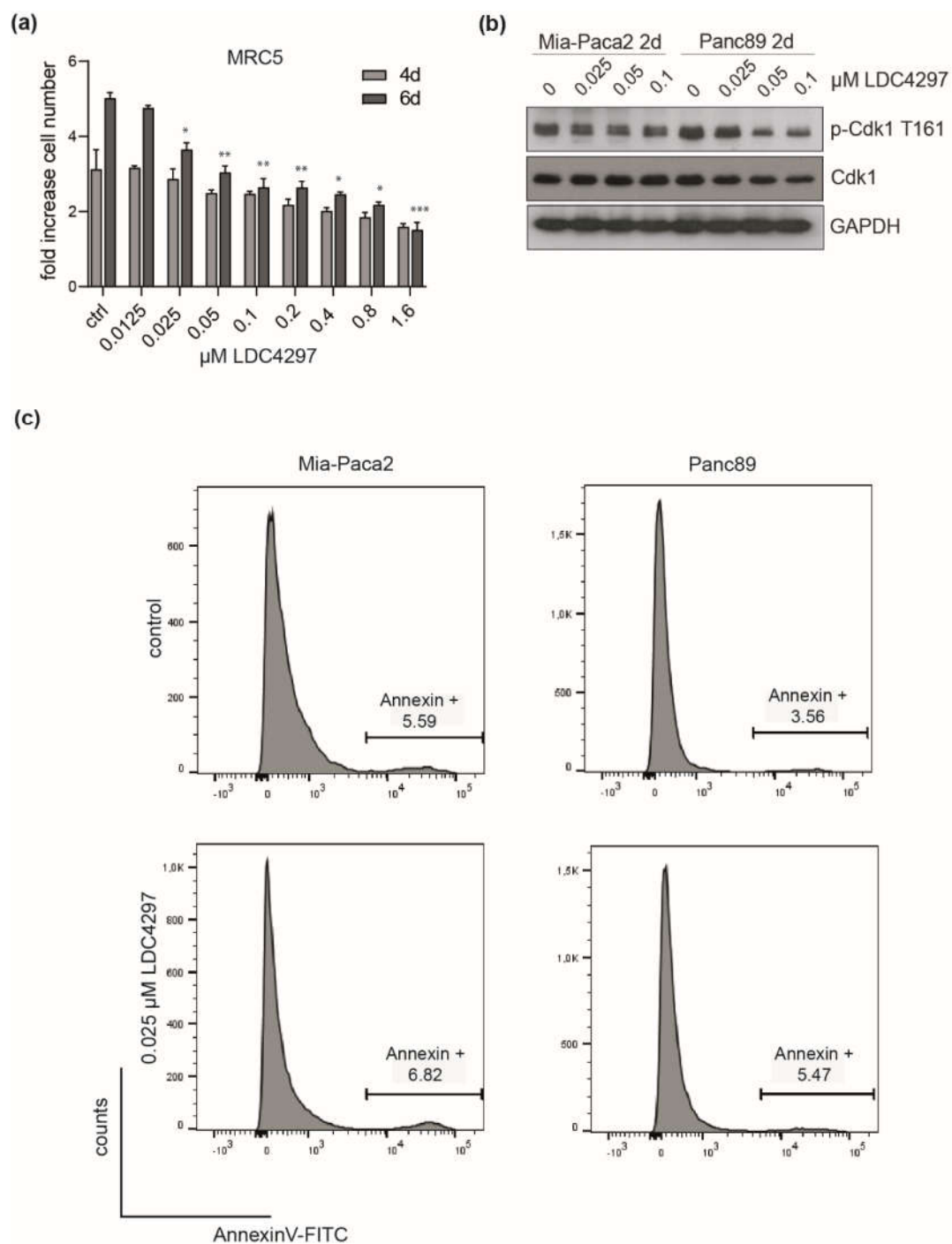
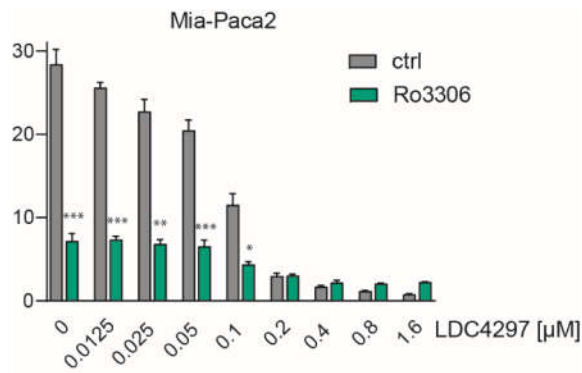


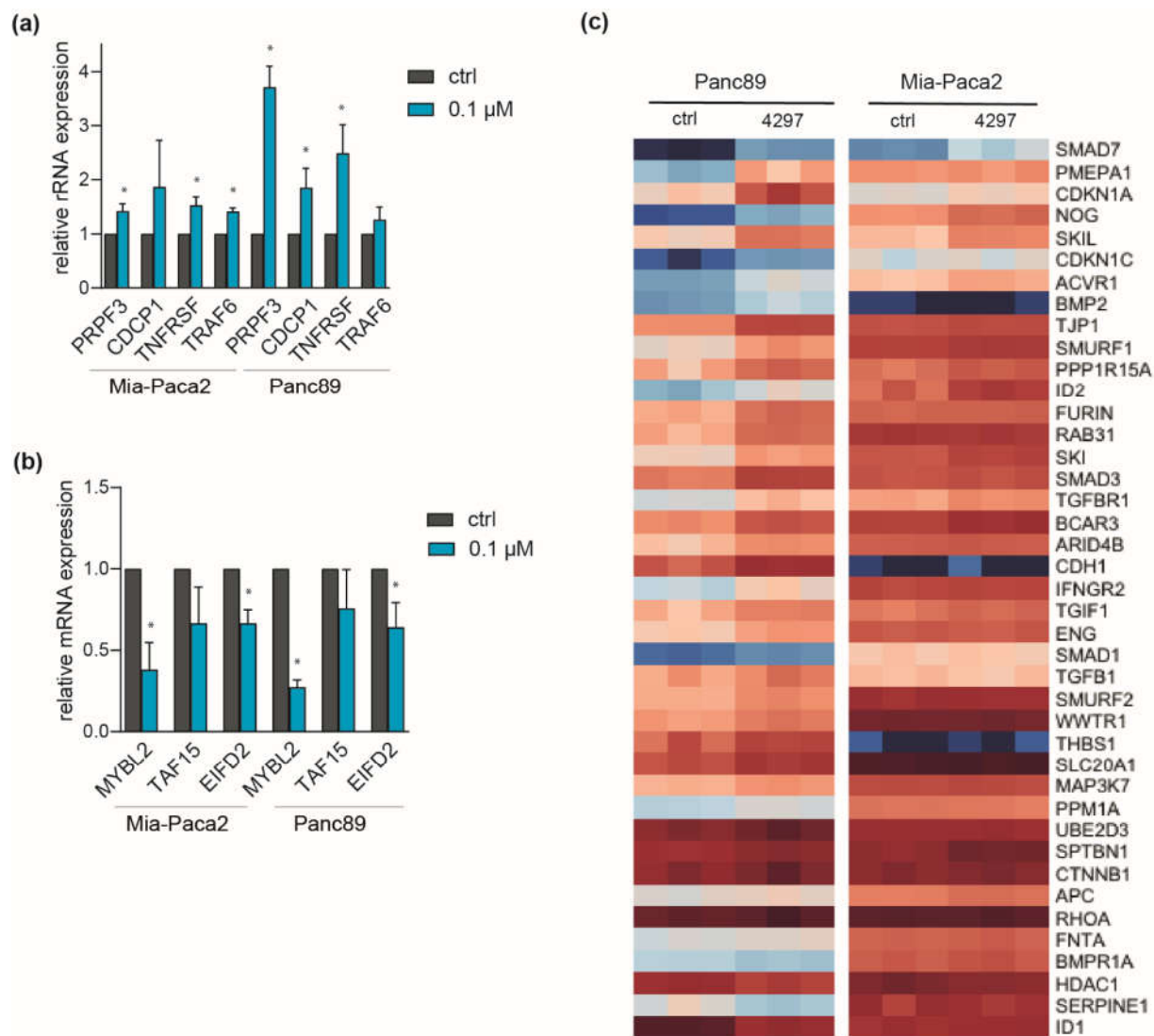
Supplementary Figures



Supplementary Figure S1: (a) MRC5 cells were treated with the indicated concentrations of LDC4297 [µM] for 4 or 6 days and cell viability analyzed ($n = 3$). Significance was analyzed by two-sided Student's t test: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. (b) Mia-Paca2 and Panc89 cells were treated with the indicated concentrations of LDC4297 [µM] or DMSO for 48 hours. Cell extracts were analyzed by SDS-PAGE and immunoblot using the indicated antibodies. (c) Mia-Paca2 and Panc89 cells were treated with 0,025 µM LDC4297 for 4 days. Cells were stained with Annexin V-FITC and analyzed by FACS.

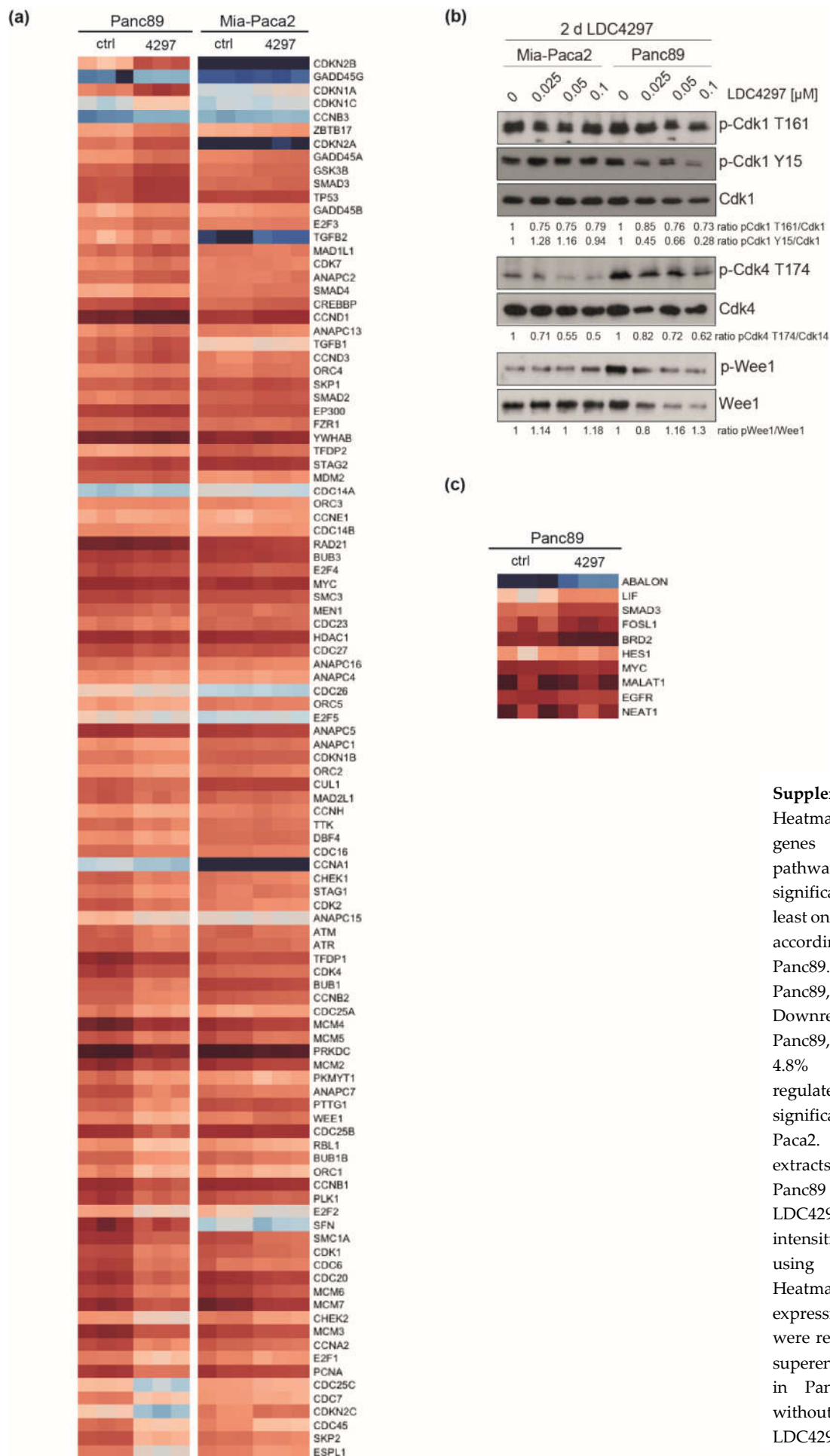


Supplementary Figure S2: Mia-Paca2 cells were treated with increasing concentrations of LDC4297 [μM] in the absence or presence of 2 μM Ro-3306 and cell viability determined ($n = 3$). Significance was analyzed by two-sided Student's t test: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$



Supplementary Figure S3: (a, b) Mia-Paca2 and Panc89 cells were treated with 0.1 μ M LDC4297 for 3 days and mRNA expression of exemplarily chosen genes either found upregulated (a) or downregulated (b) in RNAseq analysis was analyzed by RT-qPCR ($n = 2$). (c) Heatmap of TGF β target genes from RNAseq data, which are significantly regulated in Panc89, sorted according to regulation in Panc89. Upregulation: 90% in Panc89, 37% in Mia-Paca2; Downregulation: 10% in Panc89, 2% in Mia-Paca2; 61% not significantly regulated in Mia-Paca2.

Significance was analyzed by two-sided Student's t test: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$



Supplementary Figure S4: (a) Heatmap of cell cycle related genes (KEGG cell cycle pathway), which are significantly regulated in at least one of the cell lines, sorted according to regulation in Panc89. Upregulation: 29.5% in Panc89, 17.1% in Mia-Paca2; Downregulation: 65.7% in Panc89, 44.8% in Mia-Paca2; 4.8% not significantly regulated in Panc89, 38.1% not significantly regulated in Mia-Paca2. (b) Immunoblots of extracts from Mia-Paca2 and Panc89 cells treated with LDC4297 for 2 days. Band intensities were quantified using ImageJ software. (c) Heatmap depicting the expression level of genes that were reported to be driven by superenhancers in PDAC cells in Panc89 cells with and without treatment with 0.1 μM LDC4297 for 3 days.

Supplementary Tables

Supplementary Table S1. Mutational status of K-Ras, p53, CDKN2A and Smad4 in human PDAC cell lines.

Locus	Cell lines								
	Panc89 [1]	PT45 [2]	BxPc3 [3]	MP2 [4]	Panc1 [5]	AsPc1 [6]	Capan1 [7]	Capan2 [7]	A8184 [2]
<i>KRas</i>	Q61H	G13D	wt	G12C	G12D	G12D	G12V	G12V	G12R
<i>p53</i>	Y220C	R280K	Y220C	R248W	R273H/ R273C	R273H/ 135 frameshi ft	A159V	wt/ R273H	mut. in tetra- merizati on domain
<i>CDKN2A</i>	mut. meth.	mut. h.d.	wt	mut. h.d.	mut. h.d.	wt/ frame- shift	mut. h.d.	wt./ mut. ins.	mut. h.d.
<i>Smad4</i>	wt	wt	mut. h.d.	wt	wt	wt/ R100T	F557L	wt	wt
Tissue origin	lymphn ode metastas is	primary tumor	primary tumor	primary tumor	primary tumor	ascites/ metastat ic site	liver metastas is	primary tumor	ascites

Abbreviations: wt: wild-type, mut.: mutation, meth.: methylation, h.d.: homozygous deletion, ins.: insertion. Cell lines are sorted from left to right by decreasing sensitivity to LDC4297.

Supplementary Table S2. Proliferation rates of human PDAC cell lines.

	Cell lines								
	Panc89	PT45	BxPc3	Mia- Paca2	Panc1	AsPc1	Capan1	Capan2	A8184
doubling time [d]	0.899	0.8233	1.087	0.9942	1.722	1.262	1.378	1.140	1.139

Supplementary Table S3: Log2 fold changes determined from RNAseq analysis and RT-qPCR for the indicated genes

symbol	Panc89 Log2FoldChange		MiaPaca2 Log2FoldChange	
	RNAseq	qPCR	RNAseq	qPCR
<i>PRPF3</i>	1.92	4.69	0.76	1.42
<i>CDCP1</i>	2.12	1.85	1.20	1.86
<i>TNFRSF10D</i>	2.19	2.49	0.89	1.53
<i>TRAF6</i>	1.03	1.26	0.54	1.41
<i>MYBL2</i>	-2.58	-0.27	-1.59	-0.38
<i>TAF15</i>	-2.28	-0.76	-1.16	-0.66
<i>EIF2D</i>	-2.24	-0.64	-1.69	-0.67

Supplementary References

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