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Supplemental Data

Context-Dependent Transformation of Adult

Pancreatic Cells by Oncogenic K-Ras

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Supplemental Figures

Figure S1. Further characterization of $Pdx1CreER^{TM}$; LSL-Kras^{G12D} compound mice.

A-B: Immunohistochemical staining for the α cell marker Glucagon (A) and PP cell marker PYY

(B). Note positive staining in mPanINs, ductal metaplasia and in non-neoplastic islet (orange,

black and red arrows, respectively).

C-D: H&E staining of pancreata obtained from mice 120 days after TM injection. Note

developed ductal structures in the islets (arrows in C), exocrine hypoplasia, mPanINs (arrows in

D), ductal metaplasia (arrowhead in D) and strong stromal reaction.

E-F: H&E staining of pancreata derived from mice treated with either TM dissolved in corn oil

by intraperitoneal injection (E) or TM dissolved in carboxymethyl cellulose by oral gavage (F).

Note peritonitis in E and mPanIN formation in F (arrows).

Bars: A, B: 50 µm; C-E: 100µm; F: 200µm.

Figure S2. Kras^{G12D} activation in *pro-CPA*-positive cells of the adult pancreas results in mPanIN and PDAC development at low frequency.

A: X-gal staining of a pancreas derived from a TM-treated *proCPA1CreER*^{T2};*LSL-Kras*^{G12D};*LSL-LacZ* compound mouse shows mPanIN formation (arrow).

B: H&E-stained section of metastatic PDAC (m) in the liver (l) of a *proCPA1CreER*^{T2};*LSL-Kras*^{G12D}; $Trp53^{flox/flox}$ compound mouse.

Bars: A: 100 µm; B: 200µm.

Figure S3. Kras^{G12D} activation in combination with p53 or Ink4A/Arf loss in *pro-CPA*-positive and *insulin*-positive cells of the adult pancreas results in mPanIN3 and PDAC development after caerulein treatment.

A-B: H&E-stained sections of mPanIN3 (arrow in A) and PDAC (B) in caerulein- & TM-treated *proCPA1CreER*^{T2};*LSL-Kras*^{G12D};*Trp53*^{flox/flox} compound mice.

C: H&E-stained section of PDAC invading the spleen (S) of a TM- & caerulein-treated $proCPA1CreER^{T2}$; LSL-Kras^{G12D}; Ink4A/Arf^{flox/flox} compound mouse.

D: H&E-stained section of PDAC arising in a caerulein- & TM-treated *RipCreERTM;LSL*-

Kras^{G12D}; Trp53^{flox/flox};LSL-LacZ compound mouse. The tumor exhibits anaplasia with giant cells (arrows).

Bars: 200 µm.

А В С D Е F

Gidekel Friedlander_S. Fig1

Gidekel Friedlander_S. Fig2

A proCPACreER^{T2};LSL-Kras^{G12D}; LSL-LacZ



proCPACreER^{T2}; LSL-Kras^{G12D}; Trp53^{flox/flox}

B





Gidekel Friedlander_S. Fig3

Table S1: Quantification of the recombination efficiency and specificity of the different Cre strains used in the study. Mice were treated with Tamoxifen (TM) by intraperitoneal injections of 9mg/40g body weight in corn oil, one every other day for a total of 3 injections. Animals were at the age of 21-30 day old at the time of first injection and sacrificed 14 days after the last TM injection. Analysis was performed on X-gal stained sections of pancreata derived from three mice of each genotype.

after the last 1 M injectio	on. Analysis was p	eriormed on A-ga	al stained section	s of pancreata (derived from the	ree mice of each g	enotype.	_	
Genotype	% Recombined acinar cells per tissue section by	Average % recombination of acinar cells per	Number of recombined islets/ total number of islets per tissue	% Recombination per analyzed	Average % recombination per islet	Number of recombined ducts/ total number of ducts per tissue	% Recombination per analyzed dust	Average % recombination per ducts	# of recombined single cells outside the islets per tissue
	analyzeu areas	ussue section	section	Islet		section	auci		section
RipCreER TM ; LSL-LacZ	0	0	13/13	90 100 90 95 98 100 100 100 97 97 97 88 99 97	96	0	0	0	3
RipCreER [™] ; LSL-LacZ	0	0	7/7	98 100 100 97 98 85 60	91	0	0	0	2
RipCreER TM ; LSL-LacZ	0	0	10/10	99 99 99 88 98 98 98 95 99 100 97	97	0	0	0	3
Pdx1CreER TM ; LSL-LacZ	a)50 b)85 c)60 d)80 e)90 f)85 g)50 h)75 i)85	74	8/8	80 80 99 85 90 85 80 98	87	20/24	$\begin{array}{c} 50\\ 50\\ 50\\ 100\\ 70\\ 75\\ 100\\ 50\\ 80\\ 100\\ 100\\ 50\\ 80\\ 100\\ 50\\ 80\\ 100\\ 50\\ 100\\ 50\\ 100\\ 50\\ 100\\ 85\\ 100\\ 50\\ 80\\ 100\\ 85\\ 80\\ 100\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ $	79	0
Pdx1CreER TM ; LSL-LacZ	a)95 b)100 c)95 d)98 e)80 f)50	86	6/6	100 100 100 100 99 100	99.8	7/7	100 100 100 98 100 100 100	99.7	0
Pdx1CreER TM ; LSL-LacZ	a)98 b)98 c)98 d)85 e)99 f)98 g)99 h)97 I)95 j)99 k)96	97	20/20	30 85 100 90 98 95 90 85 95 95 60 80 90 80 90	87	61/77	16x0% 6x10% 2x5% 10x2% 15x100% 11x50% 4x30% 1x60% 6x80% 4x20% 2x90%	50	0

				97 90 97 98 95			
proCPA1CreER ^{T2} ; LSL-LacZ	a)45	49	4/4	50	85	10/19	100
	b)30 c)50 d)70 e)90 f)40 g)35 h)40 i)40 j)30 k)70			90 100 100			$ \begin{array}{c} 100\\ 100\\ 10\\ 50\\ 100\\ 50\\ 100\\ 100\\ 10$
proCPA1CreER ¹² ; LSL-LacZ	a)40 b)40 c)35 d)60 e)0 f)45 g)40 h)50 i)0 j)70 k)75	41	1/1	80	80	10/18	100 50 50 50 50 50 80 70 70 50
proCPA1CreER ^{T2} ; LSL-LacZ	a)5 b)20 c)25 d)3 e)20 f)60 g)45 h)25 i)60 j)50	31	3/3	7 2 98	36	5/16	70 20 100 100 100

Table S2: Quantification and characterization of pre neoplastic lesions and PDAC developed upon Kras^{G12D} activation alone or in combination with p53 or Ink4A/Arf loss by Pdx1CreERTM

	· · · · · · · · · · · ·	1		1		F F -	1	1	1	_	1		1	
Mouse Genotype	Treatment	N=	Kras ^{G12D}	Sacrificed	# of mice with	# of mice with	# of mice with	# of mice with	# of mice with	# of mice with	mucinous/ non	# of mice with	# of mice with	Metastasis
			activation at	#of days	1-2x 1A	multiple 1A	1-4x 1B lesions	multiple 1B	2-5 grade 2	grade 3 lesions	mucinous focal	Ducts (DII)/	PDAC	(met)/ invasion
			post-natal age	after the last	lesions	lesions		lesions	lesions		ductal	Acini in islets		(i)
				TM							metaplasia	(AII)		
				injection										
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	2	14	4, 7	0	0	0	0	0	0	N.A.	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	3	14	10	3	0	0	0	0	0	N.A	2x DII, 1x AII	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	2	14	20	0	0	0	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	3	14	40	0	3	1	2	0	0	N.A	2x DII	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	3	14	120	1	2	0	2	2	0	N.A	1x DII	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	1	21	40	0	1	0	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	1	24	40	0	1	1	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	2	27	10	1	0	0	0	0	0	N.A	1x DII	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	4	27	20	1	0	0	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	1	27	40	0	0	0	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	2	27	120	0	2	1	1	2	0	N.A	2x DII	0	N.A
$Pdx1CreER^{TM}$; LSL-Kras ^{G12D}	TM	1	27	188	0	1	0	1	1	1	N.A	0	1	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	2	56	10	1	0	0	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	2	56	20	1	0	0	0	0	0	N.A	0	0	N.A
$Pdx1CreER^{TM}$; LSL-Kras ^{G12D}	TM	1	56	40	0	1	1	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	TM	2	56	120	0	1	1	0	0	0	N.A	0	0	N.A
Pdx1CreER TM ; LSL-Kras ^{G12D}	Corn oil	5	14	5, 10, 20, 40,	0	0	0	0	0	0	N.A	0	0	N.A
				120										
$Pdx1CreER^{TM}$; LSL-Kras ^{G12D}	Corn oil	5	27	5, 10, 20, 40,	0	0	0	0	0	0	N.A	0	0	N.A
				120										
Pdx1CreER TM ; LSL-Kras ^{G12D}	Corn oil	5	56	5, 10, 20, 40,	0	0	0	0	0	0	N.A	0	0	N.A
				120										
Pdx1CreER TM ; LSL-Kras ^{G12D} ;	TM	6	22	18	0	3	1	2	4	4	2x non	2x DII	2x MD to PD	3x SI I(i)
Trp53 ^{flox/flox}			23	57							mucinous		1x PD with S	1x spleen and
			22	<mark>40</mark>									1x PD with A	Diaphragm
			22	<mark>60</mark>										(met)



			<mark>23</mark> 23	<mark>30</mark> 37										
Pdx1CreER TM ; LSL-Kras ^{G12D} ; Trp53 ^{flox/flox;} Luciferase ^{flox/+}	ΤΜ	6	24 23 23 23 26 54	20 45 45 45 79 30	2	2	4	1	5	3	2x non mucinous	0	3x Poor diff 1x PD with A 1x PD with S and A	1x SI (i) 1x stomach (i)
Pdx1CreER TM ; LSL-Kras ^{G12D} ; Ink4A/Arf ^{flox/flox}	ТМ	1	28	36	0	1	1	0	1	1	0	0	1x PD with S and A	1x SI (i)

N.A. not applicable

Table S3: Quantification and characterization of pre neoplastic lesions and PDAC developed upon Kras^{G12D} activation alone or in combination with p53 or Ink4A/Arf loss by *RipCreERTM* and *proCPA1CreER^{T2}*

Mouse Genotype	Treatment	N=	Kras ^{G12D} activation at post-natal age	Sacrificed #of days after the last TM injection	# of mice with 1-2x 1A lesions	# of mice with multiple 1A lesions	# of mice with 1-4x 1B lesions	# of mice with multiple 1B lesions	# of mice with 2-4 grade 2 lesions	# of mice with grade 3 lesions	# of mice with Ducts (DII)/ Acini in islets (AII)	# of mice with PDAC	Metastasis (met)/ invasion (i)	<i>K-ras</i> recombination tested by PCR/confirmed
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	TM	6	14	5, 10, 20, 40, 126, 240	0	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	TM	1	14	120, 210	1	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	TM	4	23	5, 20, 40, 240	0	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	TM	1	23	151	1	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	TM	4	26	20, 40, 126, 219	0	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	ТМ	2	27	26	0	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	ТМ	1	30	14	0	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	TM	1	51	40	0	0	0	0	0	0	0	0		YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	corn-oil	4	14	5,10, 40, 120	0	0	0	0	0	0	0	0		YES/NO
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	corn-oil	4	26	5,20, 40, 120	0	0	0	0	0	0	0	0		YES/NO
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D}	corn-oil	1	56	40	0	0	0	0	0	0	0	0		YES/NO
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D} ; Trp53 ^{flox/flox}	TM	5	14 14 28 53 53	46 97 67 <mark>81</mark> 81	0	0	0	0	0	0	0	1x MD to PD with undifferentiated areas	1X SI (i) liver and diaphragm (met)	YES/YES
proCPA1CreER ^{T2} ; LSL- Kras ^{G12D} ; Ink4A/Arf ^{flox/flox}	TM	7	14 14 25 25 15 20 35	113 188 158 309 50 50 83	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	TM	5	14	6, 22, 40, 55	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	ТМ	2	15	22, 40	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	TM	3	18	9, 40, 120	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	TM	2	20	40, 65	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	TM	1	24	40	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	TM	1	25	150	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	TM	1	28	40	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	TM	7	29	10, 20, 40, 120	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	ТМ	3	35	70, 164	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	ТМ	2	36	145, 240	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	ТМ	3	56	10, 20, 120	0	0	0	0	0	0	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D}	corn-oil	4	14	5, 10, 20, 120	0	0	0	0	0	0	0	0		YES/NO
RipCreER TM ;LSL-Kras ^{G12D}	corn-oil	5	27	5, 10, 20, 30, 120	0	0	0	0	0	0	0	0		YES/NO
RipCreER TM ;LSL-Kras ^{G12D}	corn-oil	3	56	5, 10, 20	0	0	0	0	0	0	0	0		YES/NO

RipCreER TM ; LSL-Kras ^{G12D} ;	ТМ	9	14	10	0	0	0	0	0	0	0	0	YES/YES
Ink4A/Arf ^{flox/flox}			15	22									
			15	80									
			15	80									
			20	60									
			29	22									
			29	22									
			35	70									
			35	70									
RipCreER TM ; LSL-Kras ^{G12D} ;	TM	5	28	90	0	0	0	0	0	0	0	0	YES/YES
Trp53 ^{flox/flox}			28	27									
			31	10									
			31	20									
			31	42									

Table S4: Quantification and characterization of chronic pancreatitis and Kras^{G12D} -induced pre neoplastic lesions and PDAC

Tuble 511 Quantification and chart			me puner curi	is and man	, maac	eu pre neo	plustic lesion.			-	1		-			1
Mouse Genotype	Treatment	N=	Kras ^{G12D} activation at post-natal age	Sacrificed # of days after first TM injection	caerulein for a total of N days	# of mice with 1-2x 1A lesions	# of mice with multiple 1A lesions	# of mice with 1-4x 1B lesions	# of mice with multiple 1B lesions	# of mice with 2-4 grade 2 lesions or more (m)	# of mice with grade 3 lesions	mucinous (m)/ non mucinous (nm) focal ductal metaplasia	# of mice with Ducts (DII)/Acini in islets (AII)	# of mice with PDAC	metastasis (met)/ invasion (i)	<i>K-ras</i> recombination tested by PCR/confirmed
proCPA1CreER ^{T2} ; LSL-Kras ^{G12D}	caerulein	6	60	9	44	0	1	0	0	0	0	0	1x DII	0		YES/YES
	+		60	34	69											
	TM		60	34	69											
			60	34	69											
			60	34	69											
			90	163	193											
proCPA1CreER ^{T2} : LSL-Kras ^{G12D} :	caerulein	3	59	86	121	0	2	0	2	0	0	2x m and nm	0	0		YES/YES
LSL-LacZ	+	_	63	33	66	-				-	-		-	-		
	TM		64	90	125											
proCPA1CreER ^{T2} ; LSL-Kras ^{G12D} ;	caerulein	6	52	3	38	0	3	0	3	3	0	3x m and nm	0	2x PD 1x Well to	abdominal	YES/YES
Trp53 ^{flox/flox}	+		52	57	81									PD	wall (i)	
	ΤΜ		52 50 26 99	71 78 140 9	106 105 175 44											
proCPA1CreER ^{T2} ; LSL-Kras ^{G12D} ;	TM	1	25	151	95	0	1	0	0	0	0	0	0	1X PD with S	Spleen	YES/YES
Ink4A/Arf ^{flox/flox}	+														surface,	
	caerulein														Kidney surface, Diaphragm (mets)	
proCPA1CreER ^{T2} ; LSL-Kras ^{G12D} ;	ТМ	2	25	50	81	0	0	0	0	0	0	1x nm	0	0		YES/YES
LSL-LacZ	+		33	52	38											
	caerulein															
proCPA1CreER ^{T2} ; LSL-Kras ^{G12D} ;	ТМ	1	33	52	38	0	0	0	0	0	0	1x nm	0	0		YES/YES
Ink4A/Arf ^{flox/flox} ; LSL-LacZ	+															
	caerulein															
RipCreER TM ;LSL-Kras ^{G12D} ; LSL-LacZ	caerulein	2	197	58	89	0	1	0	0	0	0	2x nm	0	0		YES/YES
	+		87	57	84											
	TM															
RipCreER TM ; LSL-Kras ^{G12D} ; Ink4A/Arf ^{dlox/flox}	caerulein + TM	1	55	23	78	0	1	0	1	0	0	1x nm	0	0		YES/YES
RipCreER TM : LSL-Kras ^{G12D} :	caerulein	5	55	1	33	2	3	0	2	1	0	5	1x AII	0		YES/YES
Ink4A/Arf ^{flox/flox} : LSL-LacZ	+	-	54	9	41	_	C	, i i i i i i i i i i i i i i i i i i i	-	-	Ŭ			Ŭ		
······································	TM		54	9	41											
			54	39	72											
			30	9	44											
RipCreER TM : LSL-Kras ^{G12D} : Trp53 ^{flox/flox} :	caerulein	3	55	71	104	0	3	1	2	1	0	1x m and nm	0	2x PD with S	1x	YES/YES
LSL-LacZ	+	_	55	71	104					_	-			and A	Abdominal	
	TM		56	53	88									1x	wall (met)	
														undifferentiated	1x lung	
														(S)	(met)	
RipCreER TM ;LSL-Kras ^{G12D}	TM + caerulein	1	29	31	17	1	0	0	0	0	0	1x nm	0	0		YES/YES
RipCreER TM ;LSL-Kras ^{G12D} ; LSL-LacZ	ТМ	6	22	99	88	0	4	2	2	1	1	3x nm and	0	2x PD+	Diaphragm,	YES/YES
	+		31	23	9							3x m and nm		undifferentiated	Liver	
	caerulein		31	78	65									<mark>(S)</mark>	border,	
			<mark>51</mark>	<mark>60</mark>	<mark>53</mark>										Peritoneal	
			51	114	101										adipose	
			<mark>51</mark>	106	<mark>93</mark>										tissue and	
															Small	
															intestine (i)	
RipCreER TM ; LSL-Kras ^{G12D} : Trp53 ^{flox/flox} :	ТМ	4	21	65	51	1	3	3	0	3 x(m)	1	1x nm+m	0	3x	Small	YES/YES
LSL-LacZ	+		24	67	52							1x nm		undifferentiated	intestine (i)	
	caerulein		24	67	52									with S	diaphragm	
			24	<mark>82</mark>	<mark>42</mark>									1x PD+	(met)	
									1		1					

			undifferentiated (S)	

MD-Moderately, PD-poorly, S-sarcomatoid, A- anaplastic Blue, green and yellow highlights designate tumors and the specific mice in which they arose

Table S5: Quantification and characterization of chronic pancreatitis-induced recombination in *RipCreER*TM mice

Mouse Genotype	Treatment	N=	Kras ^{G12D} activation at post-natal age	Sacrificed #of days after first TM injection	caerulein for a total of N days	# of LacZ ⁺ Insulin ⁺ costained islets	# of LacZ ⁺ Insulin ⁺ costained cells outside the islets	# of LacZ ⁺ insulin ⁻ cells	Tissue area in mm ²	Average # of LacZ ⁺ insulin ⁻ cells in 1mm ² per sample	Total average # of LacZ ⁺ insulin ⁻ cells in 1mm ²
RipCreER TM ; LSL-LacZ	TM + caerulein	5	375 66 39 61 59	72 70 70 72 72	65 65 65 65 65	5 1 2 3 2	38 9 14 17 5	1 1 0 4 0	16.99 1.18 0.34 12.31 9.97	0.06 0.85 0 0.32 0	0.25

Table S6: Quantification of chronic pancreatitis and Kras^{G12D} -induced pre neoplastic lesions

Table 50. Quantification of chronic	panercati	is and is	nas -muuce	i pre neopias					
Mouse Genotype	Treatment	N=	Kras ^{G12D}	Sacrificed #of	caerulein for	Total # of	Tissue area	Average # of	Total
			activation at	days after first	a total of N	lesions (of all	in mm ²	lesions in	average #
			post-natal age	TM injection	days	grades)		1mm ² per	of lesions in
								sample	1mm ² in
									both
									groups of
									mice
RipCreER TM ;LSL-Kras ^{G12D} ; LSL-LacZ	TM	5	22	99	88	8	9.13	0.88	1.77
	+		51	78	65	0	0.83	0	
	caerulein		51	60	53	0	1.42	2.11	
			51	114	101	3	10.5	4.1	
			51	106	93	43	26.43	0.61	
RipCreER TM ;LSL-Kras ^{G12D}	ТМ	1	29	31	17	2	0.68	2.94	
	+								
	caerulein								

Table S7: Phenotypic comparison of different acinar specific Cre strains

Mouse Genotype	Age (day-old) on K-Ras	Analyzed at time after oncogenic K-Ras actrivation	Phenotype	Reference
K-Ras ^{+/LSLG12Vgeo} ; Elas-tTA/tetO-Cre	10 10	6 months 12 months	4/12 (33.33%) mPanIN-1A 6/16 (37%) mPanIN-2/3 and 2/16 12% had PDAC	Guerra et al. 2007
	60	12 months 10 months	no lesions	
Ela-CreERT2 ^{Tg/+} ; LSL-Kras ^{G12D}	42	2 months 4-12 months	3/5 (60%) mPanIN-1A mPanIN-2 and mPanIN-3	Habbe et al. 2008
Mist1 ^{CreERT2/+} ; LSL-Kras ^{G12D}	42	2 months 4-12 months	mPanIN-1A mPanIN-2 and mPanIN-3	Habbe et al. 2008
ElaCreERT; LSL-Kras ^{G12D}	42	1; 2; 10 weeks	In total: at least one mPanIN was found in 12/33 (36%) pancreata examined. mPanIN-1A, 6/33 (18%) mPanIN-2 and 1/33 (3%) mPanIN-3	De La O et al. 2008
proCPA1CreER ^{T2} ; LSL-Kras ^{G12D}	14 23 26 27 30 51	5, 10, 20, 40, 126, 240, 120 days 5, 20, 40, 240, 151 days 20, 40, 126, 219 days 26 days 14 days 40 days	1/7 mPanIN-1A 1/5 mPanIN-1A or in total: 2/20 (10%)	
proCPA1CreER ^{T2} ; LSL-Kras ^{G12D} ; Trp53 ^{flox/flox}	14 14 28 53 53	46 days 97 days 67 days 81 days 81 days	1/5 moderately to poorly diffe with un differentiated areas. small intestines and metastas diaphragm	erentiated PDAC Invasion to the is to the liver and

Table S8: PCR Primers used in the study

Purpose	Primer ID	Sequence 5'-3'	Product sizes
Cre genotype (for all Cre	SageF	TGCTGTACTGGTTATGCGG	700-bp
recombinase harboring strains)	SageR	TTGCCCCTGTTTCACTATCCAG	
LSL-Kras ^{G12D} genotype	Dt5'JKNew	GTCGACAAGCTCATGCGGG	Wild-type, 1Lox - <i>Kras^{G12D}</i> alleles : 500-bp and 550-bp, res
	UniJKNew	CGCAGACTGTAGAGCAGCG	
	SD5'JKNew	CCATGGCTTGAGTAAGTCTGC	
<i>Trp53^{flox}</i> genotype	Α	CACAAAAACAGGTTAAACCCAG	A+B :Wild-type and mutant alleles: 288-bp and 379-bp, re
	В	AGCACATAGGAGGCAGAGAC	C+D: Wild-type and mutant alleles: 431-bp and 584-bp, re
	С	AAGGGGTATGAGGGACAAGG	
	D	GAAGACAGAAAAGGGGGAGGG	
Ink4A/Arf ^{flox} genotype	INK20	GTTTCCATTGCGAGGCTGCTCCGTAAGC	INK20+INK21: Wild-type and mutant alleles: 150-bp and
	INK21	CTTTAGGGCGTTCCTTTCCCACTTCTGC	INK20+KO4: Wild-type and mutant alleles: no product an
	KO3	GGTACTGCCGGGCCTCTTGAGGGGA	INK21+KO3: Wild-type and mutant alleles: no product an
	KO4	CCATTCCCCTCAAGAGGCCCGGCAGTACC	
<i>R26-LSL-LacZ</i> genotype	UnivF	AAAGTCGCTCTGAGTTGTTAT	Wild-type and mutant alleles : 500-bp and 250-bp, respect
	WtR	GGAGCGGGAGAAATGGATATG	
	MutR	GCGAAGAGTTTGTCCTCAACC	
Recombined <i>LSL-Kras^{G12D}</i>	KrasF1	GTCTTTCCCCAGCAGAGTGC	Wild-type K-ras, 2Lox and 1Lox -K-ras ^{G12D} alleles : 620-b
	KrasR1	CTCTTGCCTACGCCACCAGCTC	respectively
	KrasSD5'	AGCTAGCCACCATGGCTTGAGTAAGTCTGCA	

spectively	
spectively	
spectively	

d 250-bp, respectively and 177-bp, respectively and 130-bp, respectively

ctively

bp, 510-bp and ~1100-bp,