FIG. 1

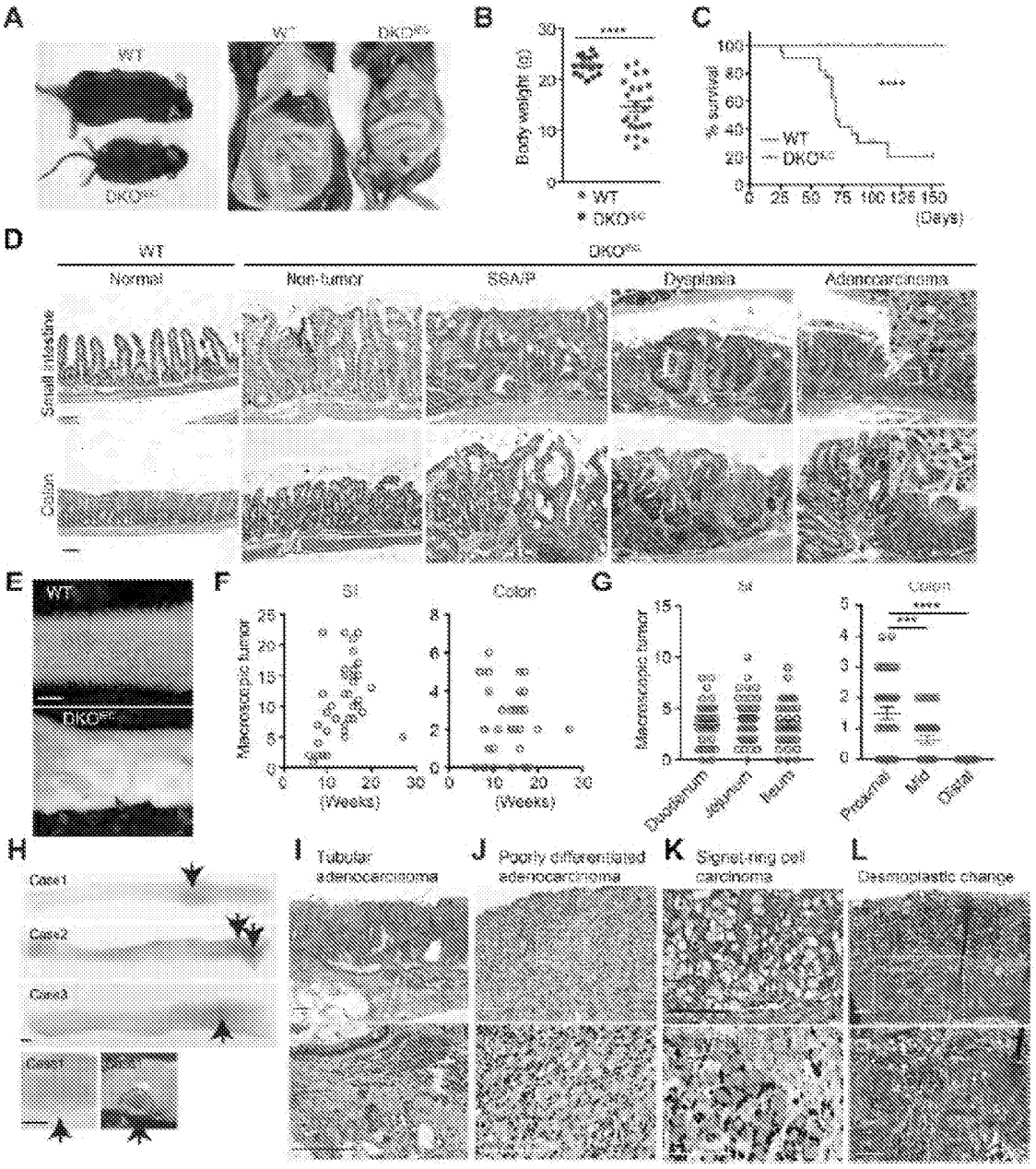
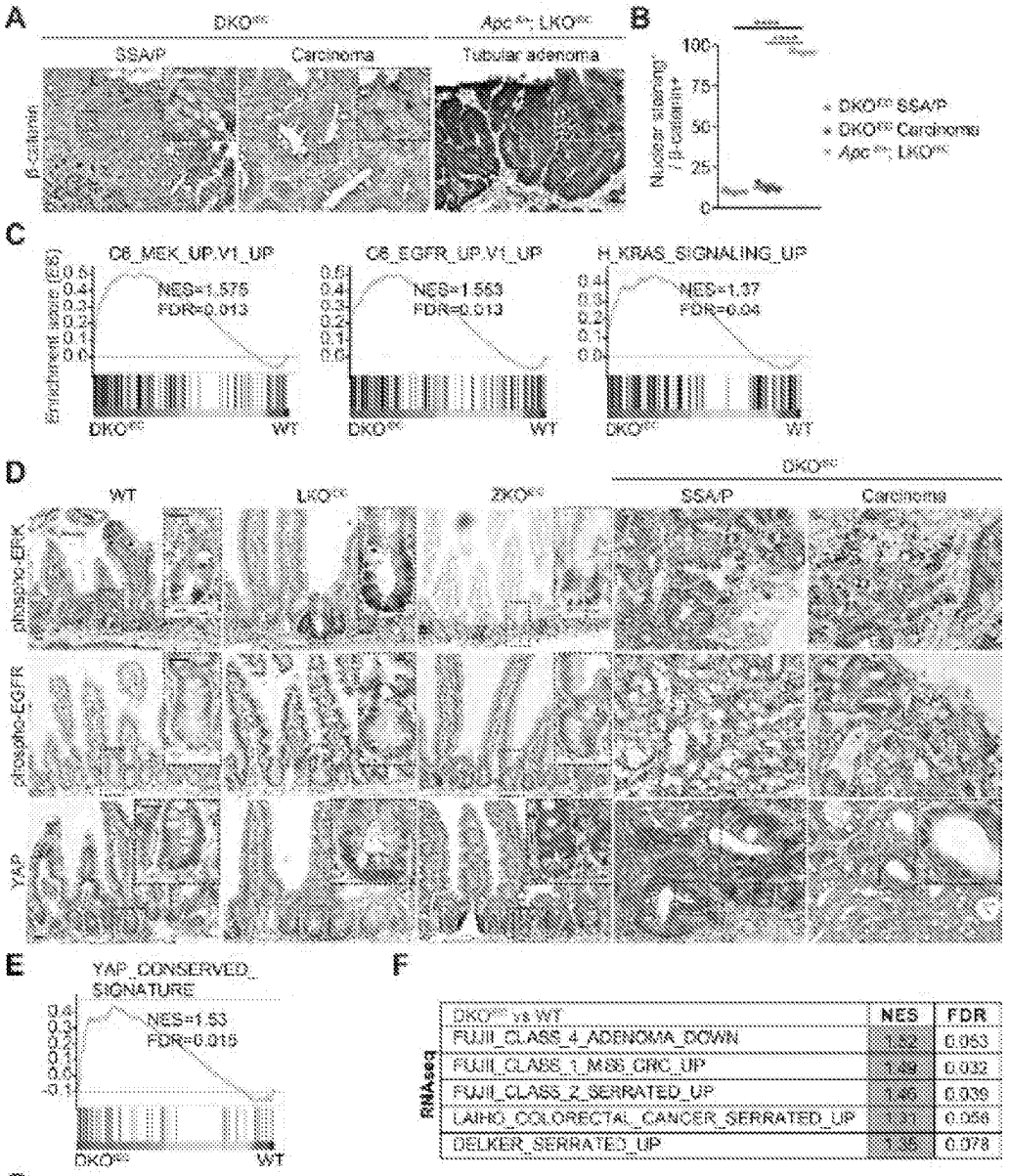

A
WT
DKO
B
Body weight (g)
WT
DKO
C
% survival
WT
DKO
(Days)
D
WT
DKO
Normal
Non-tumor
SSA/P
Dysplasia
Adenocarcinoma
Small intestine
Colon
E
WT
DKO
F
SI
Colon
Macroscopic tumor
(Weeks)
G
SI
Colon
Macroscopic tumor
Duodenum
Jejunum
Ileum
Proximal
Mid
Distal
H
Case1
Case2
Case3
I
Tubular adenocarcinoma
J
Poorly differentiated adenocarcinoma
K
Signet-ring cell carcinoma
L
Desmoplastic change

FIG. 2



F

RNAseq	DKO^IEC vs WT	NES	FDR
	FUJII_CLASS_4_ADENOMA_DOWN	1.52	0.053
	FUJII_CLASS_1_MSS_CRC_UP	1.49	0.032
	FUJII_CLASS_2_SERRATED_UP	1.40	0.039
	LAIHO_COLORECTAL_CANCER_SERRATED_UP	1.31	0.058
	DELKER_SERRATED_UP	1.26	0.078

G

		DKO_SIGNATURE	
Datasets	Comparison	NES	FDR
GSE4045	Serrated vs Conventional CRCs	1.56	<0.001
GSE76987	Sessile serrated (SSP) vs Adenoma polyps (AP)	1.49	<0.001
GSE79460	Sessile serrated (SSA) vs Tubular adenomas (TA)	1.96	<0.001
GSE43841	Sessile serrated adenoma/polyps vs Normal colons	1.36	<0.001
GSE36758	Serrated vs Conventional carcinomas	1.42	0.002
GSE46513	Sessile serrated polyps (SSPs) vs Normal colons	1.43	0.078
GSE45370	Serrated (SA) vs Tubular adenomas (TA)	2.42	0.002

FIG. 3

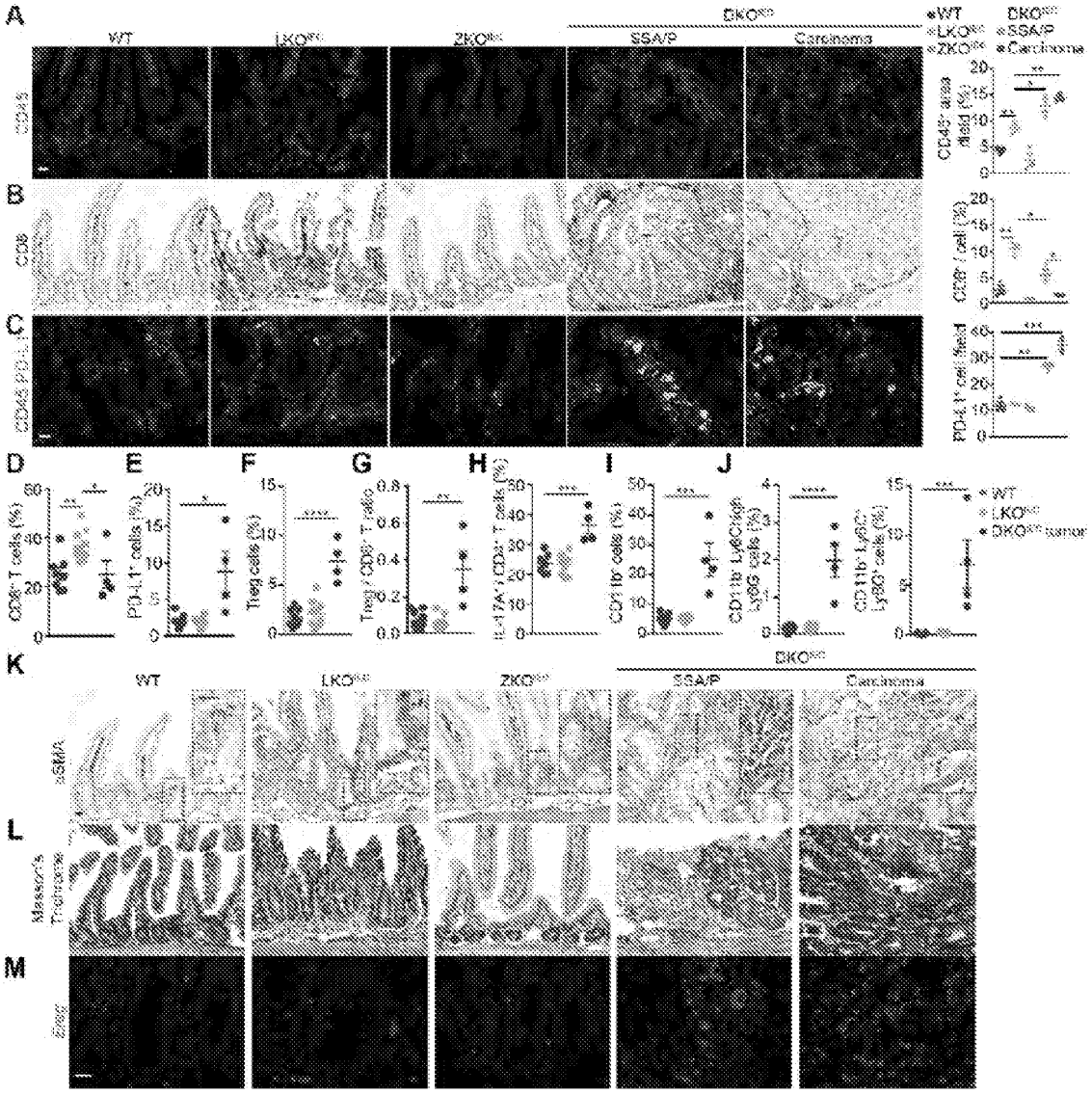

A
WT
LKO
ZKO
DKO
SSA/P
Carcinoma
CD45
B
CD8
C
CD45 PD-L1
D
E
F
G
H
I
J
K
αSMA
L
Masson's Trichrome
M
Ziehl

FIG. 4

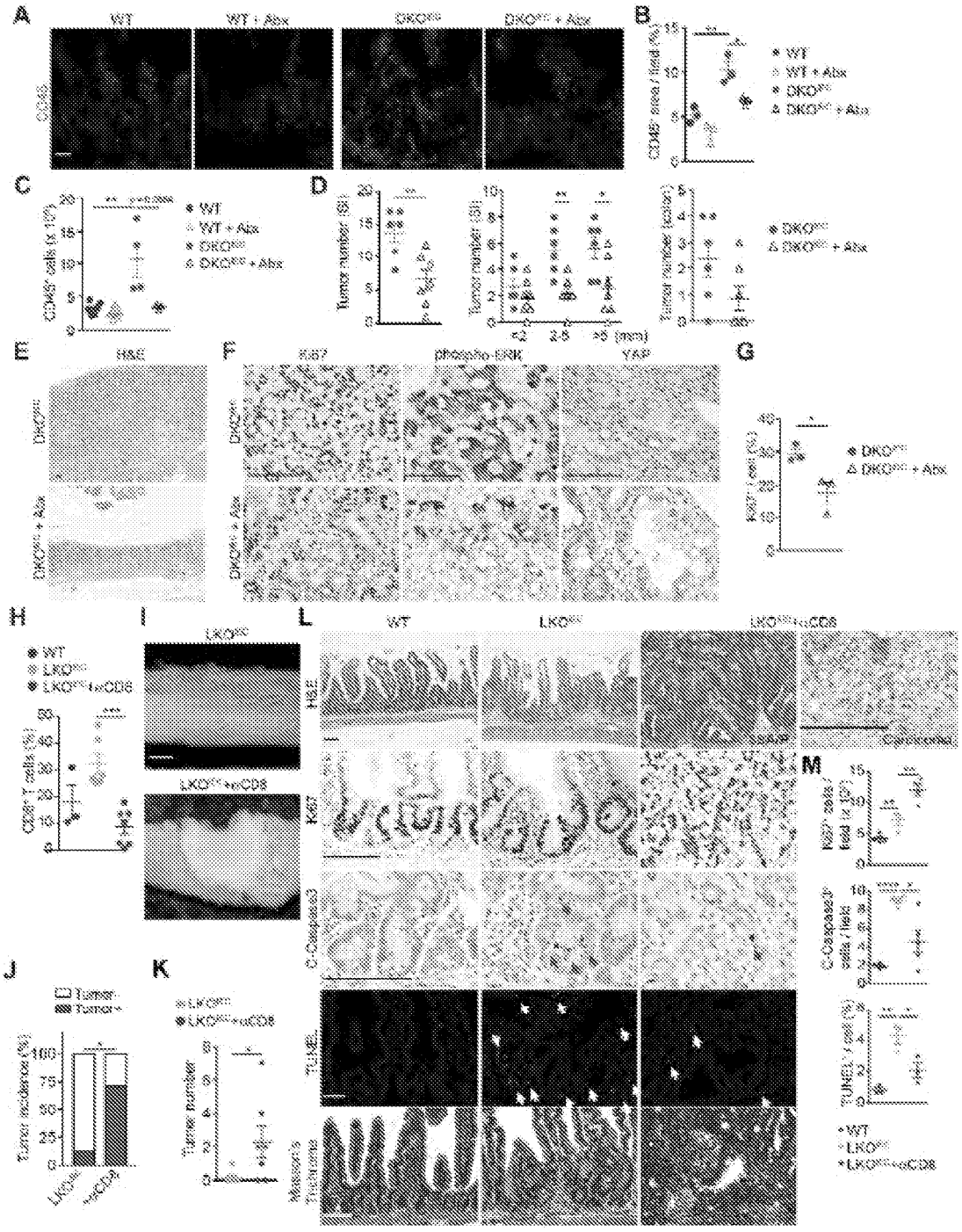

A
WT
WT + Abx
DKO
DKO + Abx
CD8
B
CD8+ area / field (%)
WT
WT + Abx
DKO
DKO + Abx
C
CD8+ cells (x 10⁴)
WT
WT + Abx
DKO
DKO + Abx
D
Tumor number (#)
Tumor number (#)
Tumor number (#)
<2
2-5
>5 (mm)
DKO
DKO + Abx
E
H&E
DKO
DKO + Abx
F
Ki67
phospho-ERK
YAP
DKO
DKO + Abx
G
Ki67+ cells (%)
DKO
DKO + Abx
H
WT
LKO
LKO + αCD8
CD8+ T cells (%)
I
LKO
LKO + αCD8
L
WT
LKO
LKO + αCD8
H&E
Ki67
Cleaved Caspase3
TUNEL
Metastasis
Adenoma
Carcinoma
M
Ki67+ cells / field (%)
C-Caspase3+ cells / field
TUNEL+ cell (%)
WT
LKO
LKO + αCD8
J
Tumor-
Tumor+
Tumor incidence (%)
LKO
LKO + αCD8
K
LKO
LKO + αCD8
Tumor number

FIG. 5

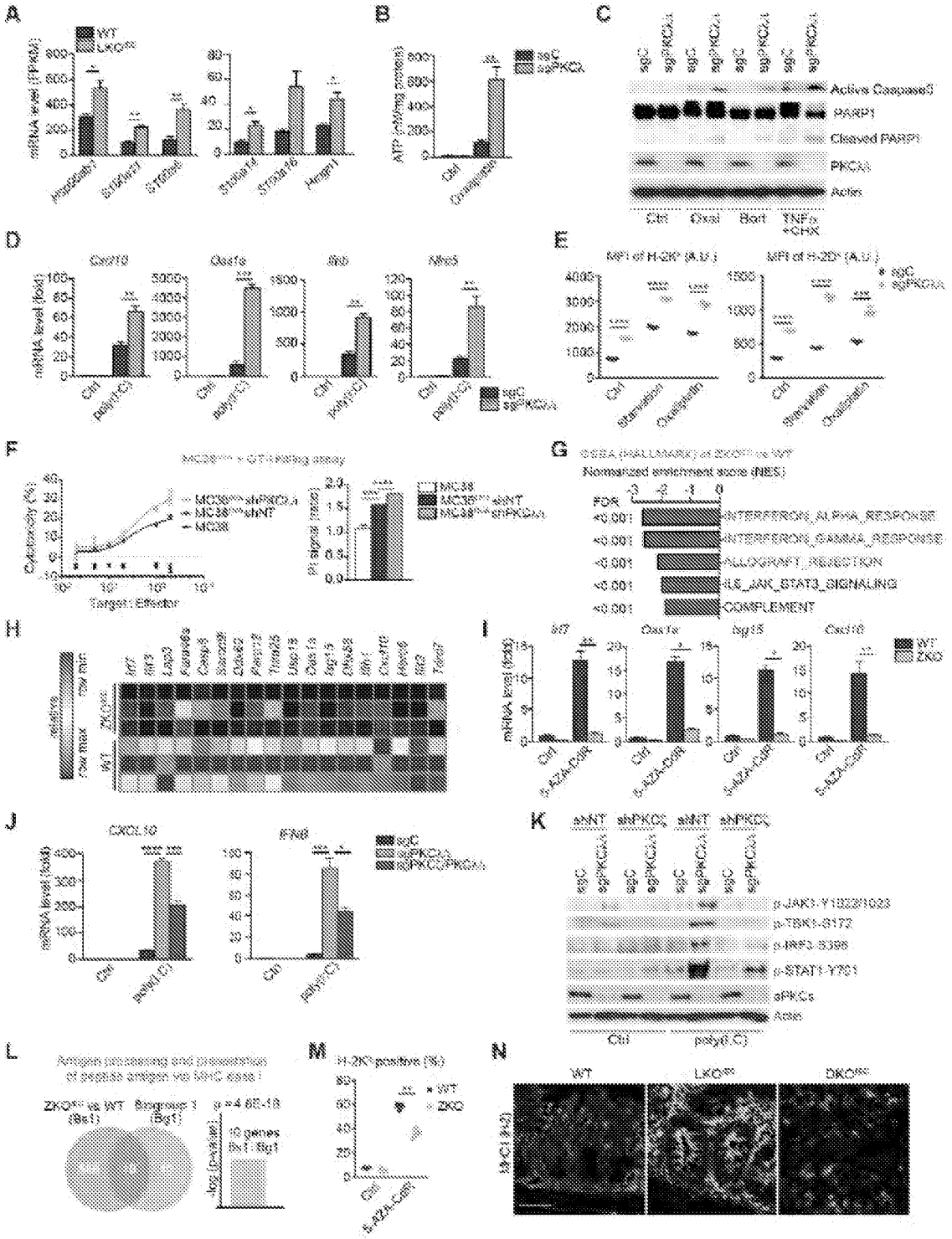

A
WT
LKO
mRNA level (FPKM)
Ifnb1
Cxcl10
Ccl5
Stat1
Stat2
Irf9
B
ATP (nM/mg protein)
siC
siPKCλ
Ctrl
Cisplatin
C
siC
siPKCλ
Active Caspase3
PARP1
Cleaved PARP1
PKCλ
Actin
Ctrl
Oxal
Bort
TNFα +CHX
D
Cxcl10
Cxcl1a
Ifnb
Mki67
mRNA level (fold)
Ctrl
poly(I:C)
siC
siPKCλ
E
MFI of H-2Kb (A.U.)
MFI of H-2Db (A.U.)
Ctrl
Staurosporin
Cisplatin
F
MC38 vs CTL killing assay
Cytotoxicity (%)
Target : Effector
MC38 shPKCλ
MC38 shNT
MC38
PI signal (ratio)
G
Normalized enrichment score (NES)
FDR
<0.001
INTERFERON_ALPHA_RESPONSE
INTERFERON_GAMMA_RESPONSE
ALLOGRAFT_REJECTION
IL6_JAK_STAT3_SIGNALING
COMPLEMENT
H
Row min
Row max
ZKO
WT
I
Ifnb
Cxcl1a
Isg15
Cxcl10
mRNA level (fold)
WT
ZKO
Ctrl
5-AZA-CdR
J
CXCL10
IFNβ
mRNA level (fold)
siC
siPKCλ
siPKCλ+PKCλ
Ctrl
poly(I:C)
K
shNT
shPKCλ
siC
siPKCλ
p-JAK1-Y1022/1023
p-TBK1-S172
p-IRF3-S396
p-STAT1-Y701
shPKCλ
Actin
Ctrl
poly(I:C)
L
Antigen processing and presentation of peptide antigen via MHC class I
ZKO vs WT
Bin genes (Bin1)
Bin genes (Bin3)
p = 4.6E-18
10 genes
Bin1 Bin3
Log2 (p-value)
M
H-2Kb positive (%)
WT
ZKO
Ctrl
5-AZA-CdR
N
WT
LKO
DKO
19-CI (HU)

FIG. 6

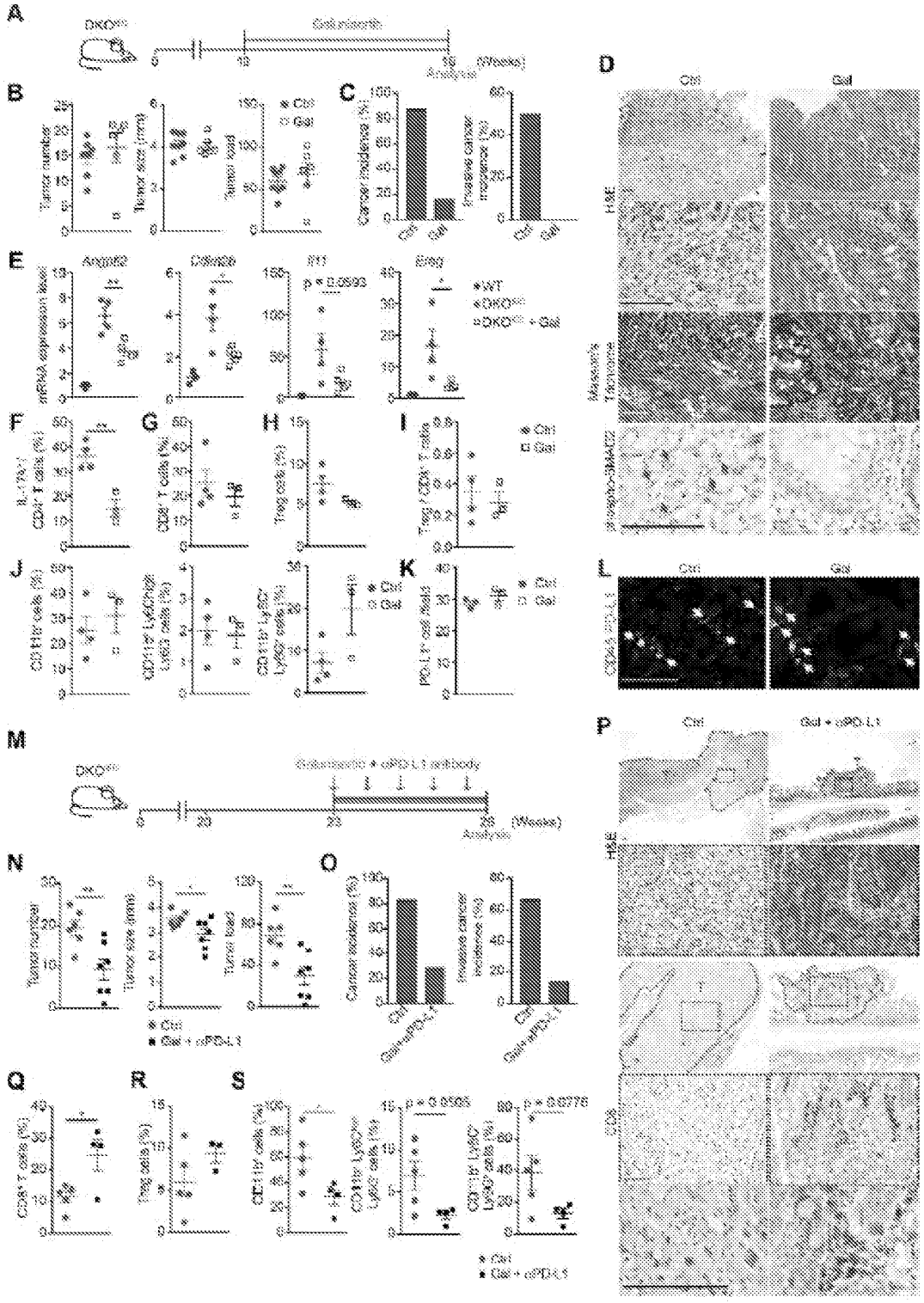

A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
Q
R
S
Ctrl
Gal
Gal + αPD-L1
H&E
Masson's Trichrome
β-catenin/DAPI
CD4/CD8
CD8
WT
DKO
DKO + Gal

FIG. 7

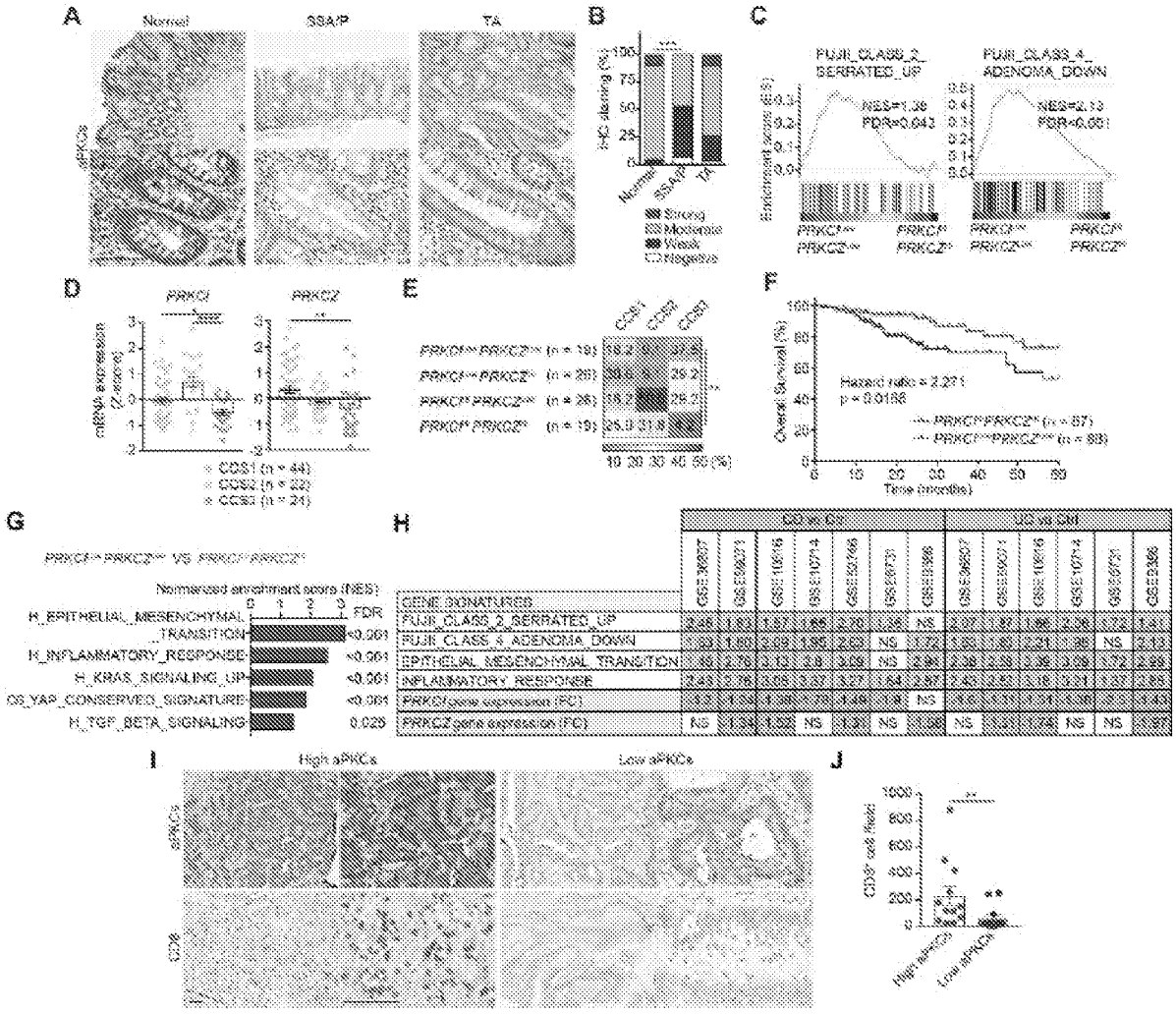

A
Normal
SSA/P
TA
aPKCs
B
IHC staining (%)
Normal
SSA/P
TA
Strong
Moderate
Weak
Negative
C
FUJI_CLASS_2_SERRATED_UP
NES=1.36
FDR=0.043
FUJI_CLASS_4_ADENOMA_DOWN
NES=2.13
FDR<0.001
Enrichment score (ES)
PRKCI^low PRKCZ^low
PRKCI^high PRKCZ^high
D
PRKCI
PRKCZ
mRNA expression (Z-score)
CCS1 (n = 44)
CCS2 (n = 22)
CCS3 (n = 24)
E
CCS1
CCS2
CCS3
PRKCI^low PRKCZ^low (n = 18)
PRKCI^low PRKCZ^high (n = 26)
PRKCI^high PRKCZ^low (n = 26)
PRKCI^high PRKCZ^high (n = 19)
18.2
0
37.8
38.5
0
25.2
18.2
28.2
25.9
31.8
0
10 20 30 40 50 (%)
F
Overall Survival (%)
Hazard ratio = 2.271
p = 0.0156
PRKCI^high PRKCZ^high (n = 67)
PRKCI^low PRKCZ^low (n = 69)
Time (months)
G
PRKCI^low PRKCZ^low VS PRKCI^high PRKCZ^high
Normalized enrichment score (NES)
H_EPITHELIAL_MESENCHYMAL_TRANSITION
H_INFLAMMATORY_RESPONSE
H_KRAS_SIGNALING_UP
GS_YAP_CONSERVED_SIGNATURE
H_TGF_BETA_SIGNALING
FDR
<0.001
<0.001
<0.001
0.029
H
CCS1 vs CCS2
CCS1 vs CCS3
GSE39582
GSE39084
GSE10846
GSE31731-4
GSE16515
GSE5364
GENE SIGNATURES
FUJI_CLASS_2_SERRATED_UP
FUJI_CLASS_4_ADENOMA_DOWN
EPITHELIAL_MESENCHYMAL_TRANSITION
INFLAMMATORY_RESPONSE
PRKCI gene expression (FC)
PRKCZ gene expression (FC)
NS
I
High aPKCs
Low aPKCs
aPKCs
CD8
J
CD8+ cell /field
High aPKCs
Low aPKCs

FIG. 8

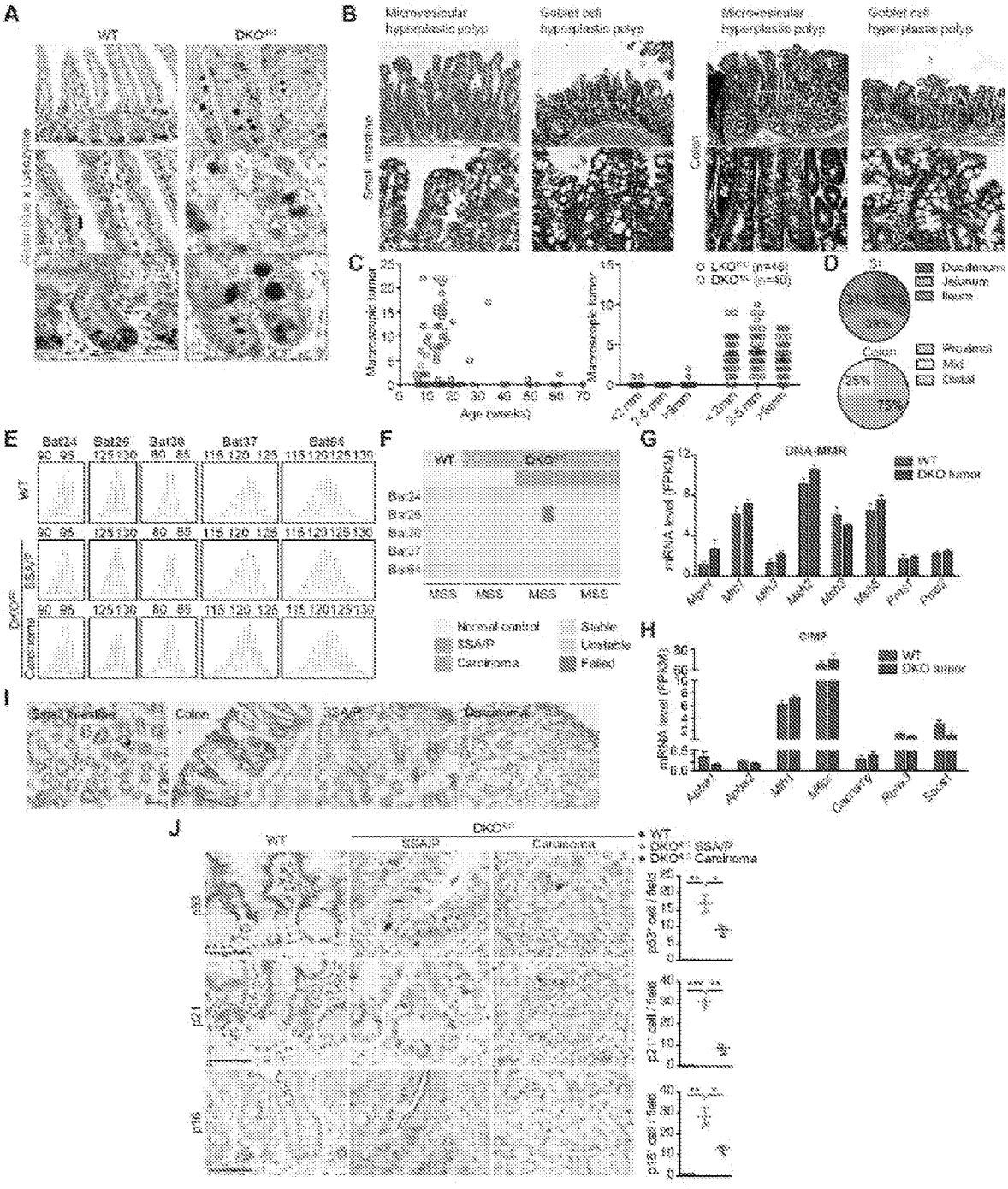

A
WT
DKO
Bowel loop x sacrifice
B
Microvesicular hyperplastic polyp
Goblet cell hyperplastic polyp
Small intestine
Colon
C
Macroscopic tumor
Age (weeks)
LKO (n=46)
DKO (n=40)
<2 mm
1-5 mm
>5mm
<2cm
2-5 mm
>5cm
D
SI
Duodenum
Jejunum
Ileum
Colon
Proximal
Mid
Distal
E
Bat24
Bat26
Bat30
Bat37
Bat64
WT
SSA/P
Carcinoma
F
WT
DKO
MSS
Normal control
SSA/P
Carcinoma
Stable
Unstable
Failed
G
DNA-MMR
mRNA level (FPKM)
WT
DKO tumor
Mlh1
Msh2
Msh6
Pms2
H
Other
I
Small intestine
Colon
SSA/P
Carcinoma
J
WT
DKO
SSA/P
Carcinoma
p53
p21
p16
p53+ cell / field
p21+ cell / field
p16+ cell / field

FIG. 9

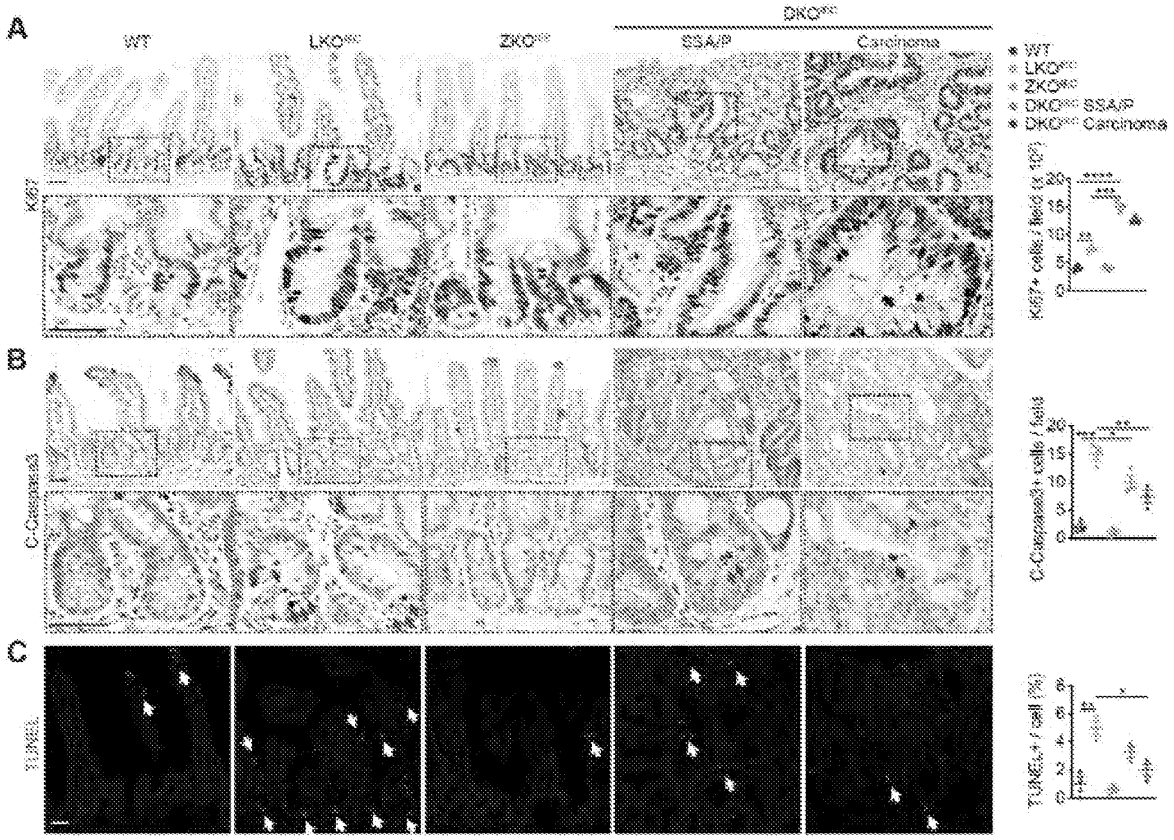

A
WT
LKO
ZKO
DKO
SSA/P
Carcinoma
Ki67
B
C-Caspase3
C
TUNEL
WT
LKO
ZKO
DKO SSA/P
DKO Carcinoma
Ki67+ cells / field (x 10²)
C-Caspase3+ cells / field
TUNEL+ / cell (%)

FIG. 10

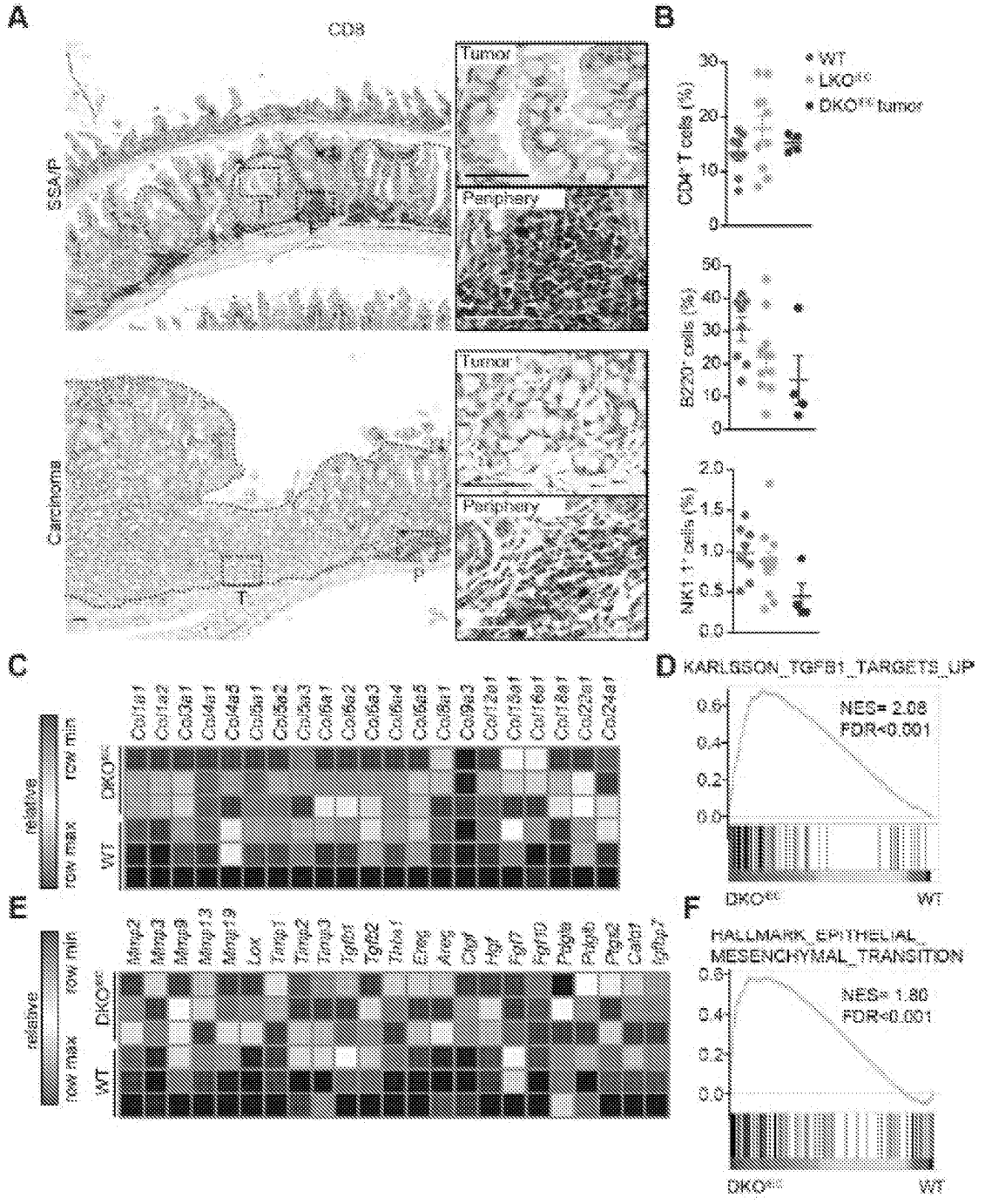

A
CD8
SCAP
Tumor
Periphery
Carcinoma
B
WT
LKO
DKO tumor
CD4+ T cells (%)
B220+ cells (%)
NK1.1+ cells (%)
C
relative
row min
row max
DKO
WT
Col1a1
Col1a2
Col3a1
Col4a1
Col4a5
Col5a1
Col5a2
Col5a3
Col6a1
Col6a2
Col6a3
Col6a4
Col6a5
Col8a1
Col9a3
Col12a1
Col13a1
Col16a1
Col18a1
Col22a1
Col24a1
D
KARLSSON_TGFB1_TARGETS_UP
NES= 2.08
FDR<0.001
DKO
WT
E
Mmp2
Mmp3
Mmp9
Mmp13
Mmp19
Lox
Timp1
Timp2
Timp3
Tgfbi
Tgfb2
Thbs1
Eng
Ares
Cbyr
Hgf
Fgf2
Fgf10
Pdgfa
Pdgfb
Pdgfc
Calcr
Igfbp7
F
HALLMARK_EPITHELIAL_
MESENCHYMAL_TRANSITION
NES= 1.80
FDR<0.001
DKO
WT

FIG. 11

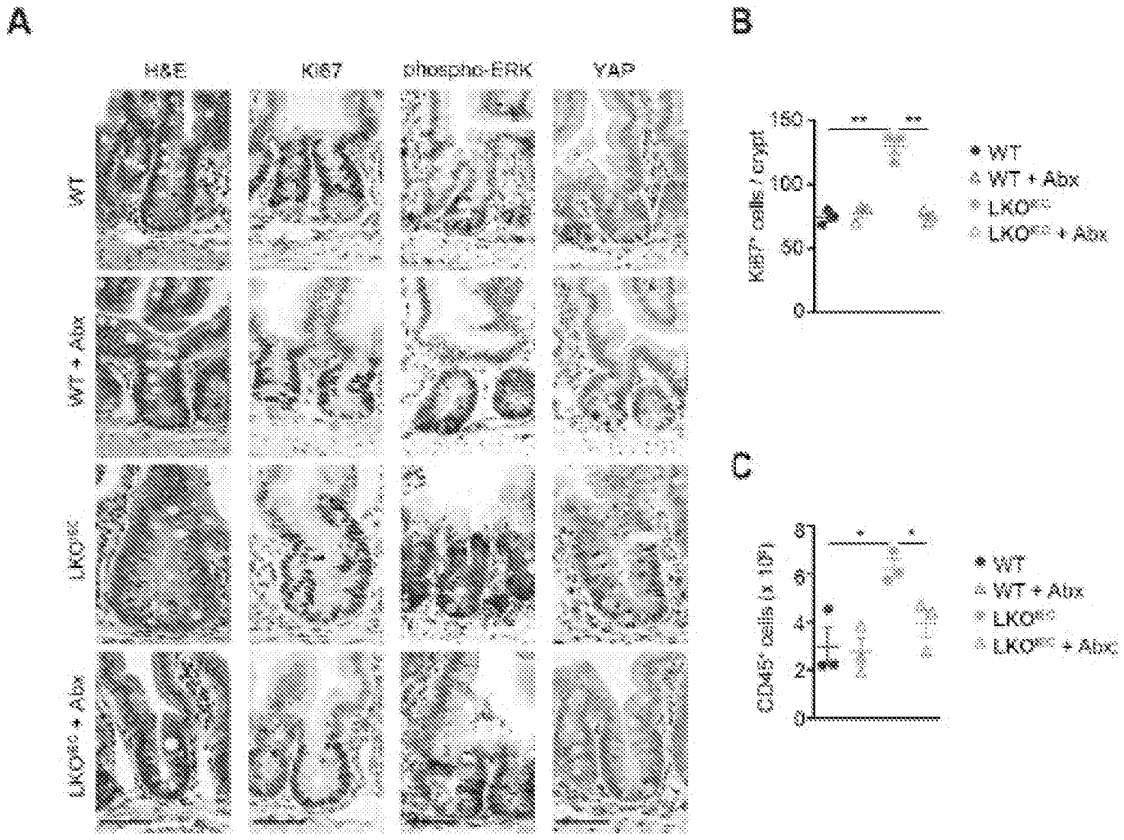

A
H&E
Ki67
phospho-ERK
YAP
WT
WT + Abx
LKO^EC
LKO^EC + Abx
B
Ki67+ cells / crypt
150
100
50
0
**
**
WT
WT + Abx
LKO^EC
LKO^EC + Abx
C
CD45+ cells (x 10^3)
8
6
4
2
0
*
*
WT
WT + Abx
LKO^EC
LKO^EC + Abx

FIG. 12

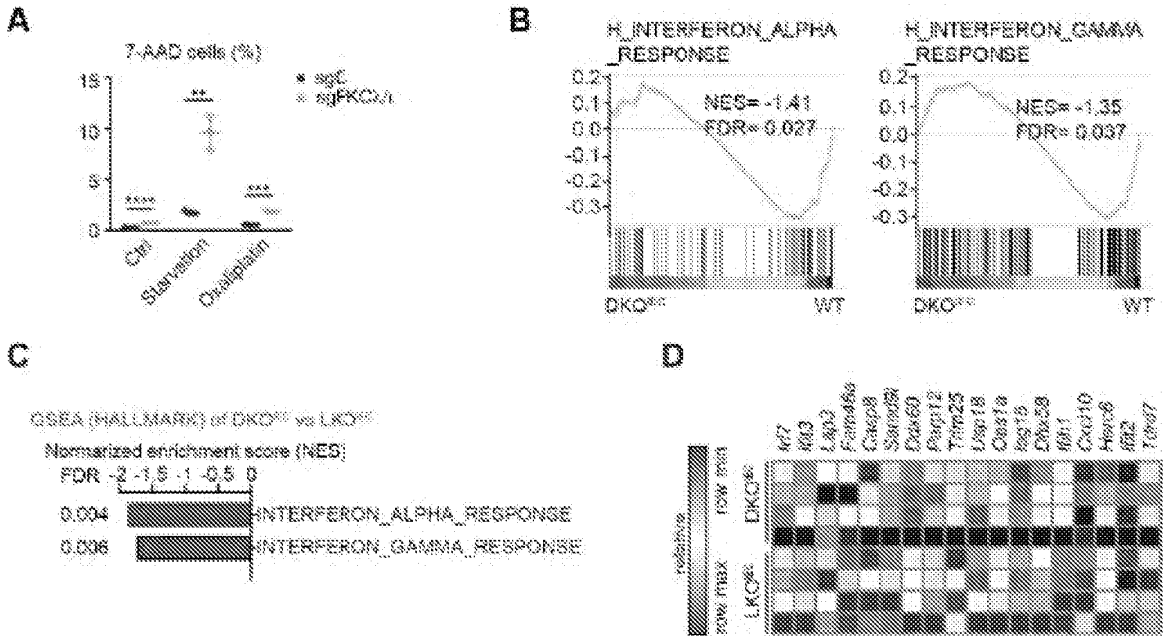

A
7-AAD cells (%)
* sgC
* sgFKO1
Ctrl
Starvation
Cisplatin
B
H_INTERFERON_ALPHA_RESPONSE
NES= -1.41
FDR= 0.027
H_INTERFERON_GAMMA_RESPONSE
NES= -1.35
FDR= 0.037
WT
C
GSEA (HALLMARK) of
Normalized enrichment score (NES)
FDR
0.004
INTERFERON_ALPHA_RESPONSE
0.006
INTERFERON_GAMMA_RESPONSE
D
row max
row min

FIG. 13

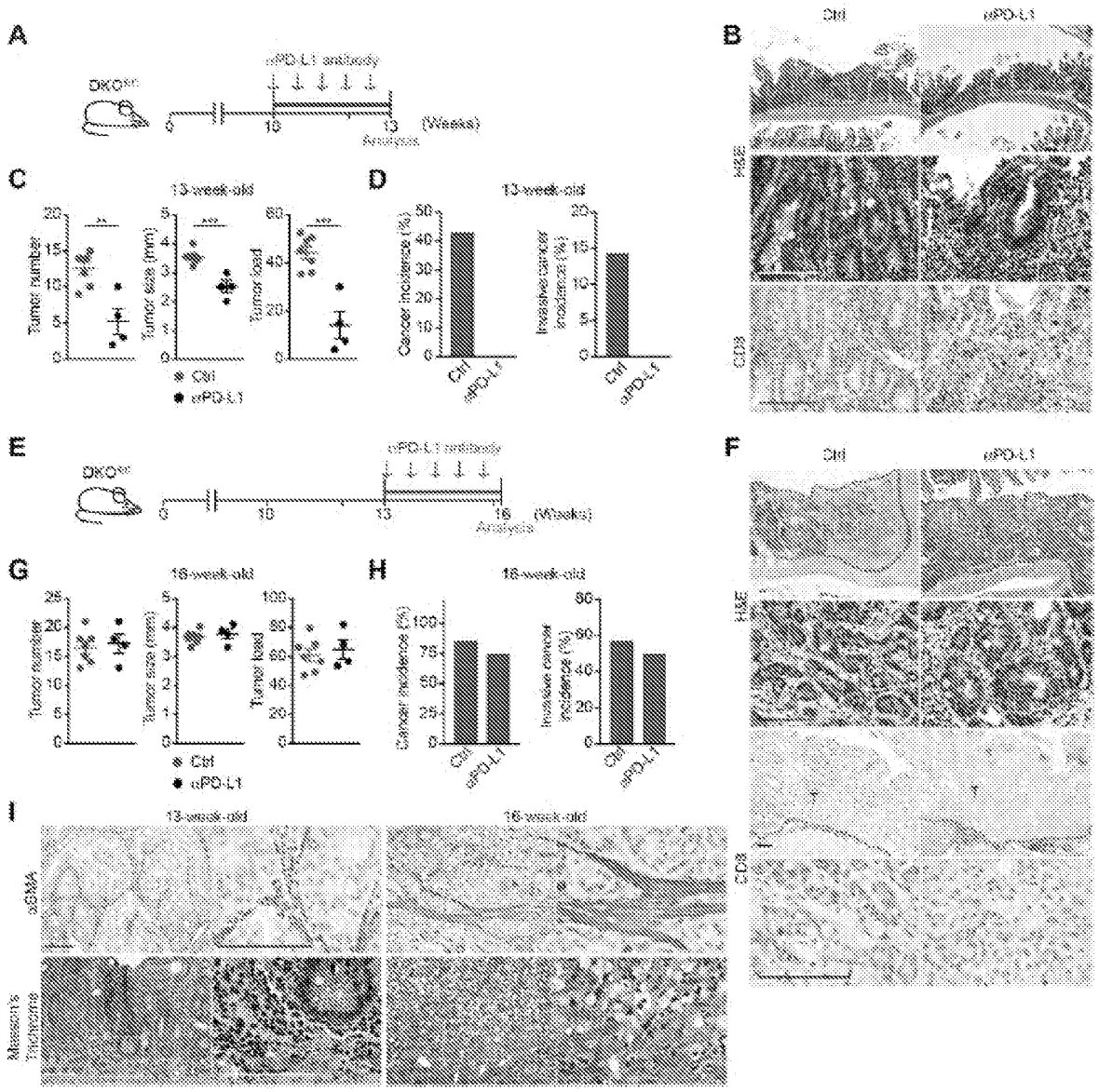

A
αPD-L1 antibody
(Weeks)
Analysis
B
Ctrl
αPD-L1
H&E
CD3
C
13-week-old
Tumor number
Tumor size (mm)
Tumor load
Ctrl
αPD-L1
D
13-week-old
Cancer incidence (%)
Invasive cancer incidence (%)
E
F
G
16-week-old
H
I
αSMA
Masson's Trichrome

FIG. 14

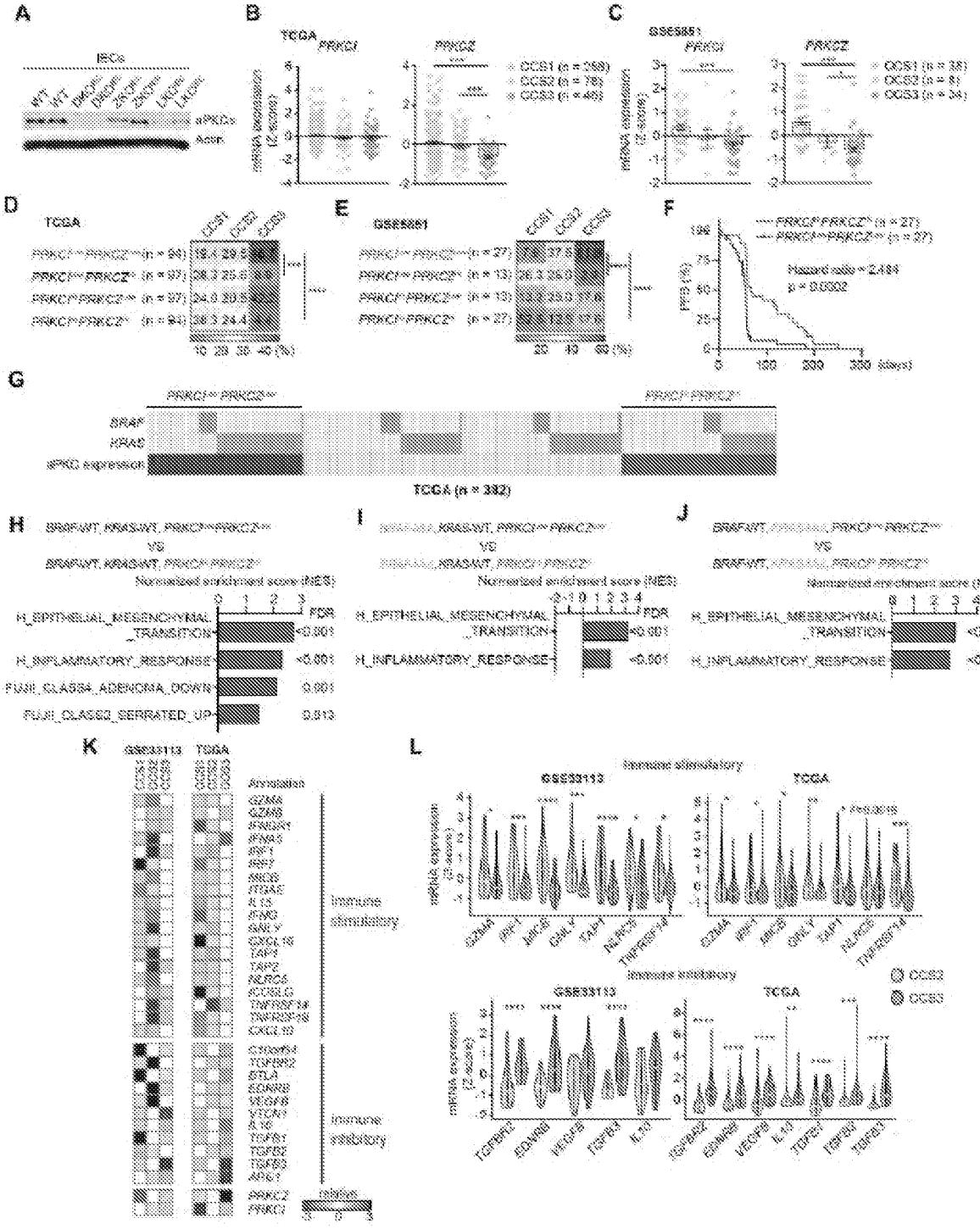

A
IECs
WT
KO
PRKCI
PRKCZ
DKO
PRKCI
PRKCZ
DKO
PRKCI
PRKCZ
DKO
PRKCI
PRKCZ
HA-PKCι
Actin
B
TCGA
PRKCI
PRKCZ
CCS1 (n = 268)
CCS2 (n = 78)
CCS3 (n = 46)
C
GSE5851
PRKCI
PRKCZ
CCS1 (n = 38)
CCS2 (n = 8)
CCS3 (n = 34)
D
TCGA
CCS1
CCS2
CCS3
PRKCI-/-PRKCZ-/- (n = 99)
PRKCI-/-PRKCZ+/+ (n = 97)
PRKCI+/+PRKCZ-/- (n = 97)
PRKCI+/+PRKCZ+/+ (n = 91)
E
GSE5851
CCS1
CCS2
CCS3
PRKCI-/-PRKCZ-/- (n = 27)
PRKCI-/-PRKCZ+/+ (n = 13)
PRKCI+/+PRKCZ-/- (n = 13)
PRKCI+/+PRKCZ+/+ (n = 27)
F
PRKCI+/+PRKCZ+/+ (n = 27)
PRKCI-/-PRKCZ-/- (n = 27)
Hazard ratio = 2.484
p = 0.0302
PFS (%)
G
PRKCI-/-PRKCZ-/-
PRKCI+/+PRKCZ+/+
BRAF
KRAS
aPKC expression
TCGA (n = 382)
H
BRAFWT, KRASWT, PRKCI-/-PRKCZ-/-
vs
BRAFWT, KRASWT, PRKCI+/+PRKCZ+/+
Normalized enrichment score (NES)
H_EPITHELIAL_MESENCHYMAL_TRANSITION
H_INFLAMMATORY_RESPONSE
FUJII_CLASS4_ADENOMA_DOWN
FUJII_CLASS3_SERRATED_UP
FDR
<0.001
<0.001
0.001
0.013
I
KRASWT, PRKCI-/-PRKCZ-/-
vs
KRASWT, PRKCI+/+PRKCZ+/+
Normalized enrichment score (NES)
H_EPITHELIAL_MESENCHYMAL_TRANSITION
H_INFLAMMATORY_RESPONSE
FDR
<0.001
<0.001
J
BRAFWT, PRKCI-/-PRKCZ-/-
vs
BRAFWT, PRKCI+/+PRKCZ+/+
Normalized enrichment score (NES)
H_EPITHELIAL_MESENCHYMAL_TRANSITION
H_INFLAMMATORY_RESPONSE
FDR
<0.001
<0.001
K
GSE33113
TCGA
CCS1
CCS2
CCS3
Annotation
GZMA
GZMB
IFNG(IF)
IFNG
IRF1
IRF7
MICB
ITGAE
IL15
STAT1
GNLY
CXCL10
TAP1
TAP2
NLRC5
CCR5LG
TNFRSF14
TNFRSF18
CXCL10
C10orf54
TGFB2
BTLA
EDNRB
VEGFB
YTHDF1
IL10
TGFB1
TGFB2
TGFB3
APOE
PRKCZ
PRKCI
Immune stimulatory
Immune inhibitory
mRNA
L
Immune stimulatory
GSE33113
TCGA
mRNA expression (Z-score)
GZMA
IRF1
MICB
GNLY
TAP1
NLRC5
TNFRSF14
Immune inhibitory
GSE33113
TCGA
CCS2
CCS3
TGFBR2
EDNRB
VEGFB
IL10
TGFB1
TGFB2
TGFB3

FIG. 15

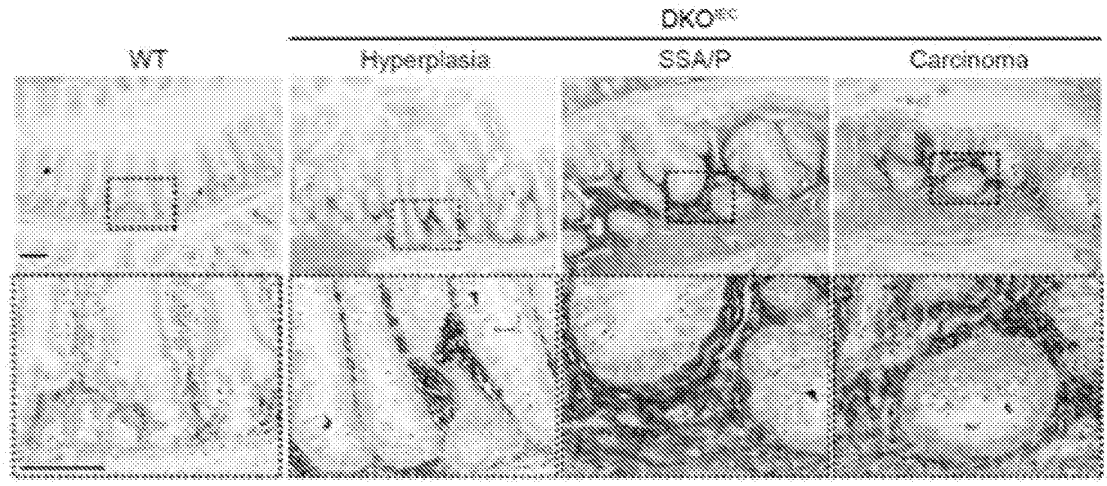


FIG. 16

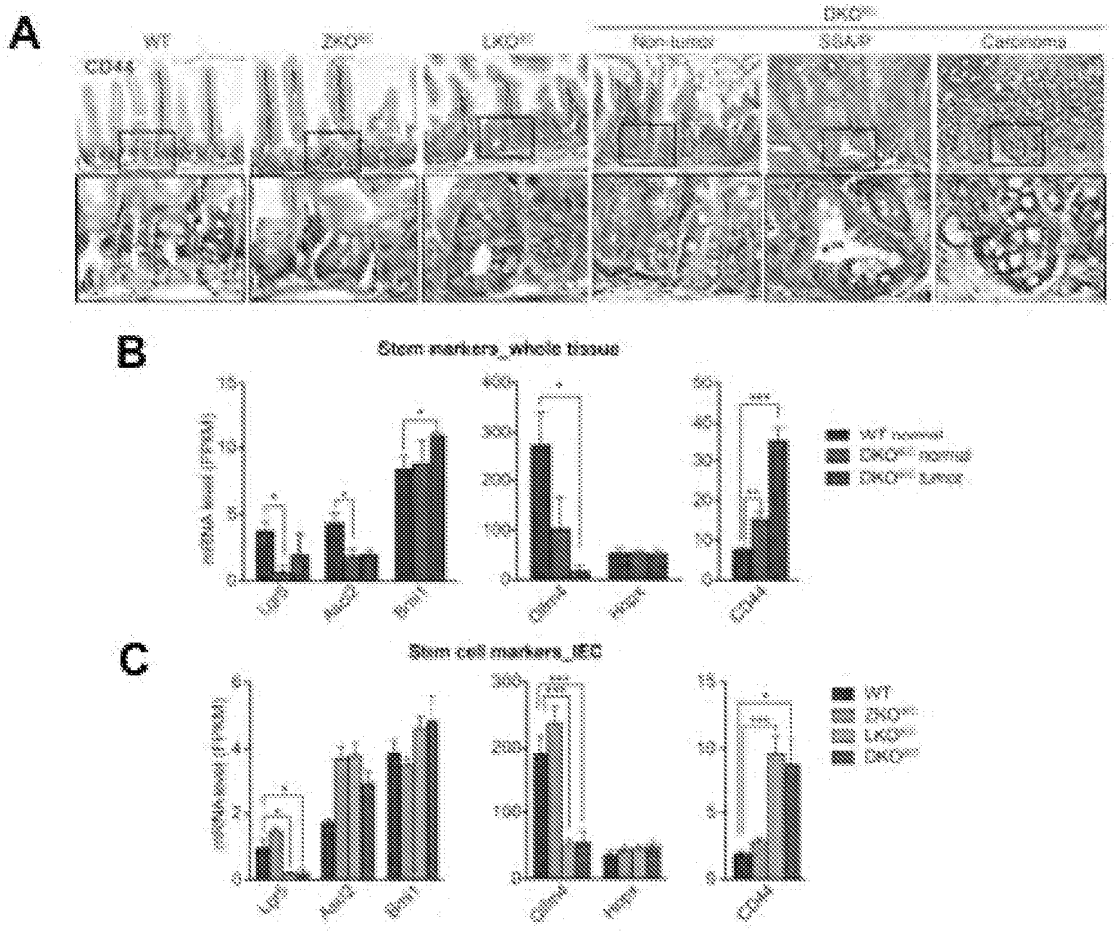

A
WT
DKO^fl
LKO^fl
DKO^fl
Non-tumor
SSA/P
Carcinoma
CD44
B
Stem markers_whole tissue
Lgr5
Ascl2
Bmi1
CBlin4
mTert
CD44
C
Stem cell markers_IEC
Lgr5
Ascl2
Bmi1
CBlin4
mTert
CD44

FIG. 17

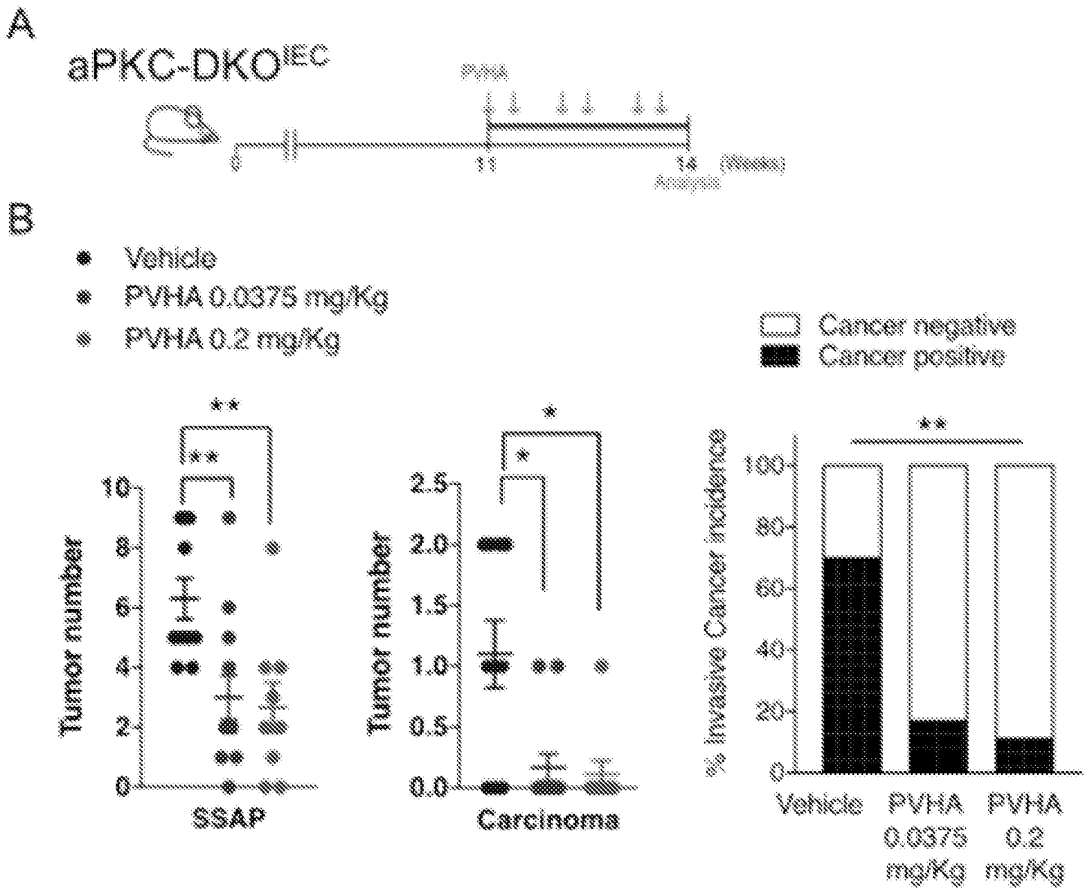

A
aPKC-DKO^IEC
PVHA
11
14
B
Vehicle
PVHA 0.0375 mg/Kg
PVHA 0.2 mg/Kg
Tumor number
SSAP
Carcinoma
Cancer negative
Cancer positive
% Invasive Cancer incidence
Vehicle
PVHA 0.0375 mg/Kg
PVHA 0.2 mg/Kg

FIG. 18

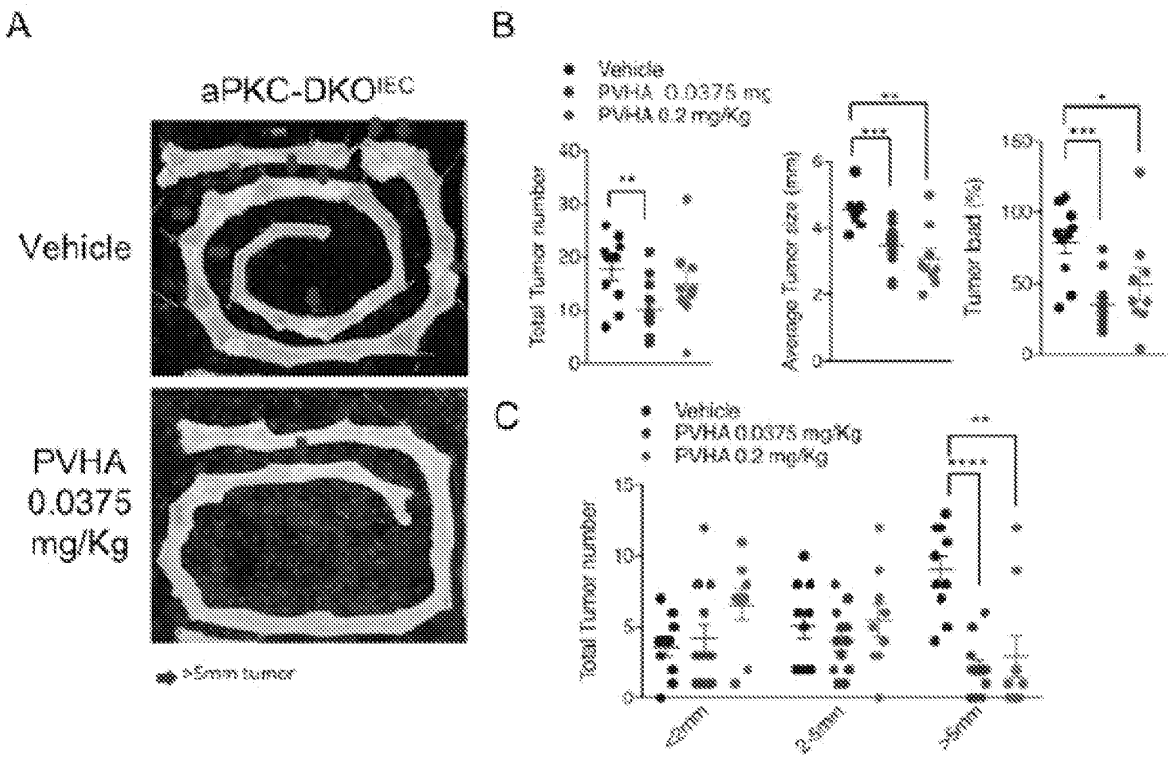

A
aPKC-DKO IEC
Vehicle
PVHA 0.0375 mg/Kg
>5mm tumor
B
Vehicle
PVHA 0.0375 mg
PVHA 0.2 mg/Kg
Total Tumor number
Average Tumor size (mm)
Tumor load (%)
C
Vehicle
PVHA 0.0375 mg/Kg
PVHA 0.2 mg/Kg
Total Tumor number
<2mm
2-5mm
>5mm

FIG. 19

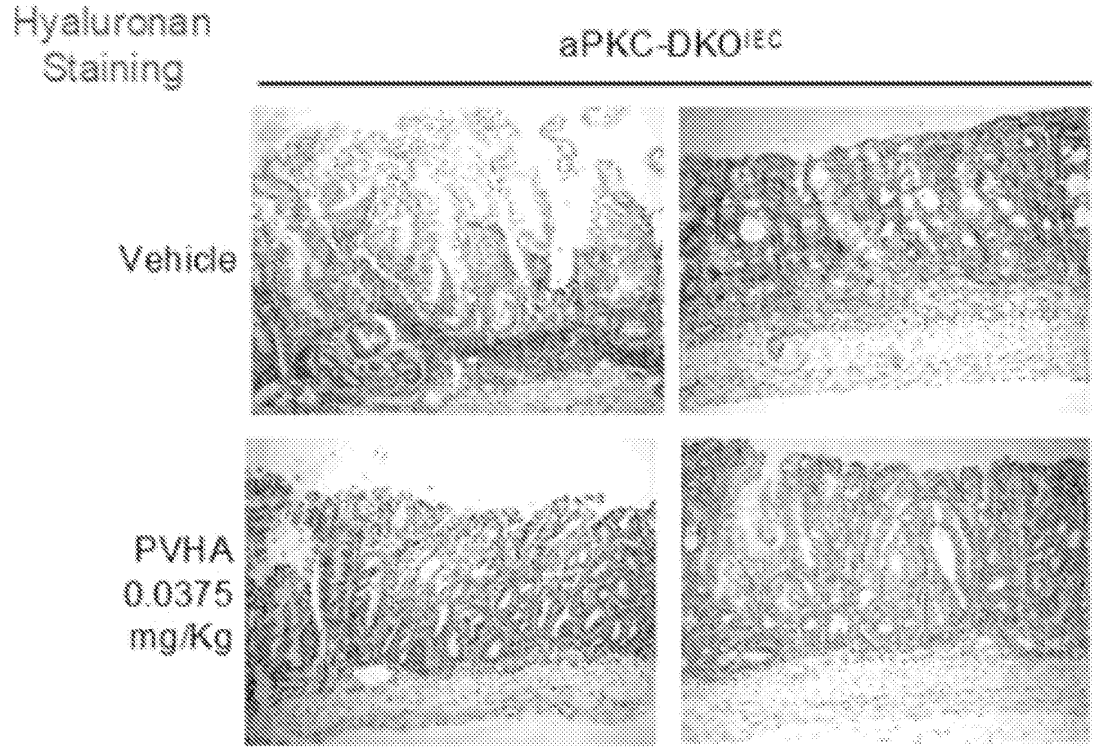


FIG. 20

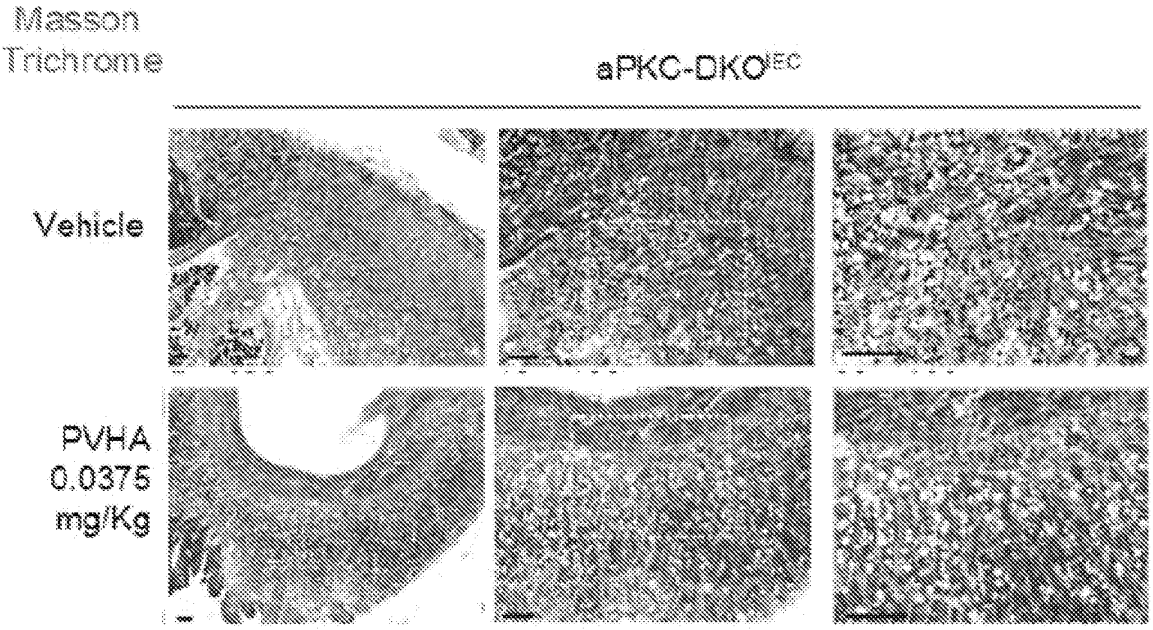


FIG. 21

