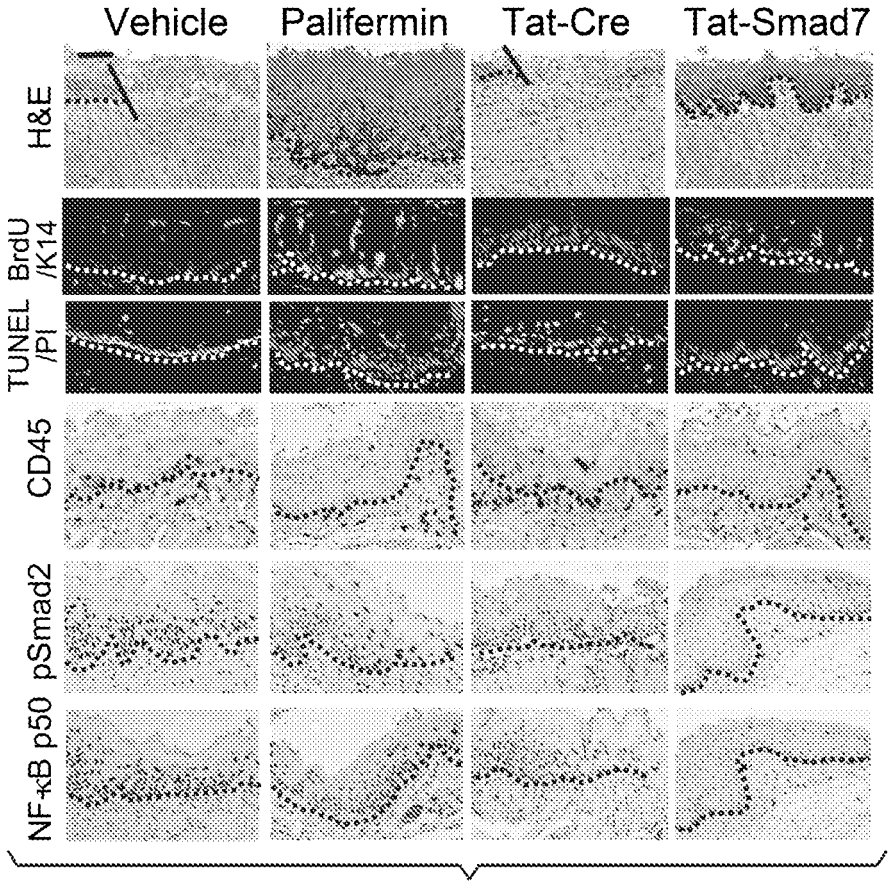

Vehicle
Palifermin
Tat-Cre
Tat-Smad7
H&E
BrdU /K14
TUNEL /PI
CD45
pSmad2
NF-κB p50

FIG. 5B

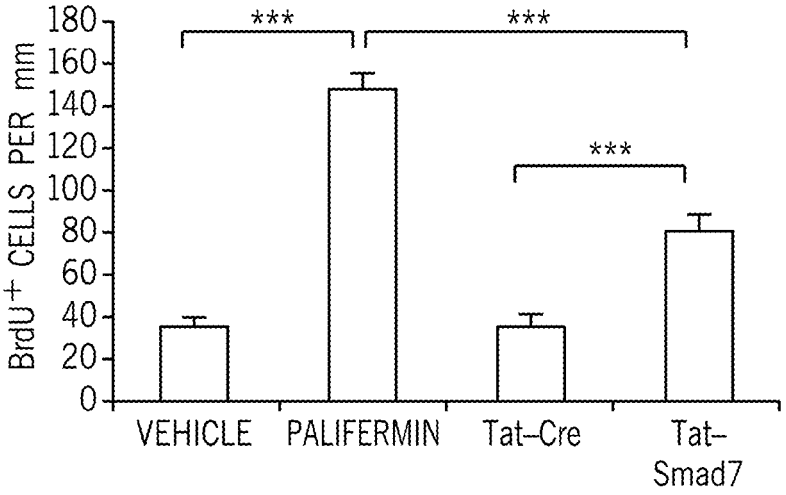


FIG. 5C

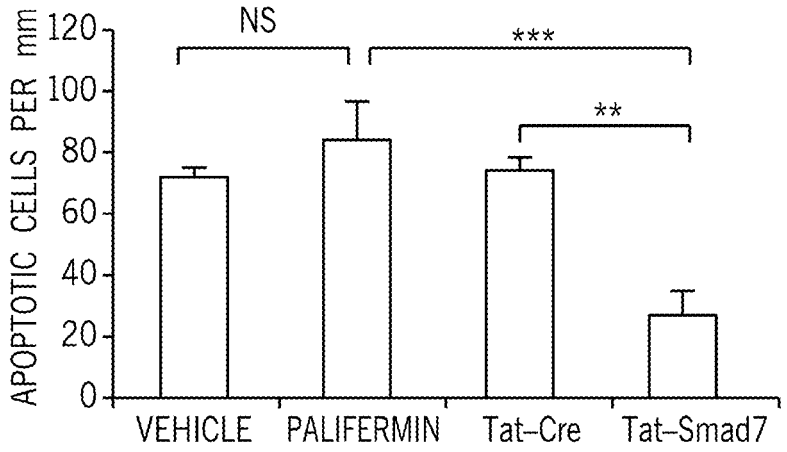


FIG. 5D

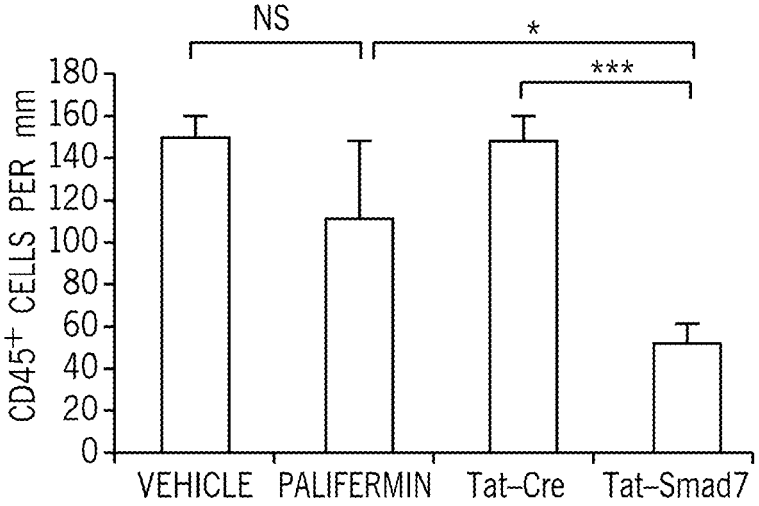


FIG. 5E

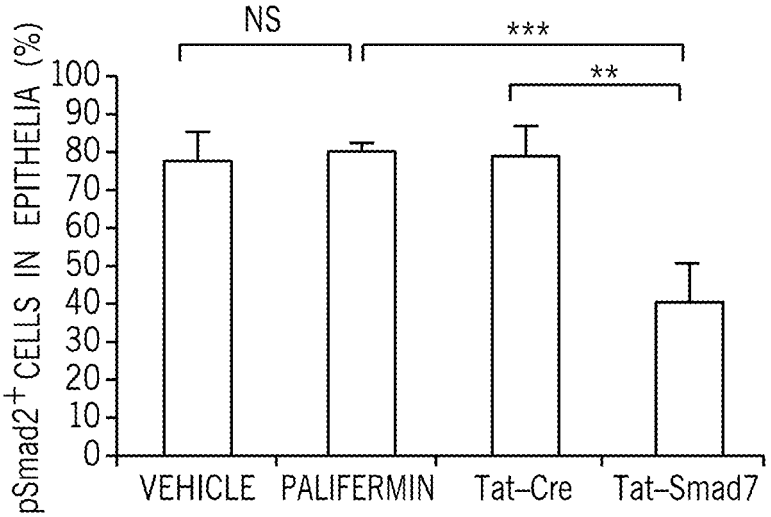

NS
***
**
pSmad2+ CELLS IN EPITHELIA (%)
100
90
80
70
60
50
40
30
20
10
0
VEHICLE
PALIFERMIN
Tat–Cre
Tat–Smad7

FIG. 5F

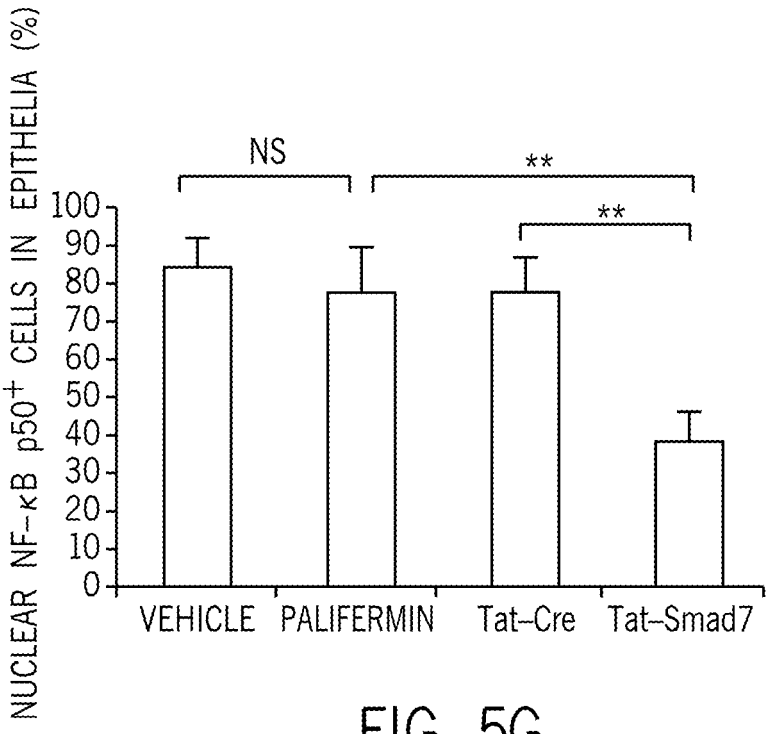

NS
**
**
NUCLEAR NF–κB p50+ CELLS IN EPITHELIA (%)
100
90
80
70
60
50
40
30
20
10
0
VEHICLE
PALIFERMIN
Tat–Cre
Tat–Smad7

FIG. 5G

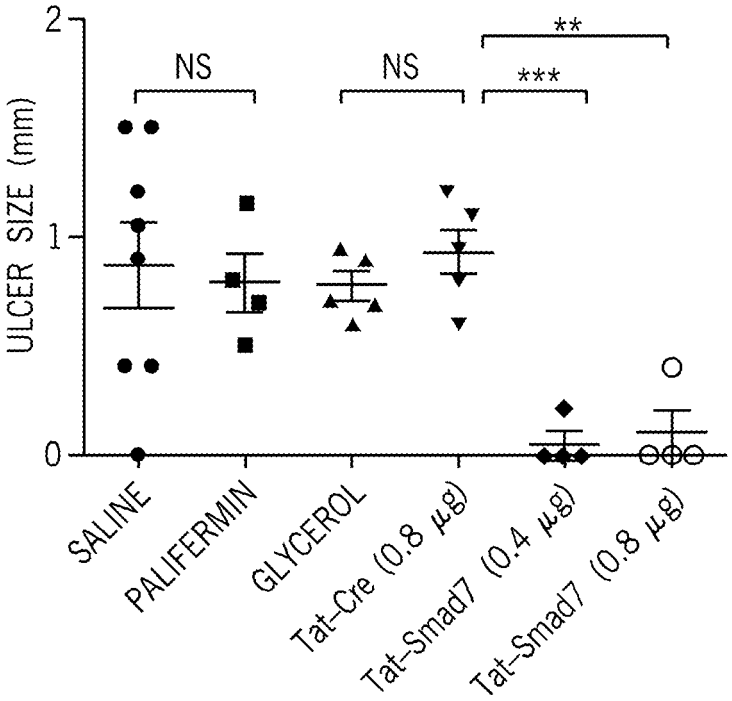

ULCER SIZE (mm)
2
1
0
NS
NS
***
**
SALINE
PALIFERMIN
GLYCEROL
Tat-Cre (0.8 μg)
Tat-Smad7 (0.4 μg)
Tat-Smad7 (0.8 μg)

FIG. 6A

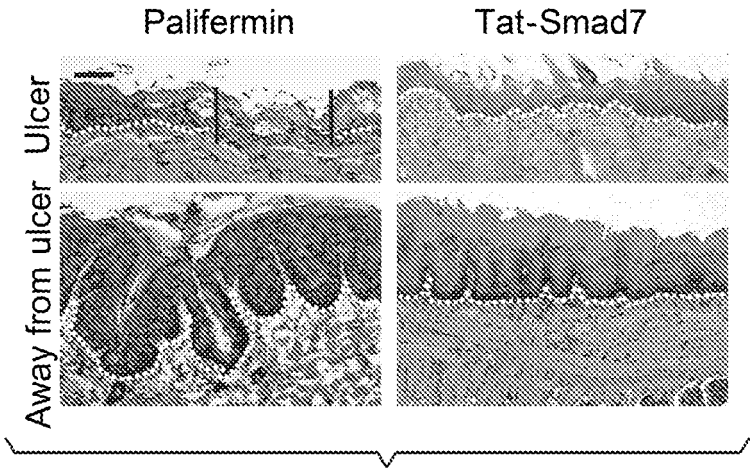

Palifermin
Tat-Smad7
Ulcer
Away from ulcer

FIG. 6B

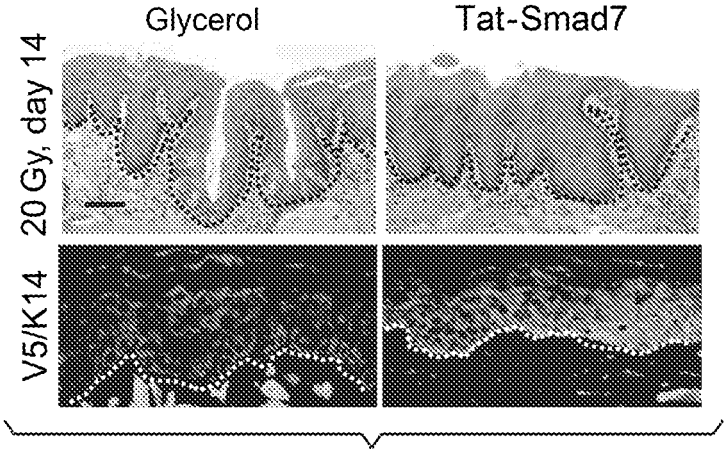

Glycerol
Tat-Smad7
20 Gy, day 14
V5/K14

FIG. 6C

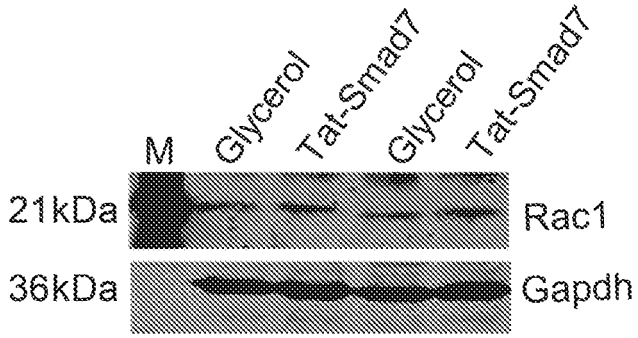

M
Glycerol
Tat-Smad7
Glycerol
Tat-Smad7
21kDa
Rac1
36kDa
Gapdh

FIG. 6D

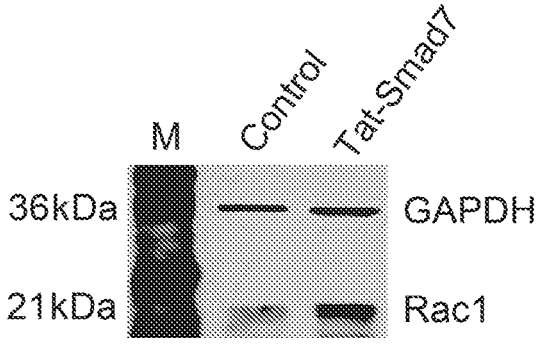

M
Control
Tat-Smad7
36kDa
GAPDH
21kDa
Rac1

FIG. 6E

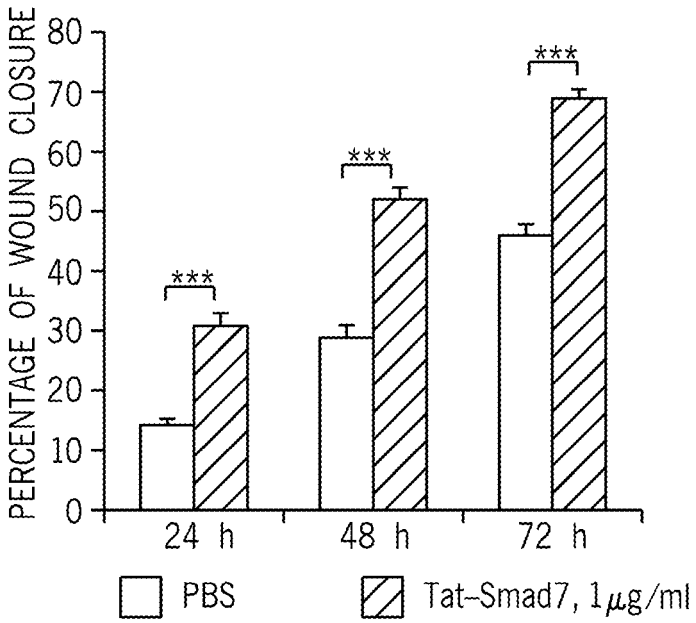

PERCENTAGE OF WOUND CLOSURE
0
10
20
30
40
50
60
70
80
***
***
***
24 h
48 h
72 h
PBS
Tat-Smad7, 1μg/ml

FIG. 6F

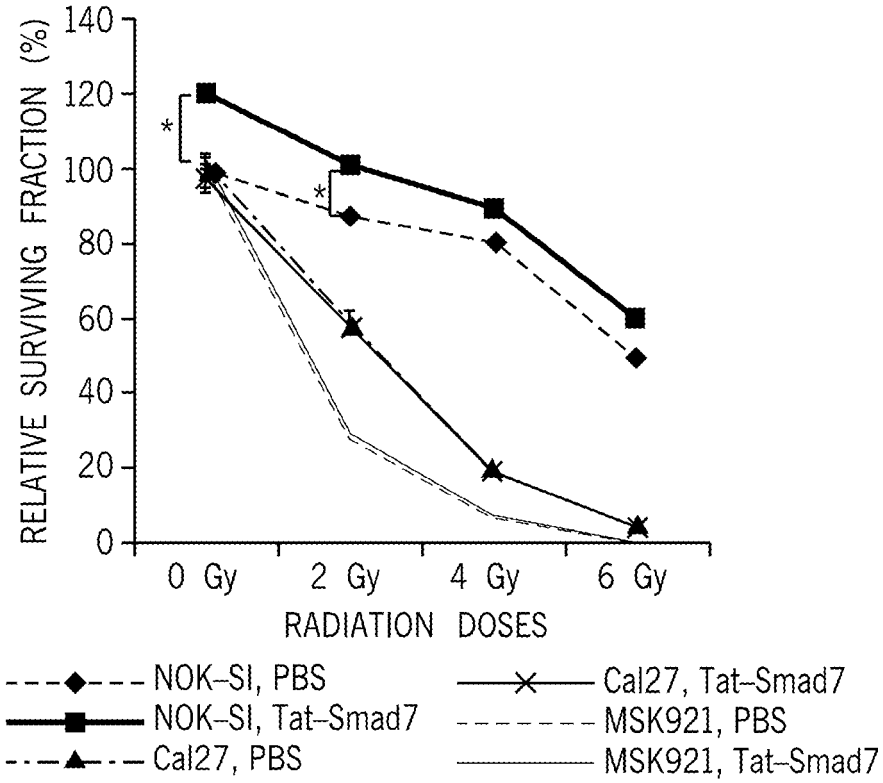

RELATIVE SURVIVING FRACTION (%)
0
20
40
60
80
100
120
140
*
*
0 Gy
2 Gy
4 Gy
6 Gy
RADIATION DOSES
NOK-SI, PBS
NOK-SI, Tat-Smad7
Cal27, PBS
Cal27, Tat-Smad7
MSK921, PBS
MSK921, Tat-Smad7

FIG. 6G

FIG. 7A

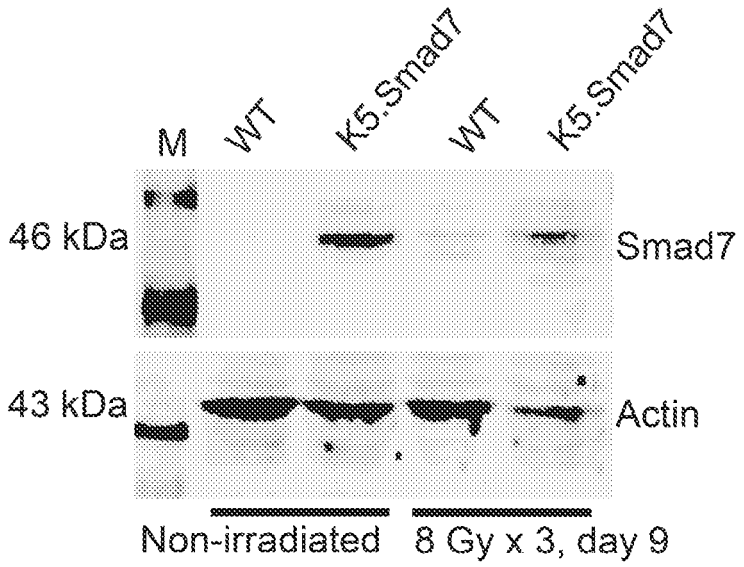


FIG. 7B

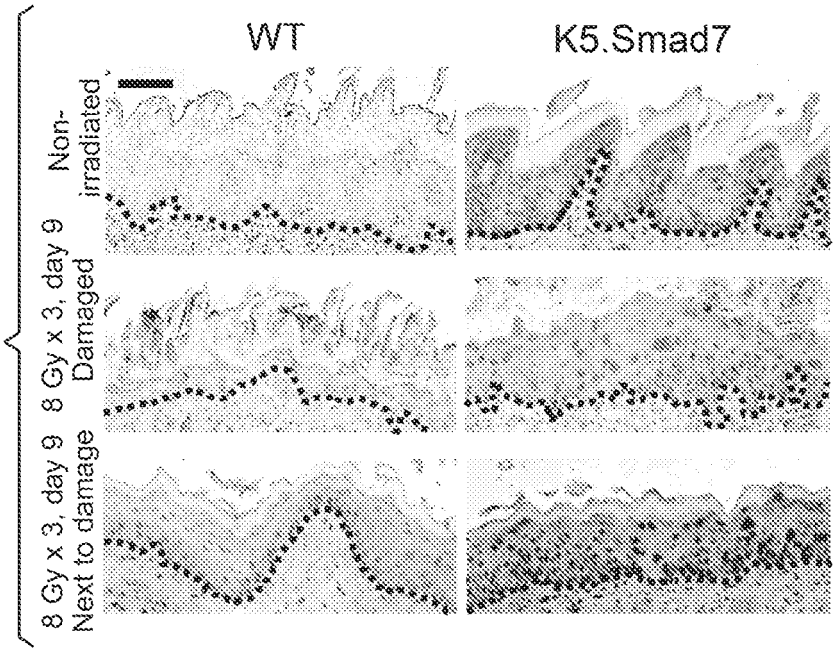
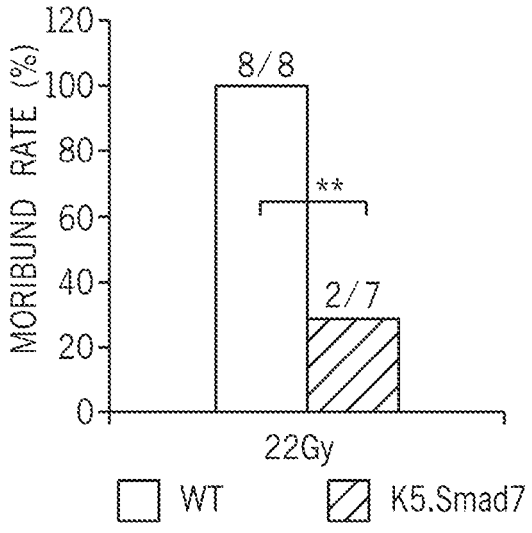


FIG. 7C



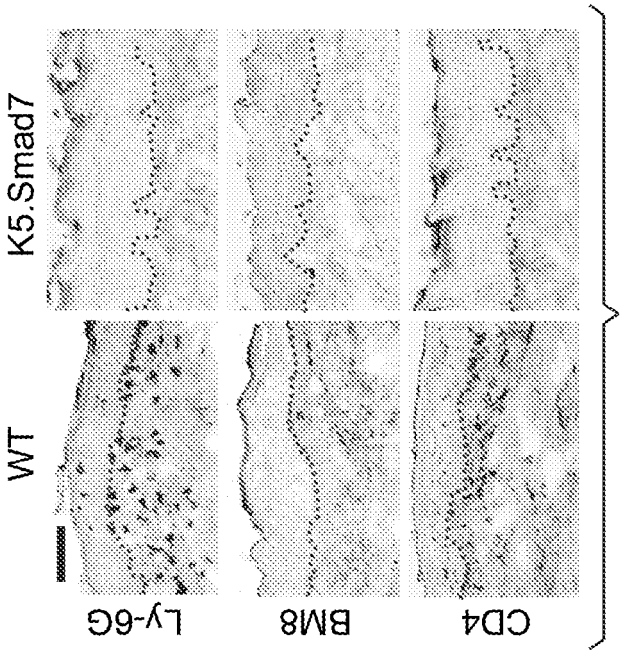

WT
K5.Smad7
Ly-6G
BM8
CD4

FIG. 7D

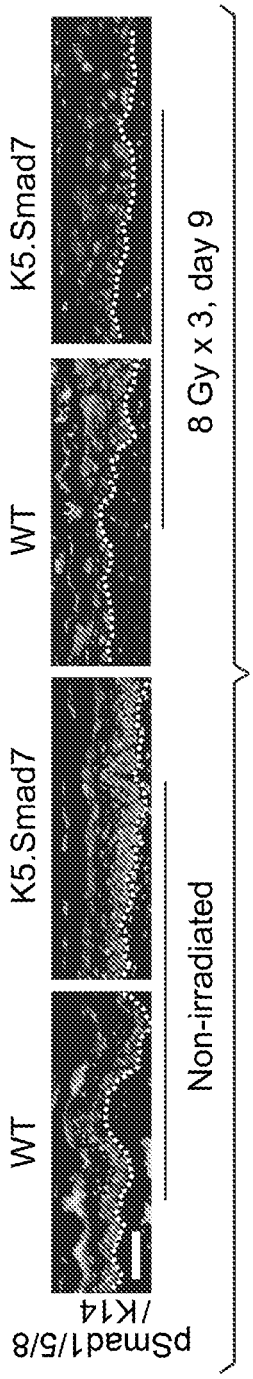

WT
K5.Smad7
WT
K5.Smad7
Non-irradiated
8 Gy x 3, day 9
pSmad1/5/8
/K14

FIG. 7E

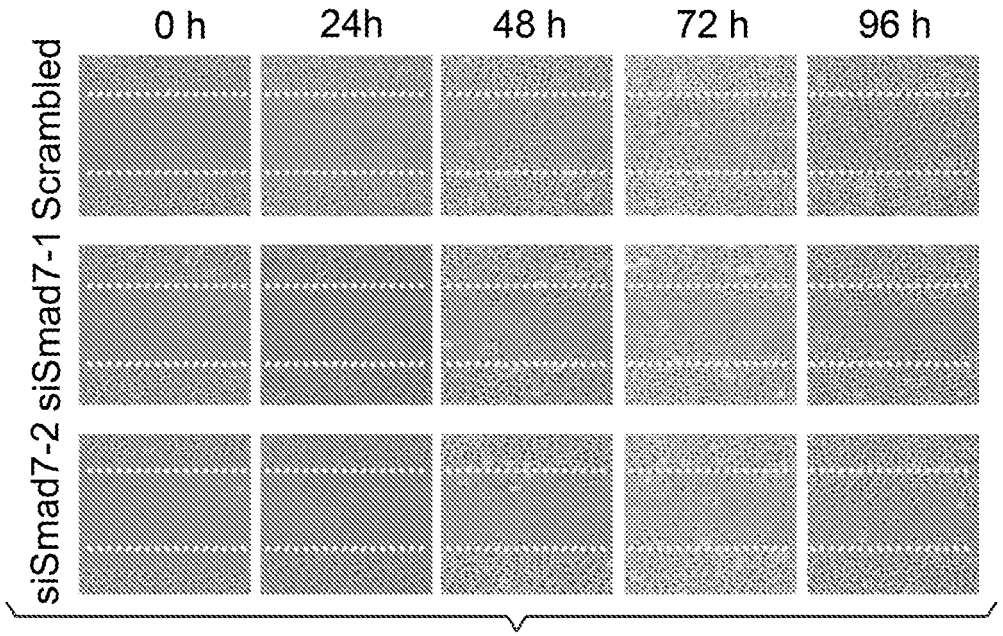

0 h
24h
48 h
72 h
96 h
Scrambled
siSmad7-1
siSmad7-2

FIG. 8A

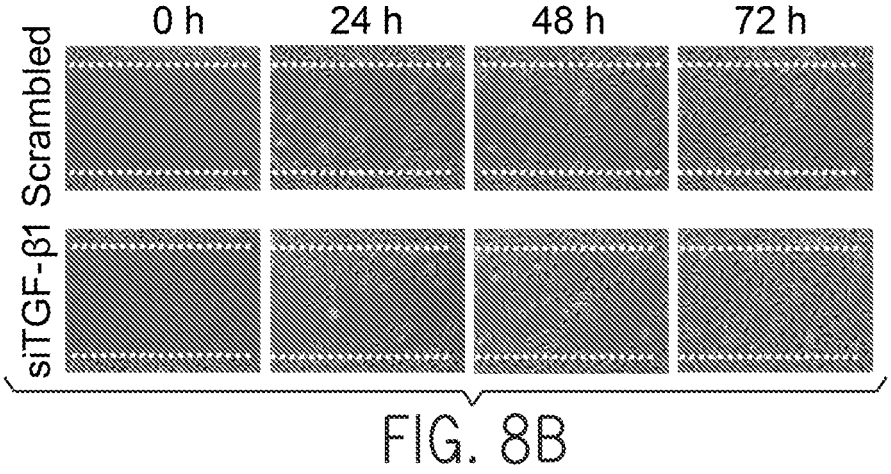

0 h
24 h
48 h
72 h
Scrambled
siTGF-β1

FIG. 8B

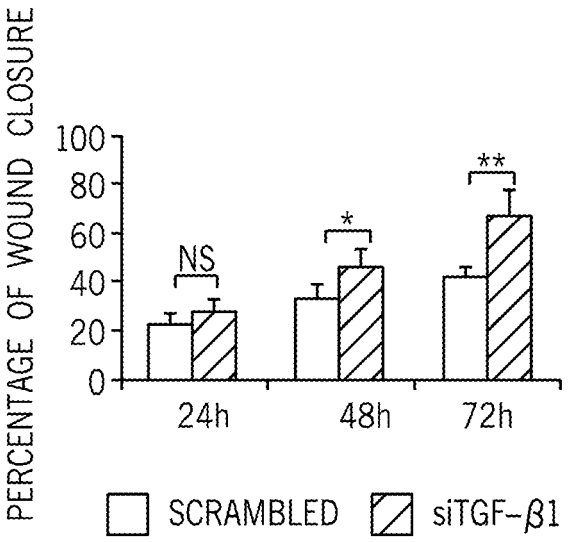

PERCENTAGE OF WOUND CLOSURE
100
80
60
40
20
0
NS
*
**
24h
48h
72h
SCRAMBLED
siTGF-β1

FIG. 8C

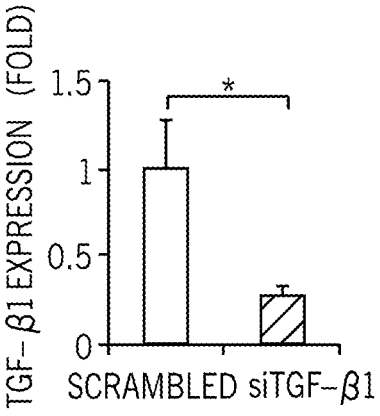

TGF-β1 EXPRESSION (FOLD)
1.5
1
0.5
0
*
SCRAMBLED
siTGF-β1

FIG. 8D

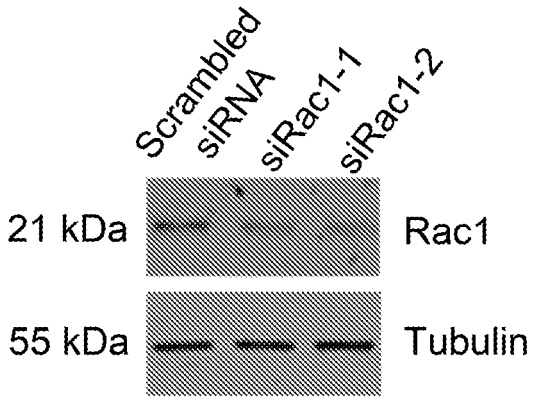

Scrambled siRNA
siRac1-1
siRac1-2
21 kDa
Rac1
55 kDa
Tubulin

FIG. 9A

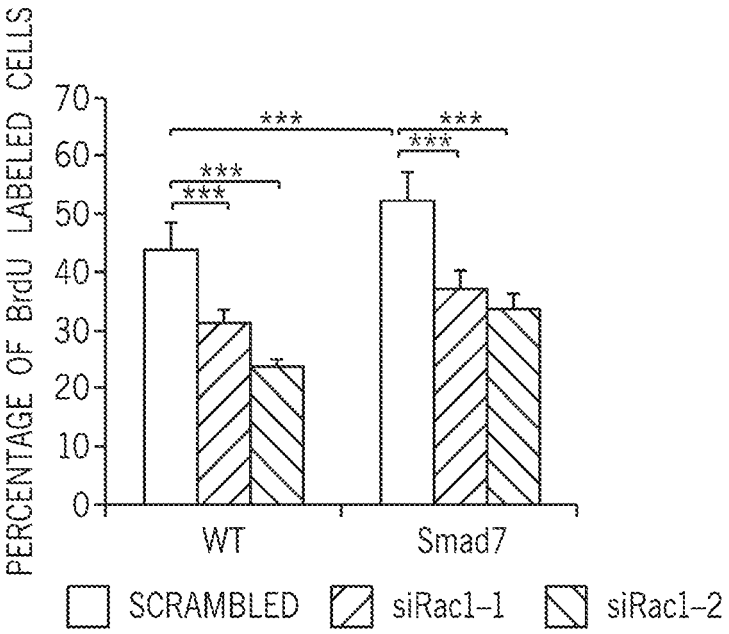

PERCENTAGE OF BrdU LABELED CELLS
70
60
50
40
30
20
10
0
***
***
***
***
***
WT
Smad7
SCRAMBLED
siRac1-1
siRac1-2

FIG. 9B

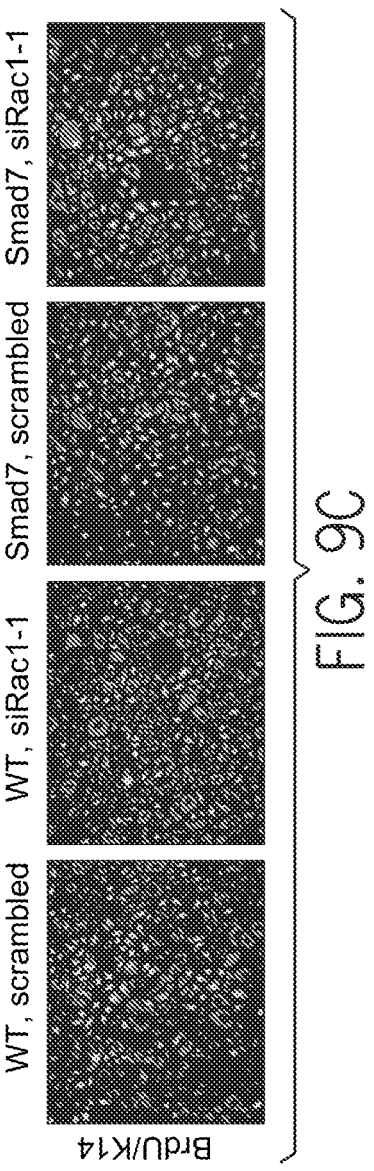

WT, scrambled
WT, siRac1-1
Smad7, scrambled
Smad7, siRac1-1
BrdU/K14

FIG. 9C

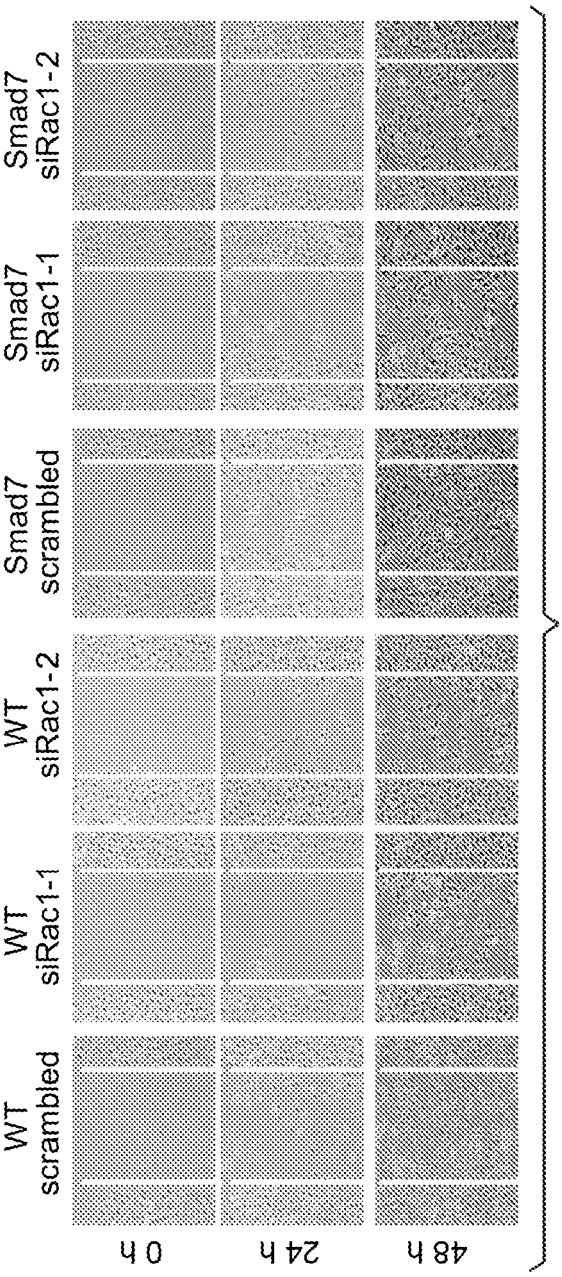

WT scrambled
WT siRac1-1
WT siRac1-2
Smad7 scrambled
Smad7 siRac1-1
Smad7 siRac1-2
0 h
24 h
48 h

FIG. 9D

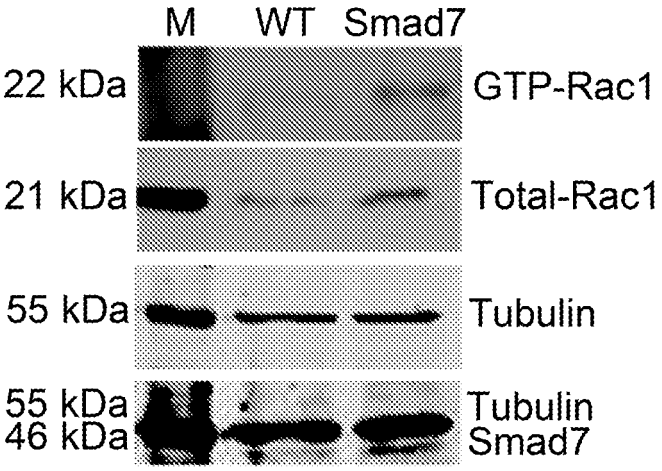


FIG. 10A

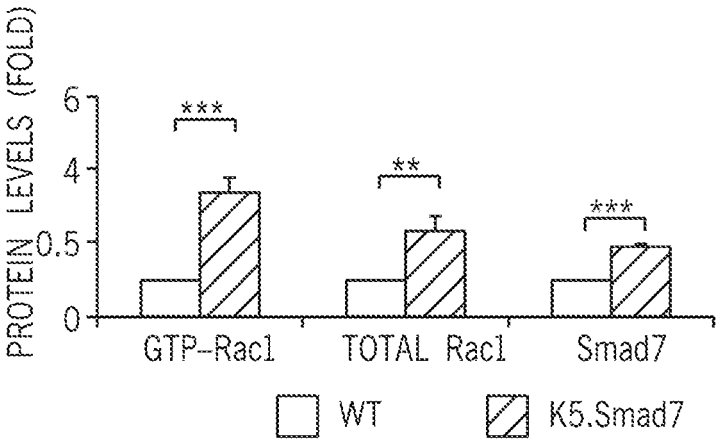


FIG. 10B

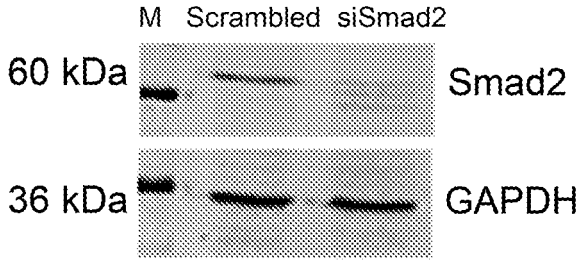


FIG. 10C

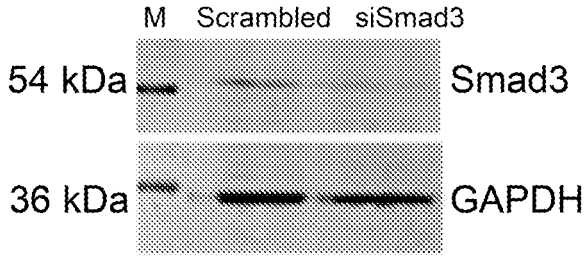


FIG. 10D

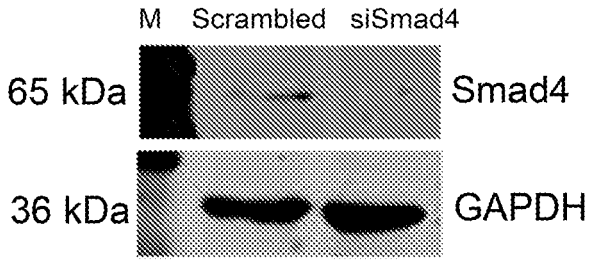


FIG. 10E

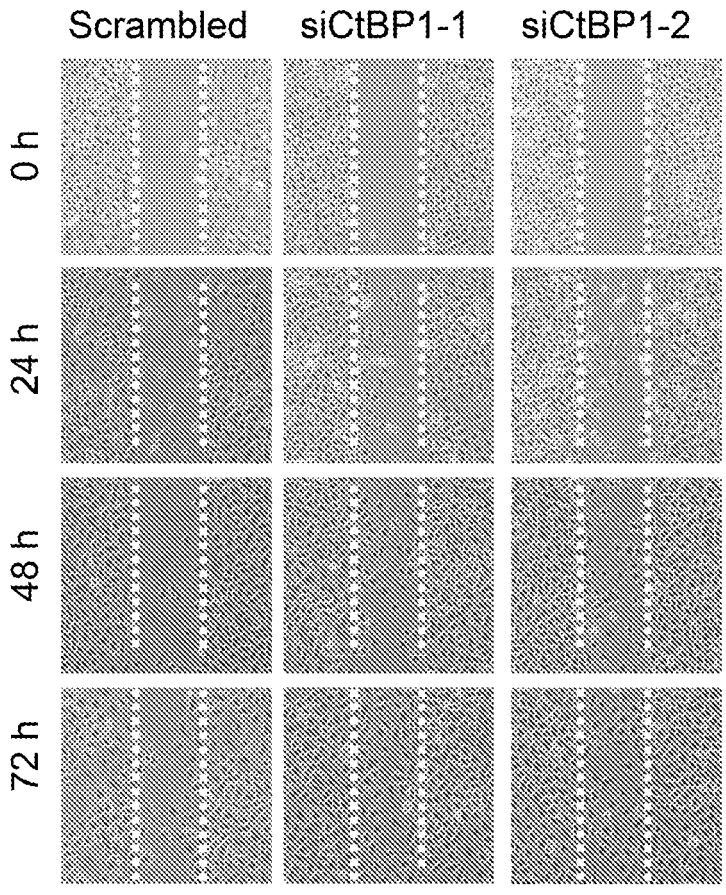


FIG. 10F

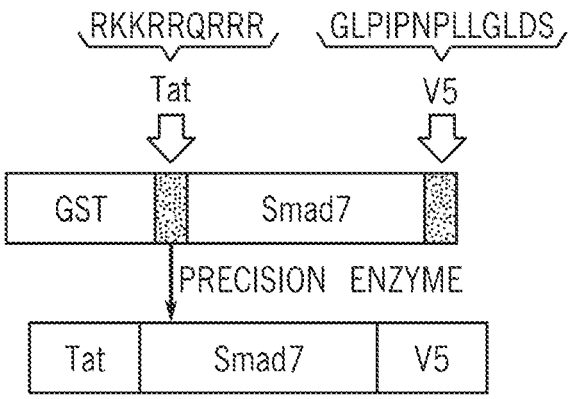


FIG. 11A

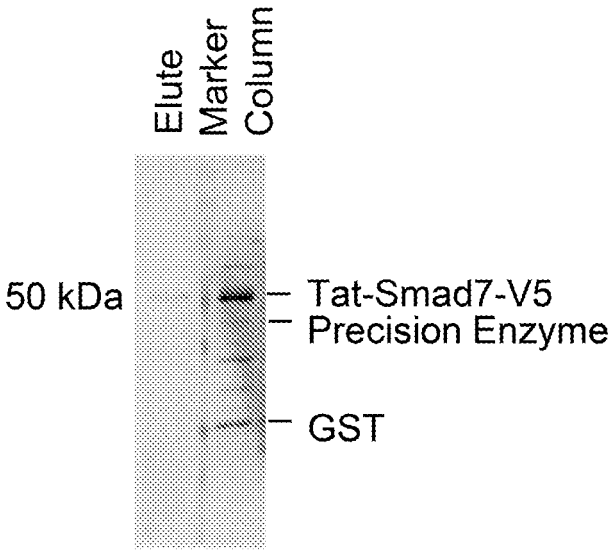


FIG. 11B

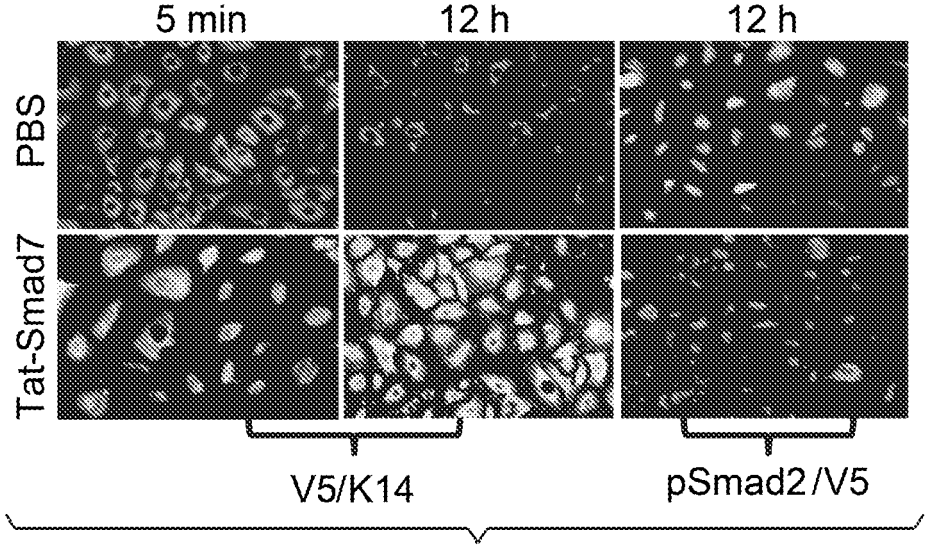


FIG. 11C

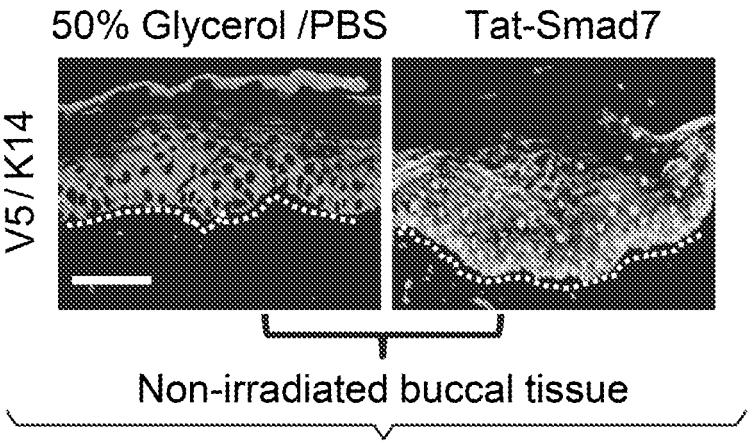


FIG. 11D

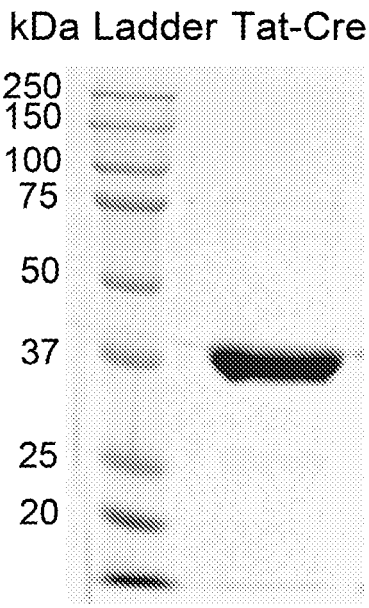


FIG. 11E

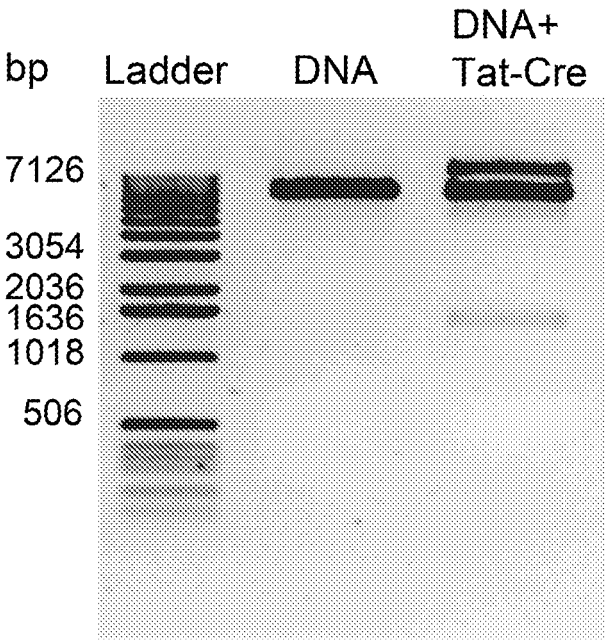
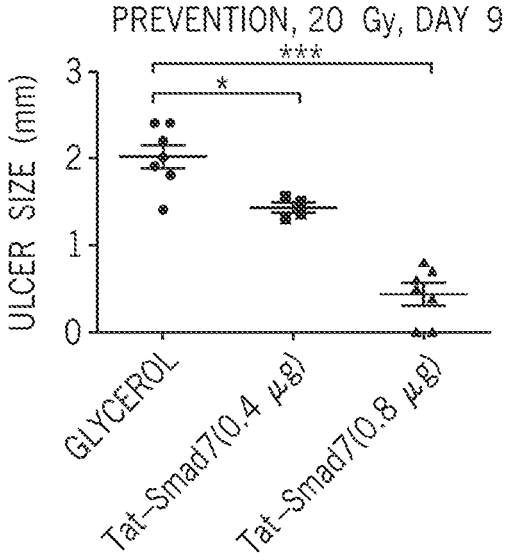


FIG. 11F

FIG. 11G



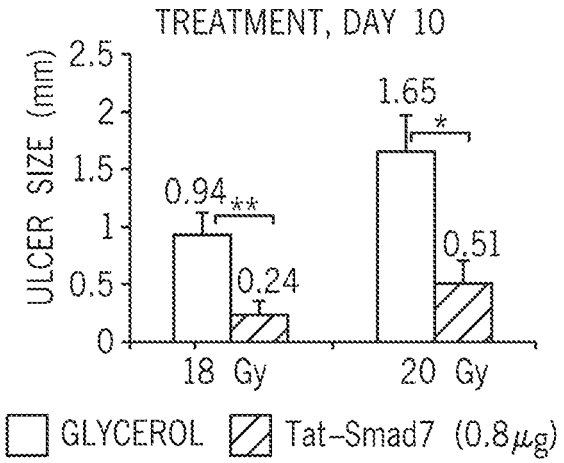


FIG. 12A

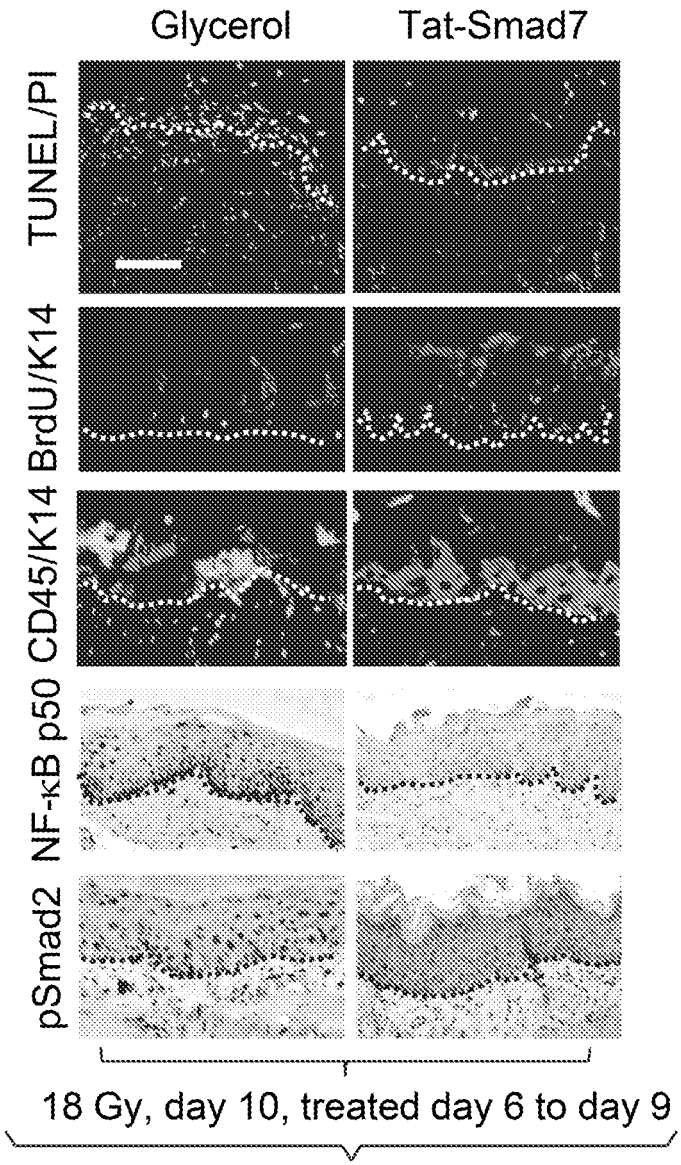


FIG. 12B

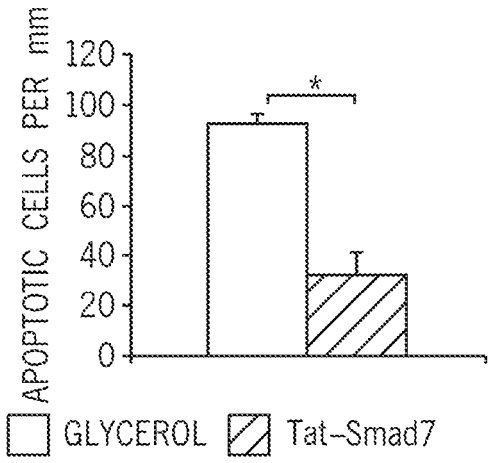


FIG. 12C

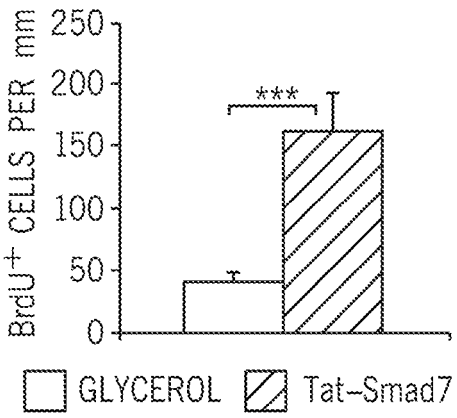


FIG. 12D

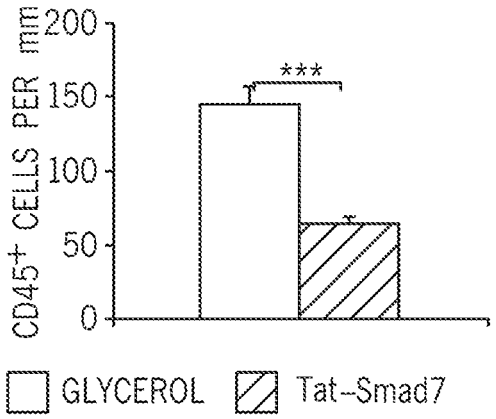


FIG. 12E

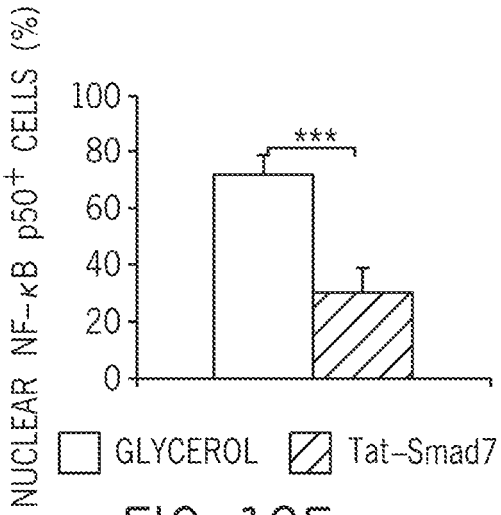


FIG. 12F

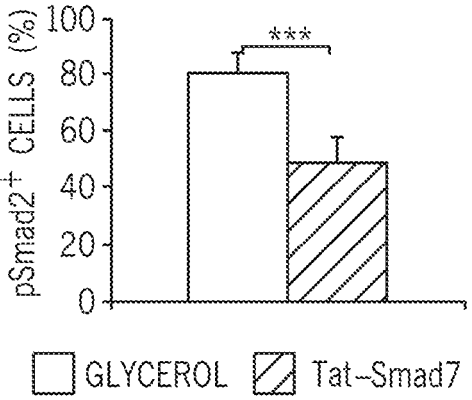


FIG. 12G

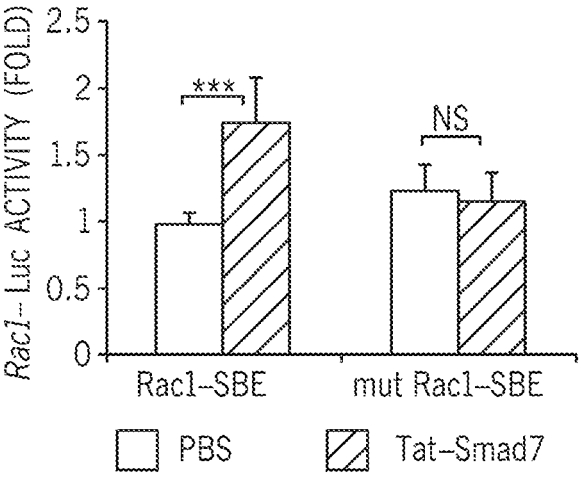


FIG. 12H

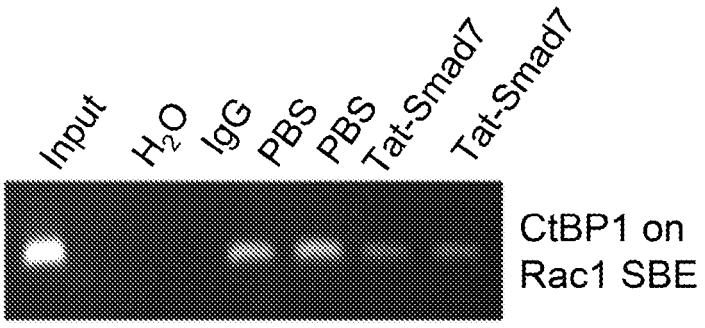


FIG. 12I

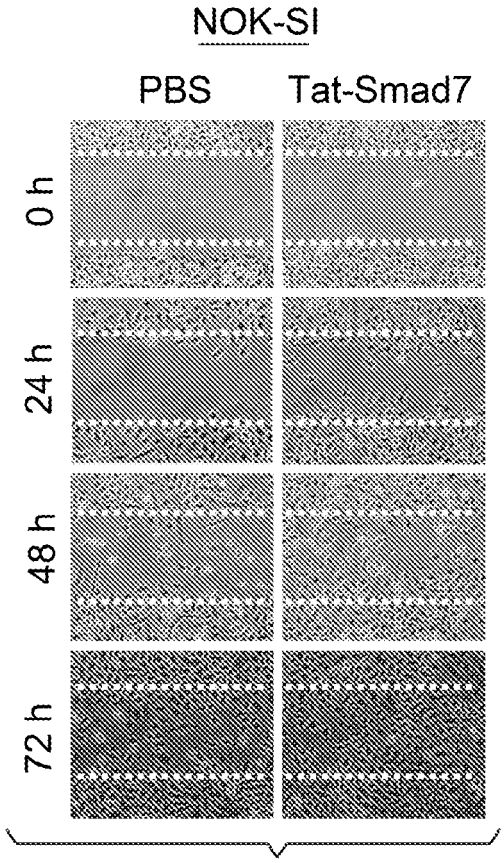


FIG. 13A

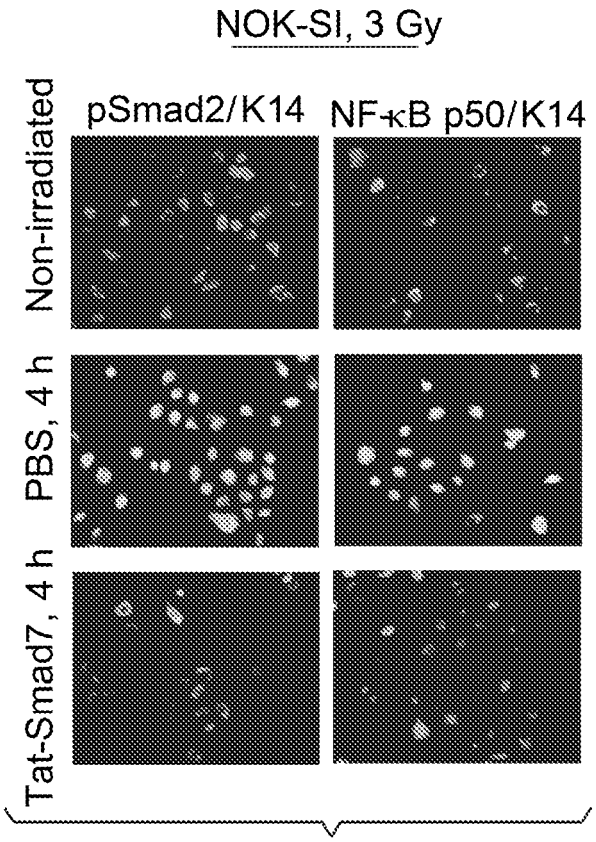


FIG. 13B

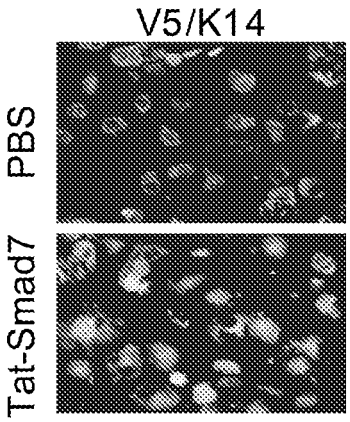


FIG. 13C

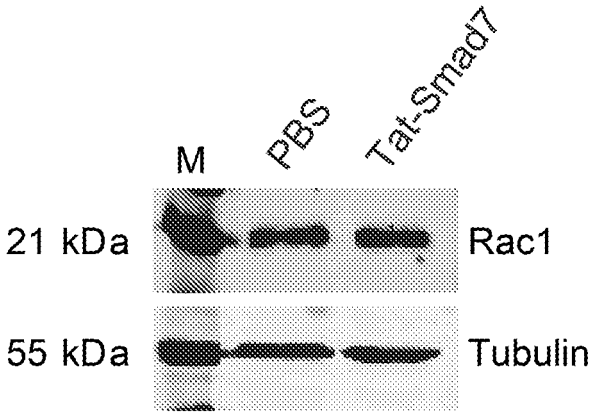


FIG. 13D

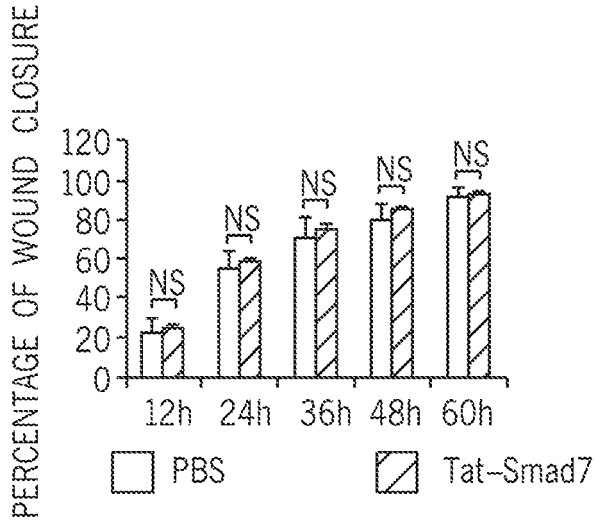


FIG. 13E

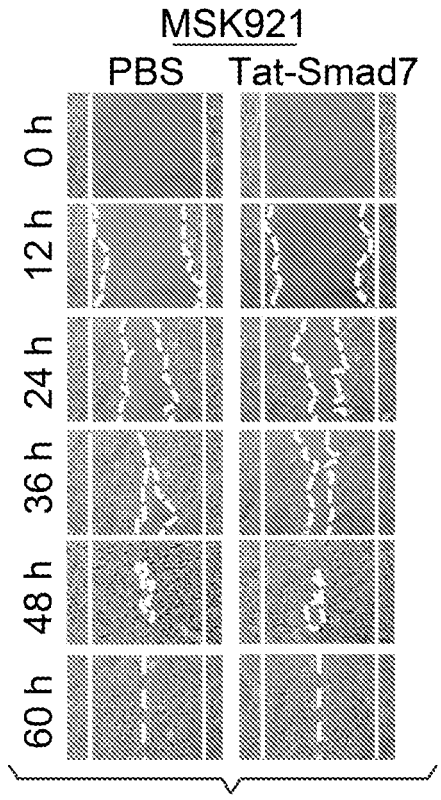


FIG. 13F

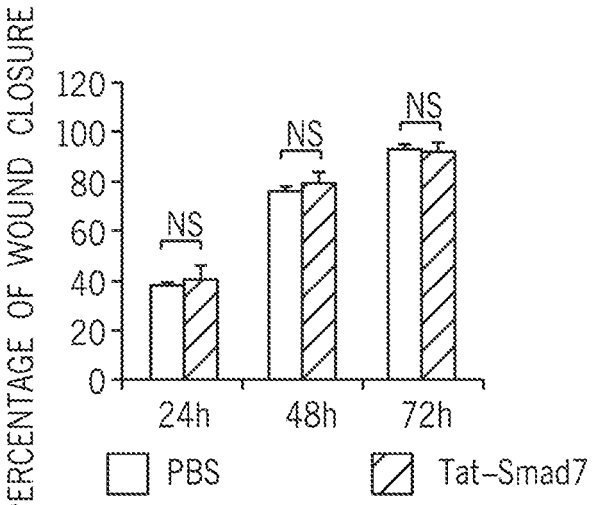


FIG. 13G

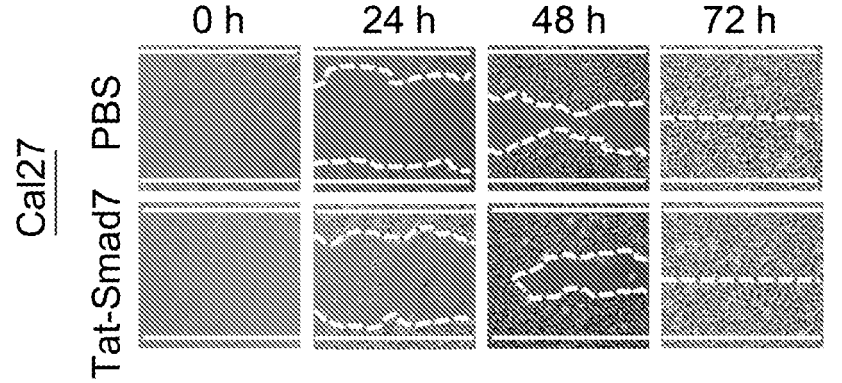


FIG. 13H

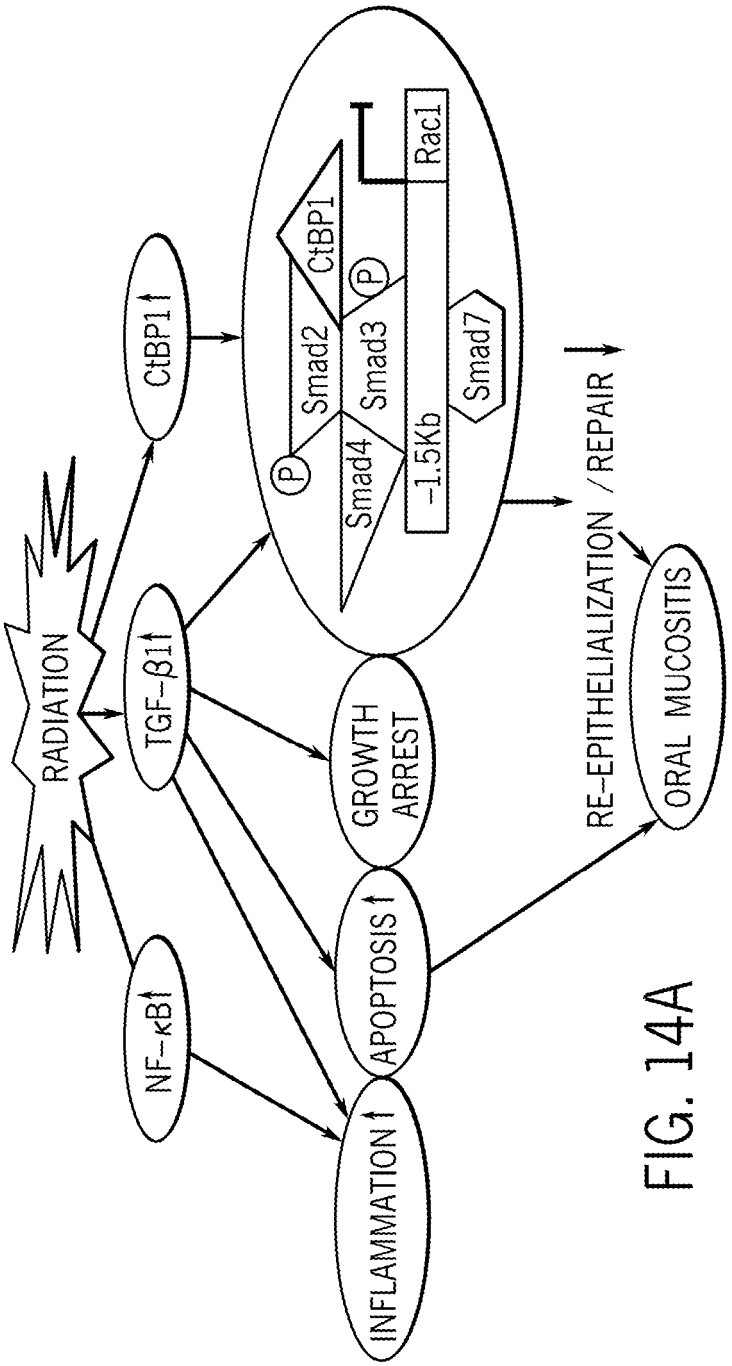

RADIATION
CtBP1↑
TGF-β1↑
NF-κB↑
Smad2
CtBP1
Smad3
Smad4
Smad7
Rac1
-1.5Kb
GROWTH ARREST
APOPTOSIS↑
INFLAMMATION↑
RE-EPITHELIALIZATION / REPAIR
ORAL MUCOSITIS

FIG. 14A

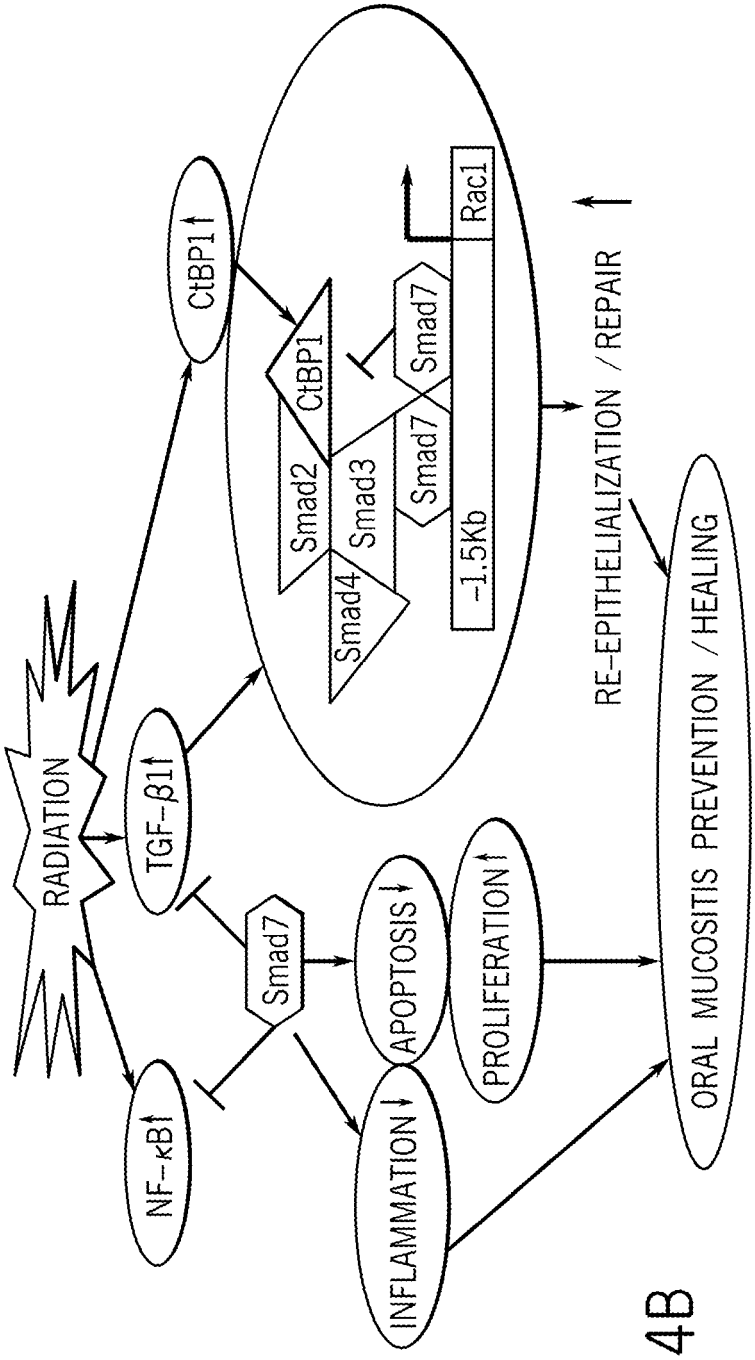

RADIATION
CtBP1↑
TGF-β1↑
NF-κB↑
Smad7
CtBP1
Smad2
Smad3
Smad4
Smad7
Smad7
-1.5Kb
Rac1
APOPTOSIS↓
PROLIFERATION↑
INFLAMMATION↓
RE-EPITHELIALIZATION / REPAIR
ORAL MUCOSITIS PREVENTION / HEALING

FIG. 14B

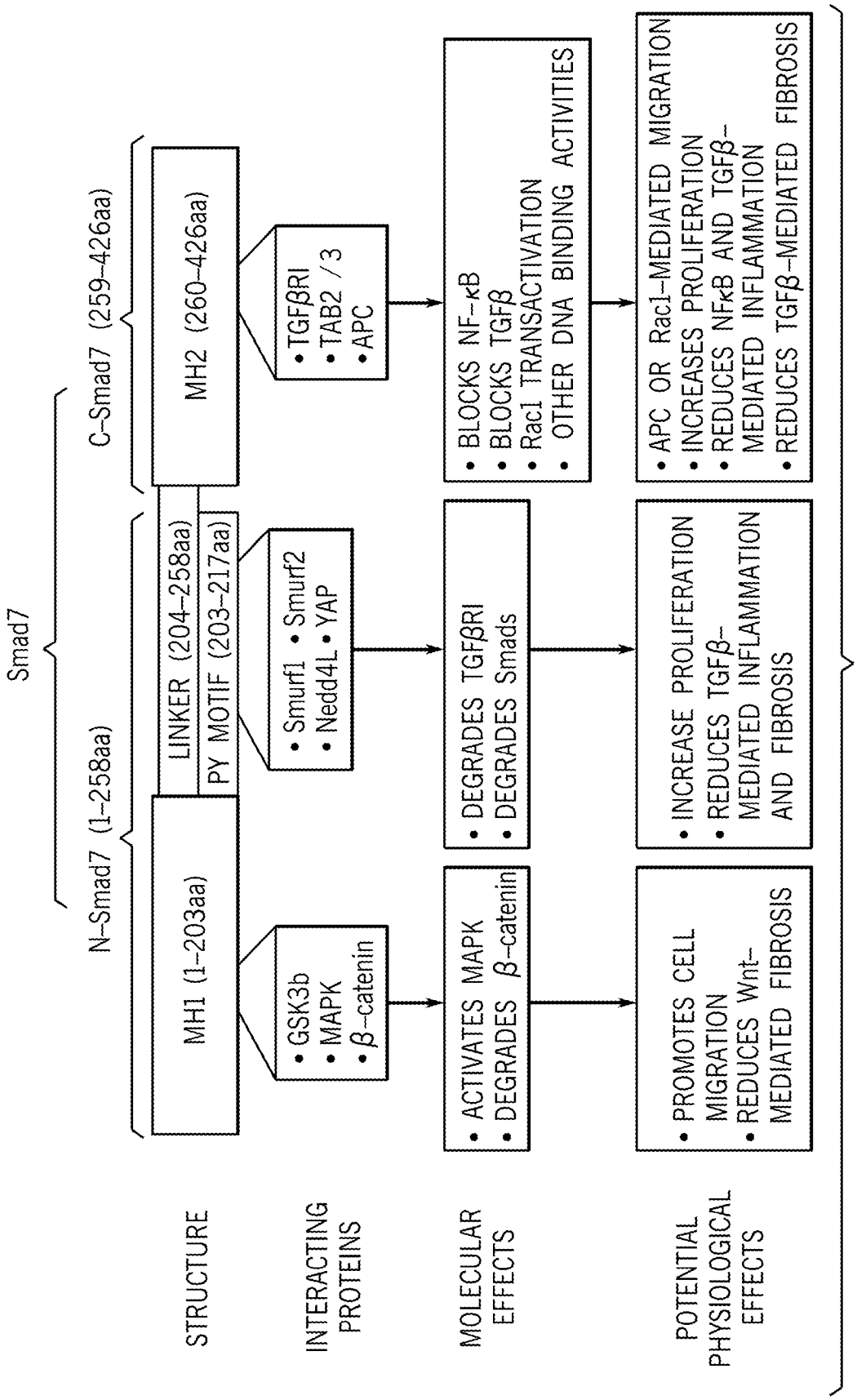

Smad7
N-Smad7 (1-258aa)
C-Smad7 (259-426aa)
MH1 (1-203aa)
LINKER (204-258aa)
PY MOTIF (203-217aa)
MH2 (260-426aa)
• GSK3b
• MAPK
• β-catenin
• Smurf1 • Smurf2
• Nedd4L • YAP
• TGFβRI
• TAB2 / 3
• APC
• ACTIVATES MAPK
• DEGRADES β-catenin
• DEGRADES TGFβRI
• DEGRADES Smads
• BLOCKS NF-κB
• BLOCKS TGFβ
• Rac1 TRANSACTIVATION
• OTHER DNA BINDING ACTIVITIES
• PROMOTES CELL MIGRATION
• REDUCES Wnt-MEDIATED FIBROSIS
• INCREASE PROLIFERATION
• REDUCES TGFβ-MEDIATED INFLAMMATION AND FIBROSIS
• APC OR Rac1-MEDIATED MIGRATION
• INCREASES PROLIFERATION
• REDUCES NFκB AND TGFβ-MEDIATED INFLAMMATION
• REDUCES TGFβ-MEDIATED FIBROSIS
STRUCTURE
INTERACTING PROTEINS
MOLECULAR EFFECTS
POTENTIAL PHYSIOLOGICAL EFFECTS

FIG. 15

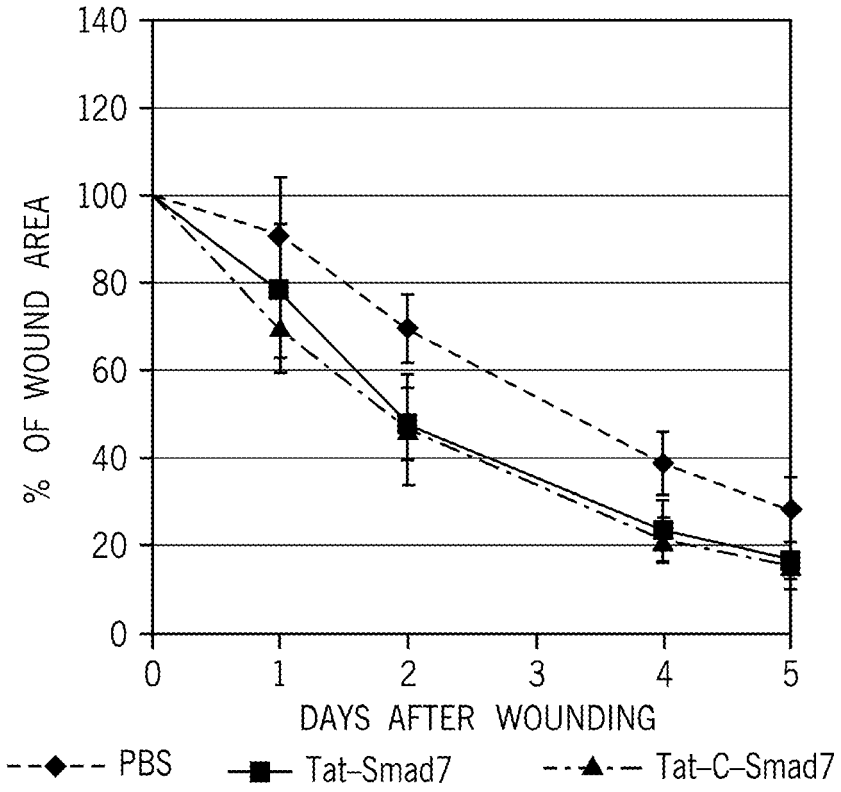


FIG. 16A

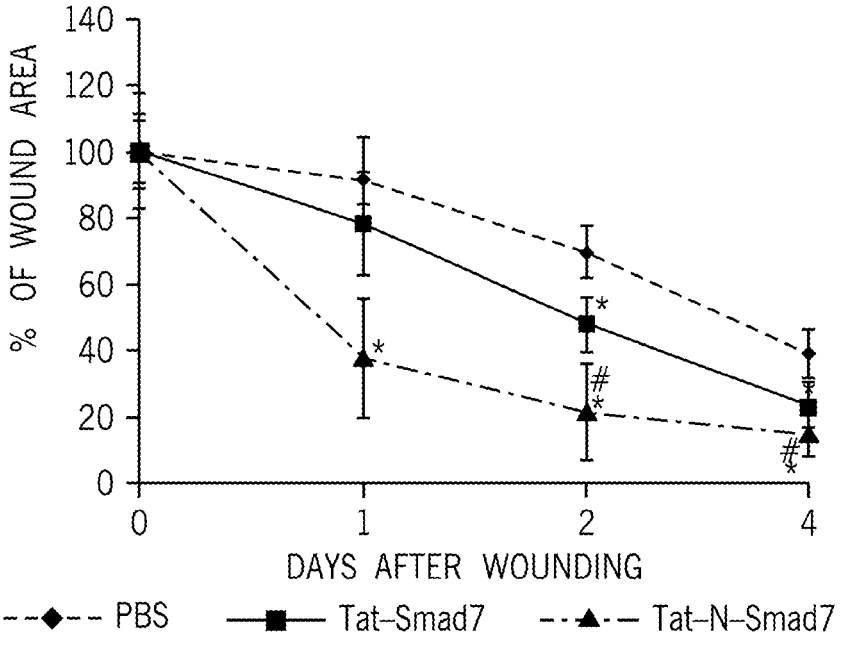


FIG. 16B

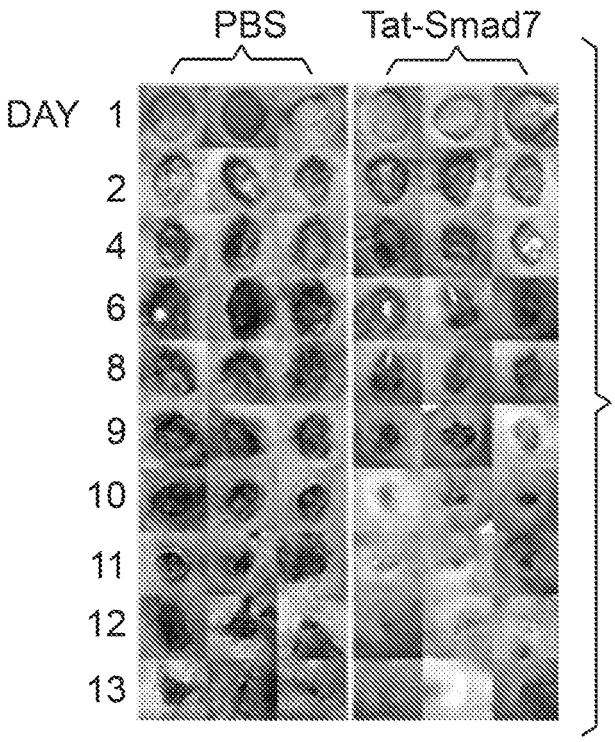


FIG. 17A

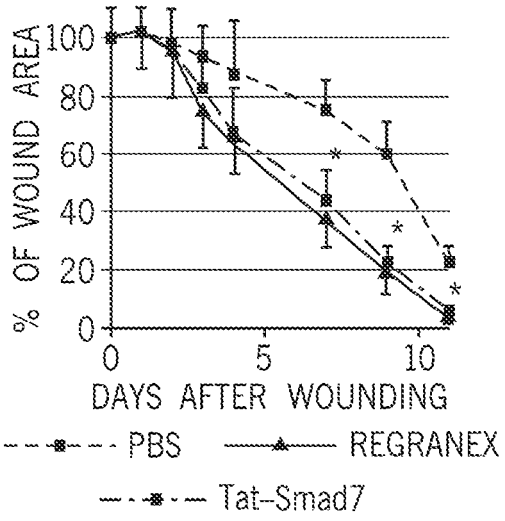


FIG. 17B

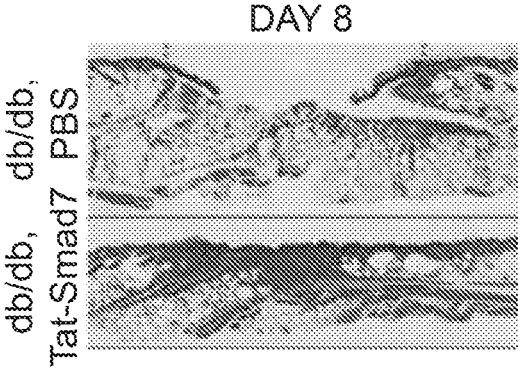


FIG. 17C