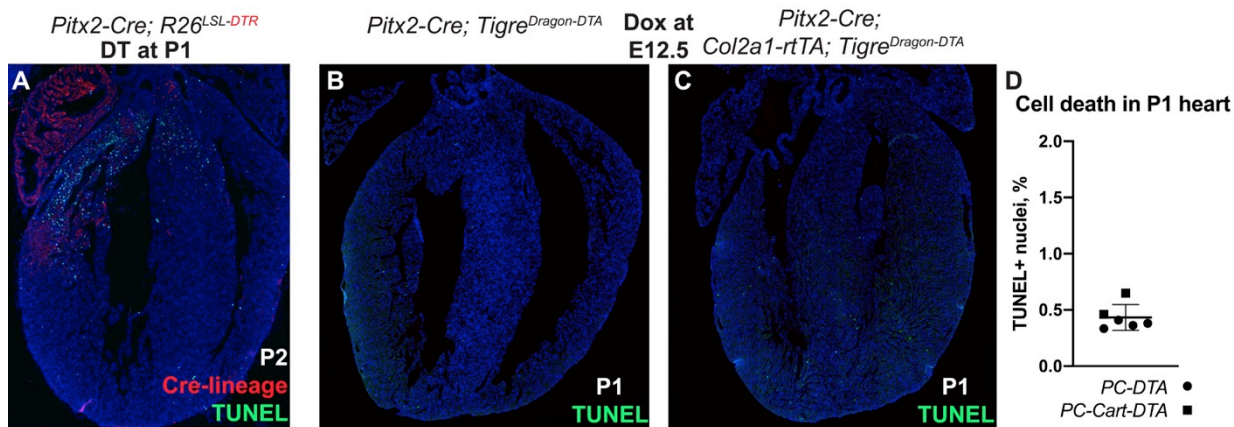


## SUPPLEMENTARY FIGURES



**Figure U1. The intersectional approach allows sparing of unwanted cell populations, such as cardiomyocytes when using *Pitx2-Cre*.** A) Representative image showing the cell death distribution (TUNEL) in the P2 heart when diphtheria toxin receptor (DTR, red) is activated by *Pitx2-Cre* and DT is injected at P1 (modified from (Rosello-Diez et al., 2017), subject to a free-distribution license). B, C) Negligible cell death is observed in the hearts of P1 *PC-DTA* (B) and *PC-Cart-DTA* (C), with Dox provided at E12.5. D) Quantification of cell death in *PC-DTA* and *PC-Cart-DTA* hearts (mean±SD, n=4 and 2 respectively).

**Table S1. Reagents and resources**

REAGENT or RESOURCE	SOURCE	IDENTIFIER
<b>Antibodies</b>		
Rat monoclonal anti-mCherry	ThermoFisher	M11217; RRID:AB_2536611
Rabbit polyclonal anti-p21	Santa Cruz Biotechnology	M19; RRID:AB_632123
Mouse monoclonal anti-NeuN	Millipore	MAB377;RRID:AB_2298772
Rabbit polyclonal anti-MEIS2	<a href="#">Mercader et al., 2005</a>	N/A
Goat anti-rat IgG (H+L) Cross-Adsorbed, AlexaFluor 555	ThermoFisher	A-21434; RRID:AB_141733
Donkey anti-mouse IgG (H+L), Highly Cross-Adsorbed, AlexaFluor 488	ThermoFisher	A-21202; RRID:AB_141607
Donkey anti-rabbit IgG (H+L), Highly Cross-Adsorbed, AlexaFluor 647	ThermoFisher	A-31573; RRID:AB_2536183
Anti-Digoxigenin-AP Fab fragments	Sigma-Aldrich	11093274910; RRID:AB_514497
<b>Chemicals, recombinant proteins</b>		
Paraformaldehyde (powder)	Sigma-Aldrich	
Triton X-100	Sigma-Aldrich	T9284-500ML
Fluoromount aqueous mounting medium	Sigma-Aldrich	F4680-25ml
40,6-diamidino-2-phenylindole (DAPI)	ThermoFisher	D1306
SYTOX green	ThermoFisher	S7020
Doxycycline hyclate	Sigma-Aldrich	D9891-10 gr
Affigel blue beads	Biorad	1537301
Biotin 16-dUTP	Sapphire Bioscience	JBS-NU-803-BIO16-S
TAT-Cre	Millipore	SCR-508
Terminal transferase recombinant	Merck	3333566001
<b>Electroporation tools</b>		
Platinum wire, 0.25 mm	SDR Scientific	711000
Tungsten wire, 0.5 mm	Sigma-Aldrich	356972
Pulse generator and amplifier	Intracel	TSS20
Glass capillaries	Harvard apparatus	GC120T-10
<b>Experimental Models: Organisms/Strains</b>		
Mouse <i>Tigre</i> <sup>Dragon-p21</sup>	<a href="#">Rosello-Diez et al., 2018</a>	RRID:IMSR_JAX:034777
Mouse <i>Tigre</i> <sup>TRE-p21</sup>	This paper	N/A
Mouse <i>Tigre</i> <sup>Dragon-DTA</sup>	This paper	RRID:IMSR_JAX:034778
Mouse <i>Tigre</i> <sup>Dragon-Ctgf</sup>	This paper	RRID:IMSR_JAX:034779
Mouse B6.Cg-Gt(ROSA)26Sortm1.1 (CAG-rtTA3)Slowe/LdowJ	<a href="#">Dow et al., 2014</a>	RRID:IMSR_JAX:029627
Mouse <i>Atoh1-tTA</i>	<a href="#">Willett et al., 2019</a>	N/A
Mouse <i>TetO-Cre</i>	<a href="#">Perl et al., 2002</a>	RRID:IMSR_JAX:006234
Mouse <i>En1-Cre</i>	<a href="#">Kimmel et al., 2000</a>	RRID:IMSR_JAX:007916
Mouse <i>Col2a1-tTA</i>	<a href="#">Rosello-Diez et al., 2018</a>	N/A

B6C3(129)-Tg(Pitx2ASE-cre)16Hmd/HmdRbrc Mus musculus	<a href="#">Shiratori et al., 2006</a>	RRID:IMSR_RBRC03487
Tg(Col2a1-rtTA)1Jath	<a href="#">Posey et al., 2009</a>	RRID:MGI:4361029
<b>Plasmids</b>		
pDragon-p21	<a href="#">Rosello-Diez et al., 2018</a>	RRID:Addgene_140894
pDragon-DTA	This paper	RRID:Addgene_140895
pDragon-Ctgf	This paper	RRID:Addgene_140896
pPB-CA-rtTA-Adv	Addgene	RRID:Addgene_20910
pPB-CAG-rtTA-IRES-Hygro	Addgene	RRID:Addgene_102423
pT2-CAG-H2B-TagBFP	<a href="#">Sieiro et al., 2016</a>	N/A
pCAGGs-rtTA-IRES-Cre	This paper	AR98
Ai62(TITL-tdT) Flp-in replacement vector	<a href="#">Madisen et al., 2015</a>	RRID:Addgene_61576

**Table U2. Primers and PCR conditions used for genotyping**

Allele	Program	Primer name	Primer sequence (5' to 3')
Cre	94°C 2', 33x(94°C 20", 60°C 20", 72°C 30"), 72°C 5', 10°C forever)	Cre F Cre R	GCGGTCTGGCAGTAAAACTATC GTGAAACAGCATTGCTGTCCTT
Dragon WT	94°C 2', 33x(94°C 20", 55°C 20", 72°C 30"), 72°C 5', 10°C forever)	Dragon F Dragon R WT	CCCAACGGTCACTTACTTCC CACACCTTTAATCCCGATGC
Dragon Mut	94°C 2', 10x(94°C 20", 65°C-0.5/cycle 15", 68°C 10"), 72°C 5', 10°C forever), 28x(94°C 15", 60°C 15", 72°C 10"), 72°C 2', 10°C forever)	Dragon F Dragon R Mut	CCCAACGGTCACTTACTTCC GGTAACCGCGGCATAAAAC
p21rec	94°C 2', 33x(94°C 20", 55°C 20", 72°C 30"), 72°C 5', 10°C forever)	Pmin F WPRE Rev	AGTGAACCGTCAGATCGC GCGTATCCACATAGCGTAAAAG
Col2- rtTA	94°C 2', 33x(94°C 20", 61°C 20", 72°C 30"), 72°C 5', 10°C forever),	rtTA F rtTA R	ATGCCCTTGGAATTGACGAGTACGG CGAGGCTTGCAGGATCATAATCAG
Col2- tTA	94°C 2', 33x(94°C 20", 55°C 20", 72°C 30"), 72°C 5', 10°C forever)	Col2a1 F tTA R	CCAGGGTTTCCTTGATGATG GCTACTTGATGCTCCTGATCCTCC
CAG- rtTA3	94°C 2', 33x(94°C 20", 55°C 20", 72°C 30"), 72°C 5', 10°C forever)	Mut F Common Rev WT F	AAAGTCGCTCTGAGTTGTTAT GCGAAGAGTTTGTCTCAACC GGAGCGGGAGAAATGGATATG