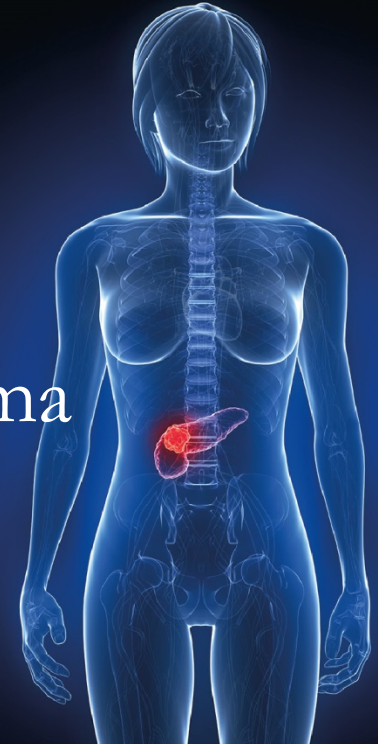


CDK4 Targeting Treatment in preclinical models of pancreatic ductal adenocarcinoma



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Research Fellow, Garvan Institute of Medical Research

Chou et al. GUT accepted September 2017



THE UNIVERSITY OF
SYDNEY

cancer
diagnosis & pathology

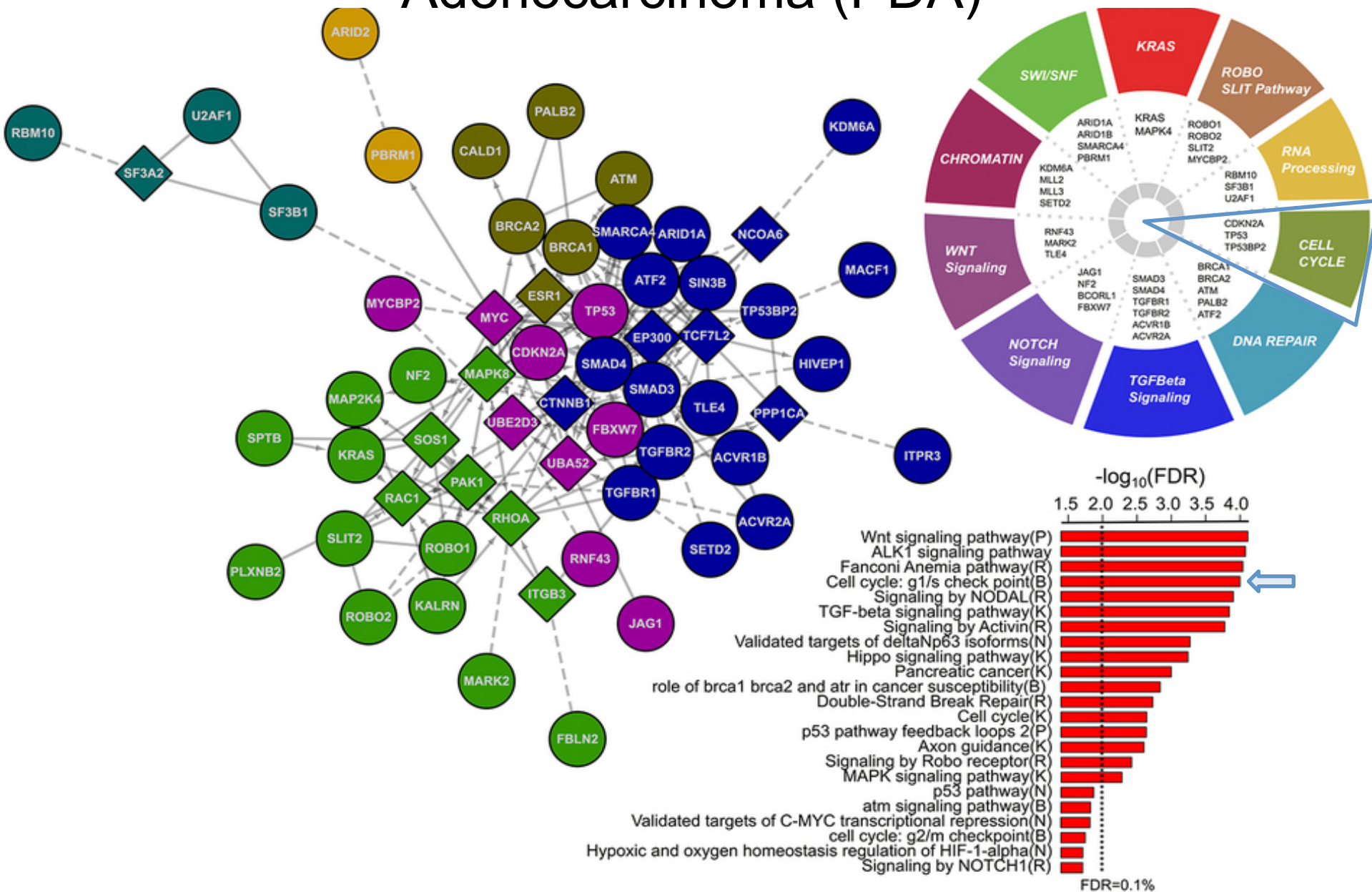
Pancreatic Cancer – Dismal Prognosis



- 4th cause of cancer death (7% alive at 5 years)
- Chemotherapy modestly effective
 - Intrinsic and acquired chemoresistance
- Molecularly heterogeneous disease^{1,2,3,4}

1. Biankin et al. *Nature* 2012
2. Jones et al. *Science* 2008
3. Waddell N, Pajic et al *Nature* 2015
4. Bailey et al *Nature* 2016

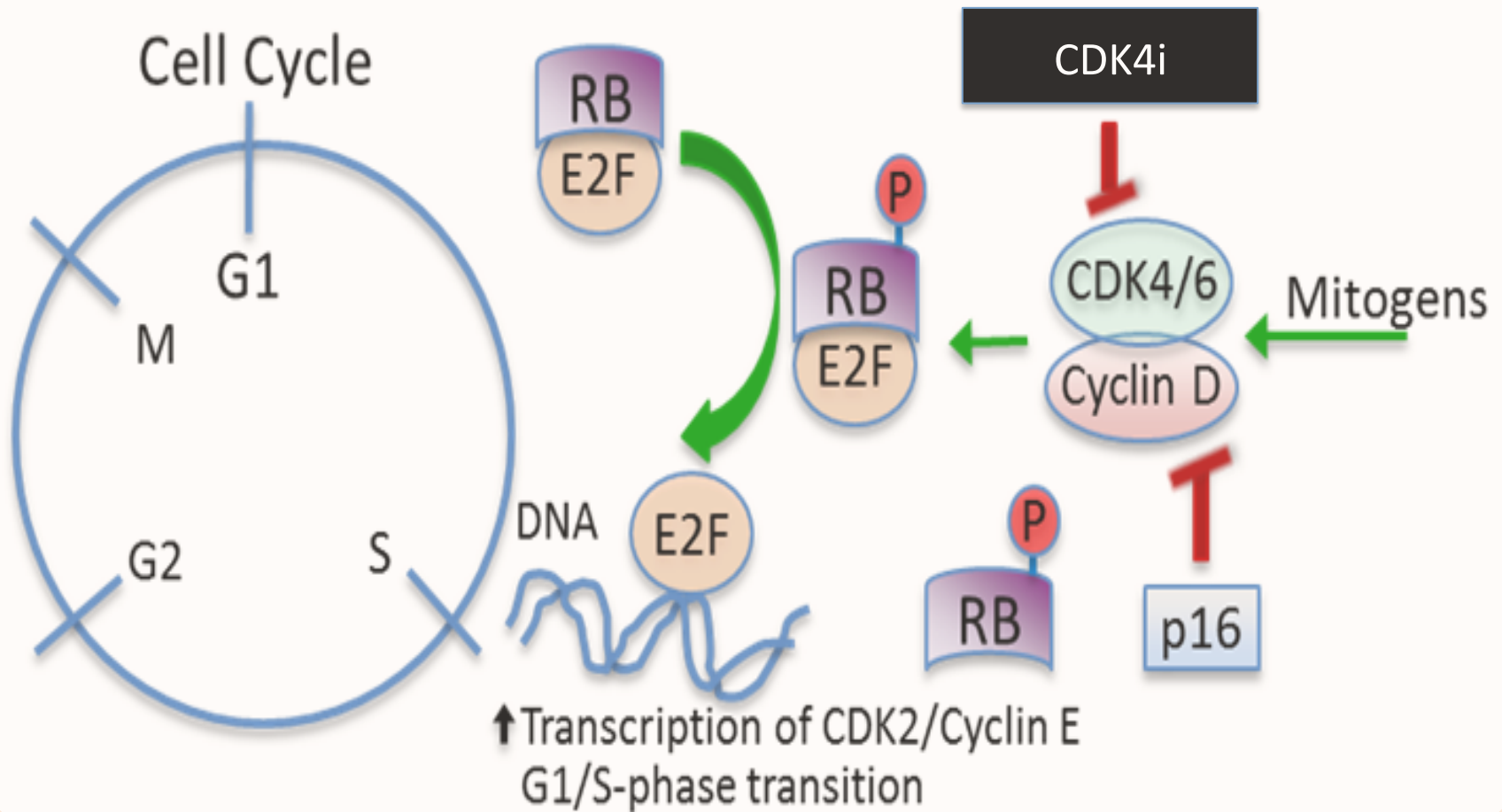
Molecular Subtypes of Pancreatic Ductal Adenocarcinoma (PDA)



The CDK4 Pathway in PDA



CDK4 regulation of cell cycle progression



AIM and HYPOTHESIS



Aim:

1. Assess CDK4i efficacy compared to clinically application chemotherapies with long-term follow-up in patient derived xenograft models
2. Assess mechanism of action of CDK4i
3. Assess for potential biomarker of CDK4i response in clinical samples

Hypothesis:

- CDK4i shows selective efficacy in PDAC with deranged CDK4 pathway

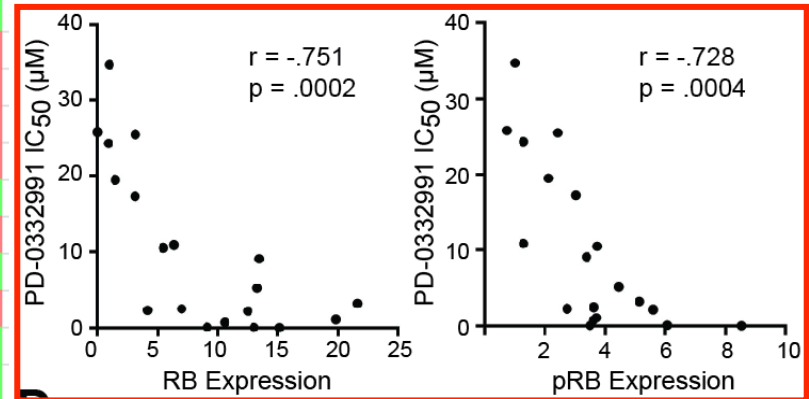
CDK4i sensitivity in PDCL correlates with high total RB and pRB expression



In vitro drug screens

PDCL	PD-0332991		Gemcitabine		5-Fluorouracil		Taxol		nab-Paclitaxel	
	IC ₅₀ (μM)	S.D.	IC ₅₀ (μM)	S.D.	IC ₅₀ (μM)	S.D.	IC ₅₀ (μM)	S.D.	IC ₅₀ (μM)	S.D.
TKCC-02	17.330	4.0	0.0052	0.0010	4.21	0.50	0.0065	0.0007	0.016	0.0033
TKCC-03	0.008	0.004	0.027	0.005	221	41.7	3.03	0.69	2.51	0.68
TKCC-04	10.900	1.9	1211.7	187.5	123.8	22.6	14.2	2.7	10.4	1.8
TKCC-05	0.085	0.011	0.045	0.010	11.8	1.1	0.005	0.0008	0.014	0.004
TKCC-06	25.500	6.36	14.4	1.0	292.2	35.7	58.7	3.7	93.4	7.4
TKCC-07	10.510	0.66	2653.5	454.3	134.6	37.8	35.1	5.7	64.3	3.6
TKCC-09	2.235	0.33	0.064	0.009	342.1	60.0	75.1	6.6	3.4	0.65
TKCC-10	2.455	0.96	0.020	0.002	204.6	23.4	28.7	4.5	17.4	1.8
TKCC-12	24.330	0.75	0.011	0.003	262.6	31.6	0.015	0.003	0.11	0.002
TKCC-14	2.333	0.33	6.0	1.0	353.4	46.9	0.36	0.1	0.348	0.08
TKCC-15	0.738	0.15	0.007	0.002	10.5	3.6	0.008	0.003	0.012	0.003
TKCC-16	34.680	0.53	3434.5	595.9	72.8	3.3	0.11	0.005	0.474	0.13
TKCC-17	0.043	0.004	0.0014	0.0005	17.5	3.8	0.007	0.002	0.019	0.005
TKCC-18	1.090	0.055	0.017	0.008	6.16	1.0	0.008	0.001	0.023	0.007
TKCC-19	5.221	0.80	0.008	0.0002	40.1	5.0	0.041	0.024	0.092	0.021
TKCC-22	3.217	0.029	0.060	0.02	92.8	11.4	62.1	7.5	80.0	7.3
TKCC-23	0.520	0.127	1314.5	114.4	174.7	32.6	0.020	0.005	0.068	0.021
TKCC-26	9.110	0.35	0.024	0.003	140.3	13.8	6.4	0.84	8.1	1.35
TKCC-27	25.750	0.53	20.59	6.06	24.3	6.0	0.012	0.004	0.205	0.073

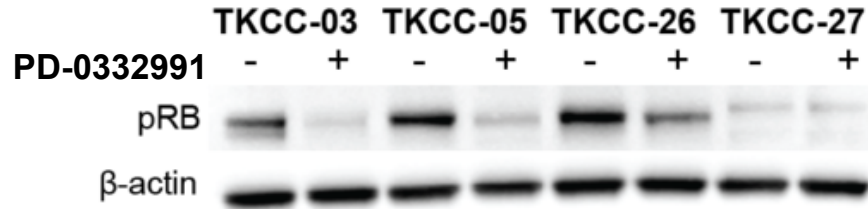
Resistant
Moderate
Sensitive



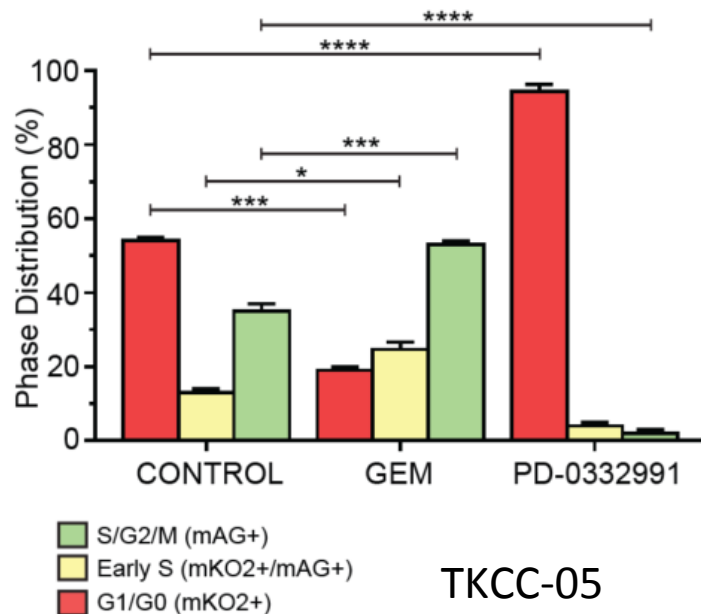
Cytostatic Activity of PD-0332991 in Pancreatic Cancer



A. Decrease in pRB in selected PDCLs post-treatment



B. Effective target modulation (G0/G1 arrest)

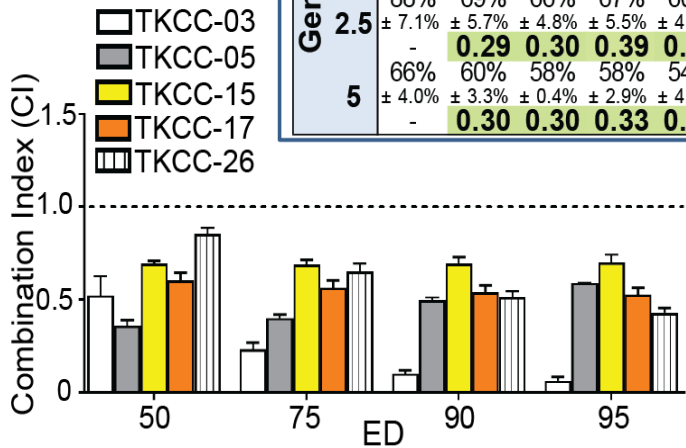


Standard Therapy (Gemcitabine) Synergizes with PD-0332991 in RB-High PDCLs



RB-high PDCLs

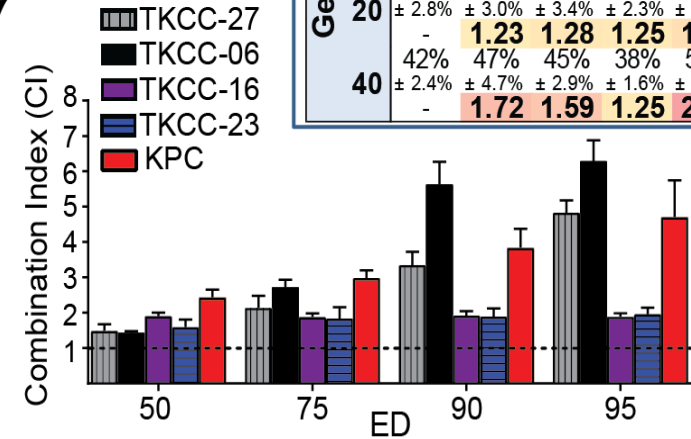
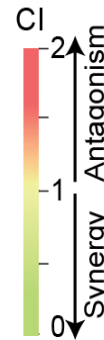
Gemcitabine (nM)	% live CI	PD-0223991 (μM)					
		0	0.7	1	1.5	2.2	3.3
0	100% -	90% ± 0.7%	85% ± 0.3%	84% ± 0.6%	80% ± 2.2%	77% ± 1.9%	
0.3	99% ± 5.0%	82% ± 3.4%	82% ± 2.8%	80% ± 9.9%	76% ± 9.2%	71% ± 1.2%	
0.6	97% ± 2.6%	83% ± 3.5%	81% ± 4.3%	78% ± 1.5%	77% ± 1.1%	68% ± 3.7%	
1.3	96% ± 4.2%	80% ± 6.0%	79% ± 0.8%	72% ± 3.9%	69% ± 0.1%	67% ± 3.6%	
2.5	88% ± 7.1%	69% ± 5.7%	66% ± 4.8%	67% ± 5.5%	60% ± 4.8%	59% ± 3.2%	
5	66% ± 4.0%	60% ± 3.3%	58% ± 0.4%	58% ± 2.9%	54% ± 4.1%	54% ± 2.1%	



Synergy

RB-low/ negative PDA cells

Gemcitabine (μM)	% live CI	PD-0223991 (μM)					
		0	0.9	1.9	3.75	7.5	15
0	100% -	100% ± 5.8%	103% ± 7.8%	102% ± 2.4%	93% ± 5.8%	70% ± 2.9%	
2.5	83% ± 4.1%	87% ± 2.0%	86% ± 4.6%	87% ± 3.5%	81% ± 4.7%	57% ± 4.6%	
5.0	71% ± 3.4%	70% ± 5.1%	71% ± 3.4%	74% ± 5.1%	74% ± 2.2%	60% ± 2.1%	
10	51% ± 2.6%	55% ± 5.6%	58% ± 3.6%	57% ± 4.4%	58% ± 1.1%	47% ± 4.8%	
20	43% ± 2.8%	42% ± 3.0%	46% ± 3.4%	44% ± 2.3%	52% ± 4.1%	43% ± 1.1%	
40	42% ± 2.4%	47% ± 4.7%	45% ± 2.9%	38% ± 1.6%	50% ± 3.5%	28% ± 3.3%	



Antagonism

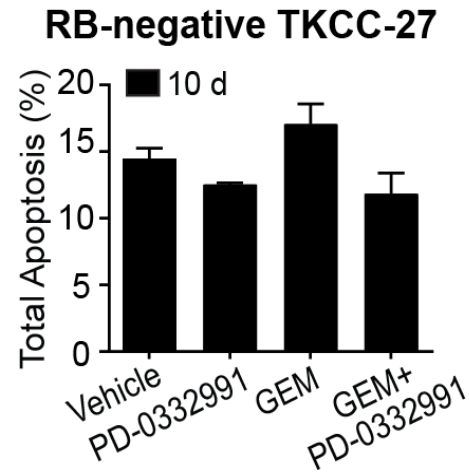
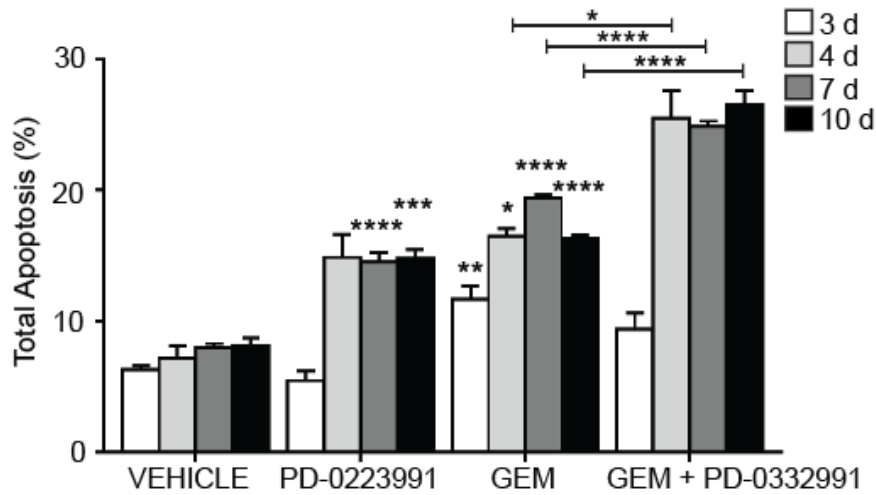
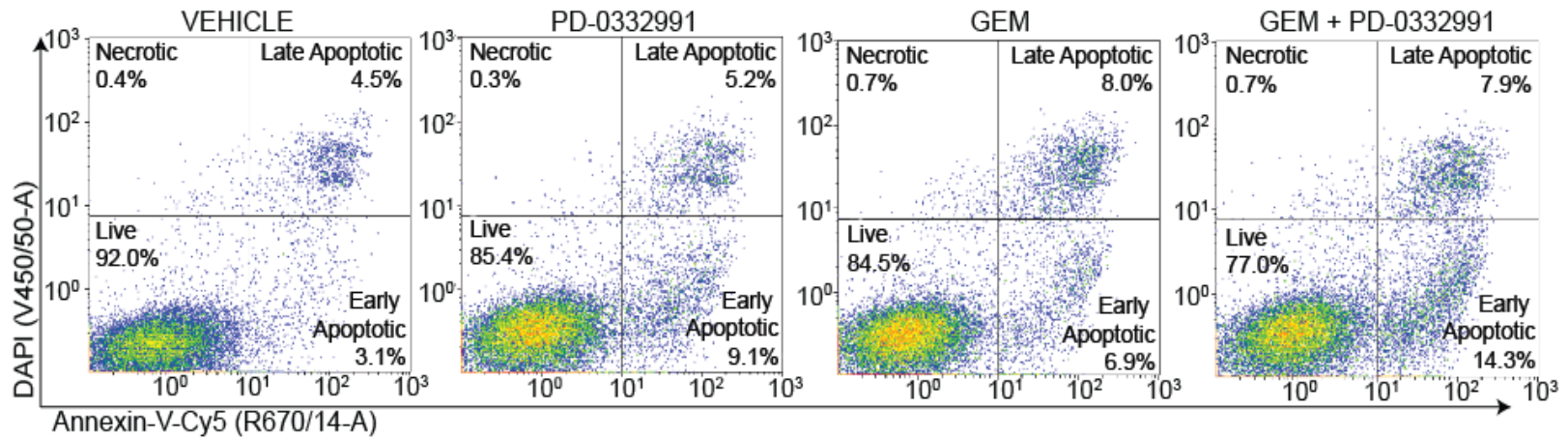
Combination index (CI)

<1 synergistic

1 = additive

>1 antagonistic

Observed synergy is associated with increased apoptosis



Effects of CDK4/6i on the tumour microenvironment



Nature. 2017 Aug 24;548(7668):471-475. doi: 10.1038/nature23465. Epub 2017 Aug 16.

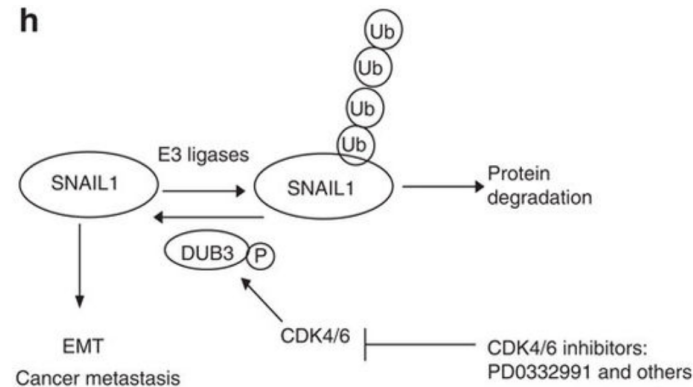
CDK4/6 inhibition triggers anti-tumour immunity.

Goel S^{1,2}, DeCristo MJ^{3,4}, Watt AC¹, BrinJones H¹, Sceneay J^{3,4}, Li BB¹, Khan N¹, Ubellacker JM^{3,4}, Xie S¹, Metzger-Filho O², Hoog J⁵, Ellis MJ⁶, Ma CX⁵, Ramm S^{7,8}, Krop IE², Winer EP², Roberts TM¹, Kim HJ^{9,10}, McAllister SS^{3,4,11,12}, Zhao JJ^{1,12,13}.

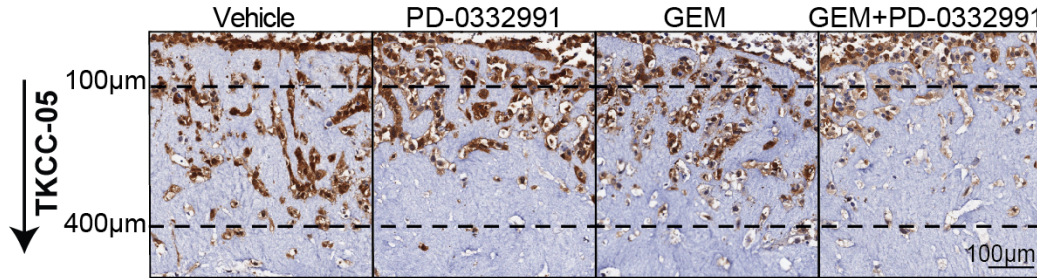
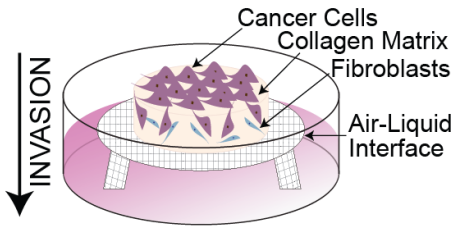
Nat Commun. 2017 Jan 9;8:13923. doi: 10.1038/ncomms13923.

CDK4/6-dependent activation of DUB3 regulates cancer metastasis through SNAIL1.

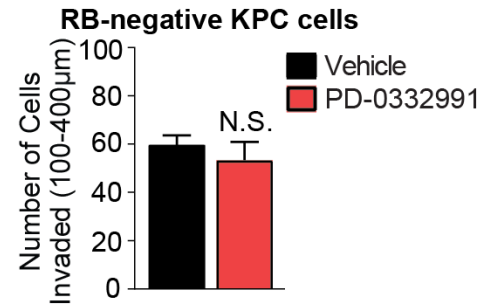
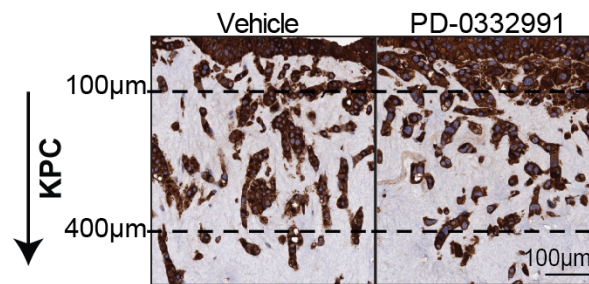
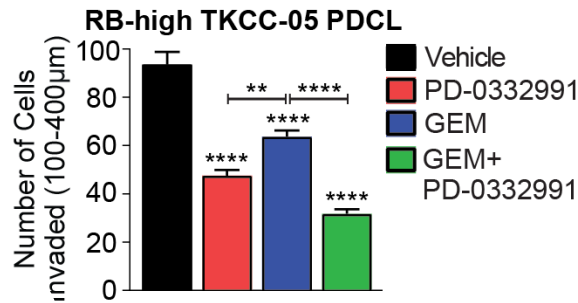
Liu T^{1,2}, Yu J³, Deng M², Yin Y^{4,5}, Zhang H⁶, Luo K^{2,4,5}, Qin B², Li Y^{4,5}, Wu C^{4,5}, Ren T⁷, Han Y⁸, Yin P⁹, Kim J², Lee S², Lin J¹⁰, Zhang L¹¹, Zhang J¹¹, Nowsheen S¹², Wang L³, Boughey J¹³, Goetz MP^{2,3}, Yuan J^{2,4,5}, Lou Z².



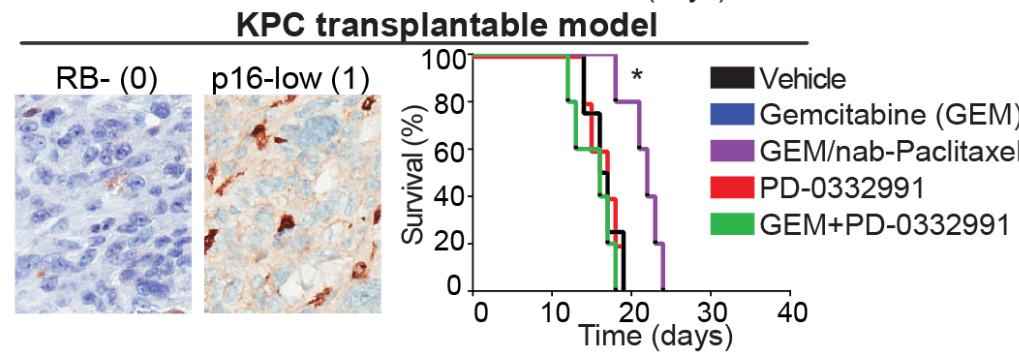
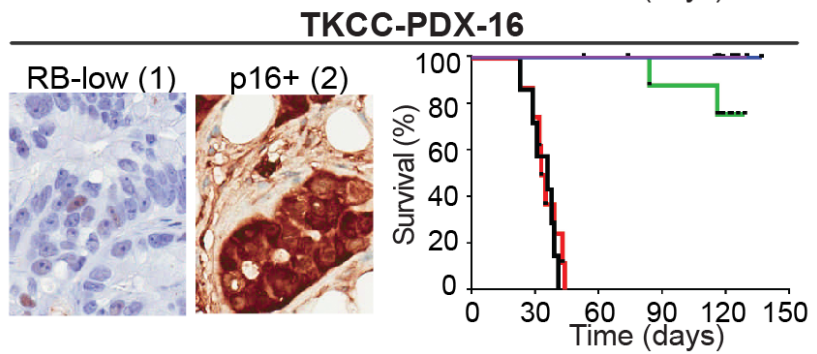
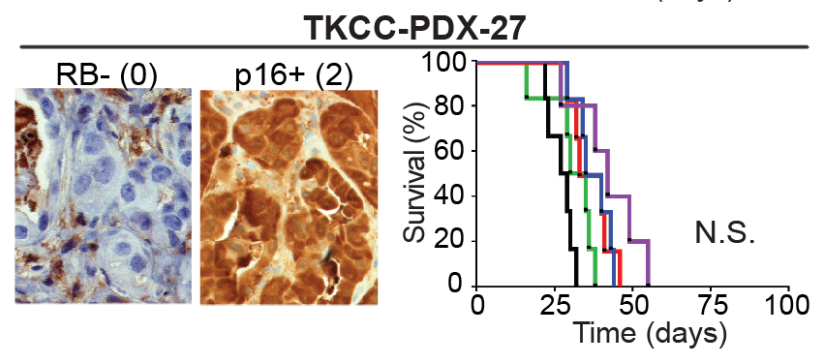
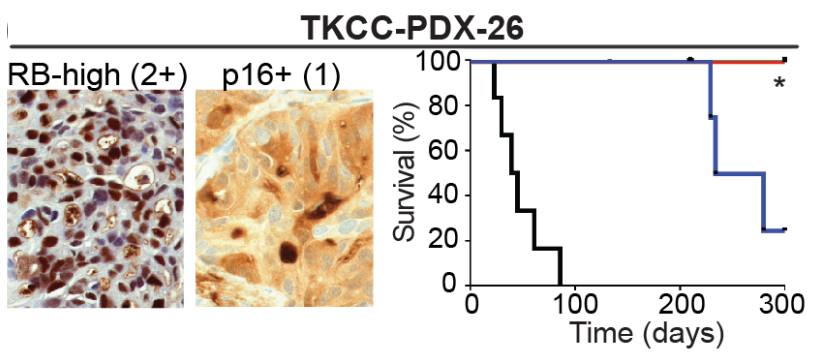
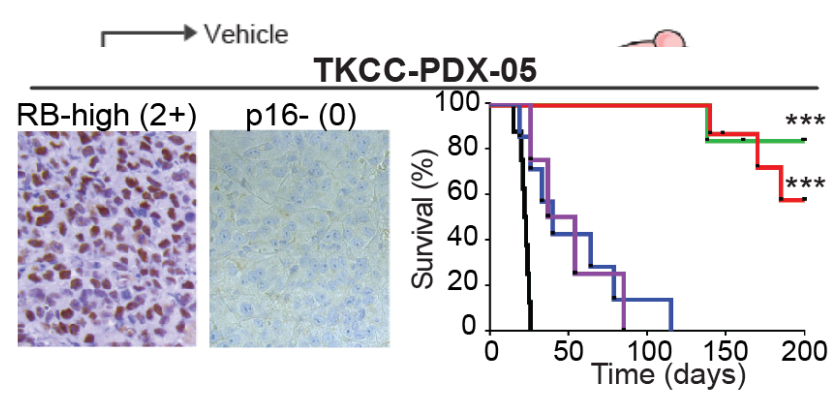
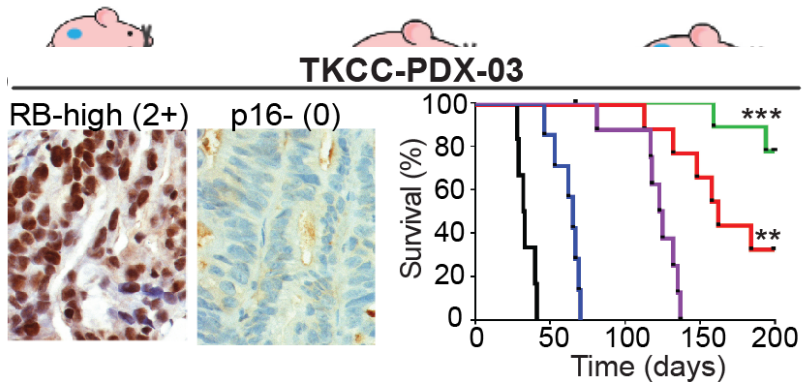
CDK4/6 Inhibition Modulates Invasion in the RB-high PDA Setting



3D organotypic model



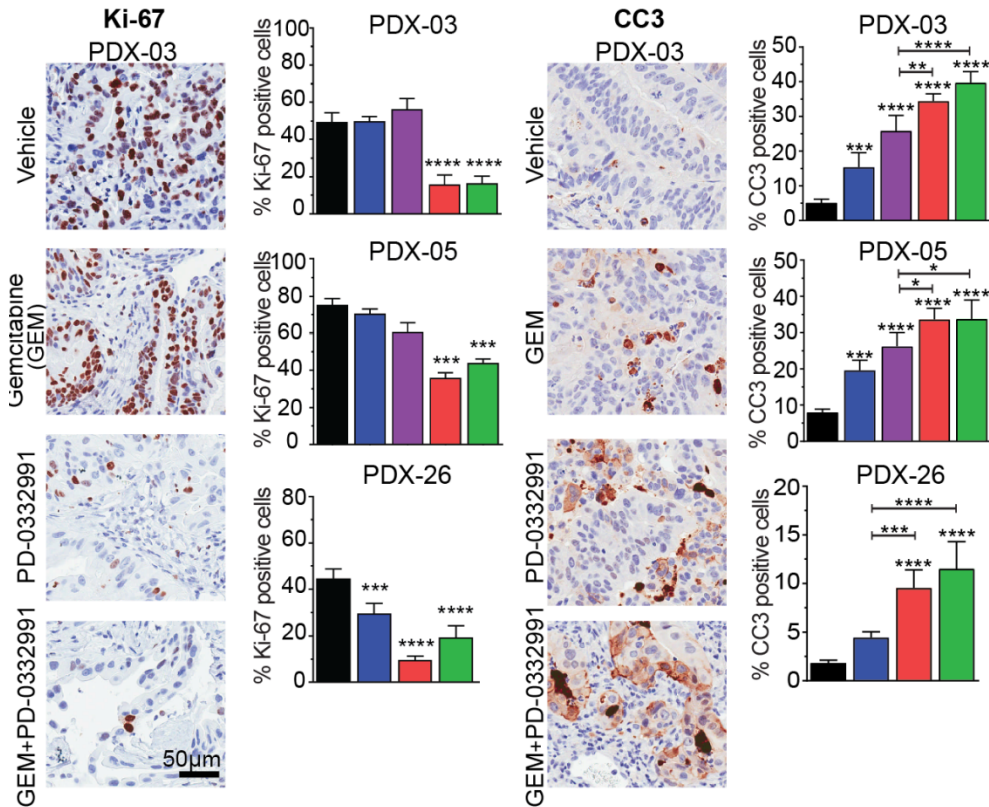
In vivo efficacy of CDK4/6i in RB-high PDA



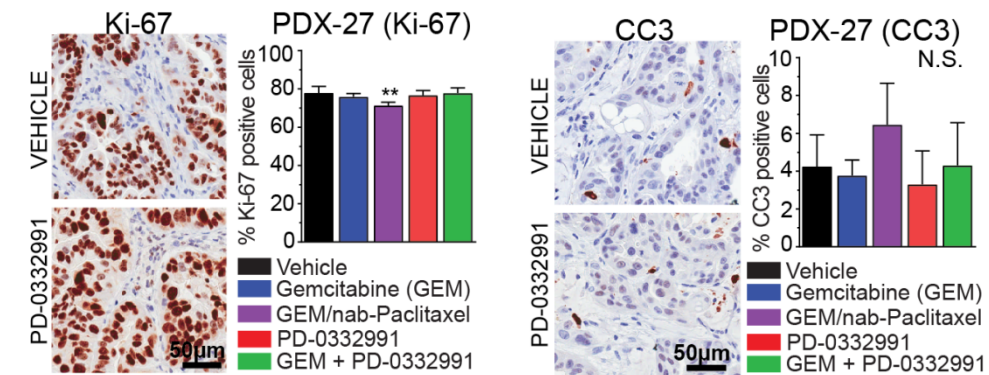
...Associated with Quiescence and apoptosis in RB-High Settings



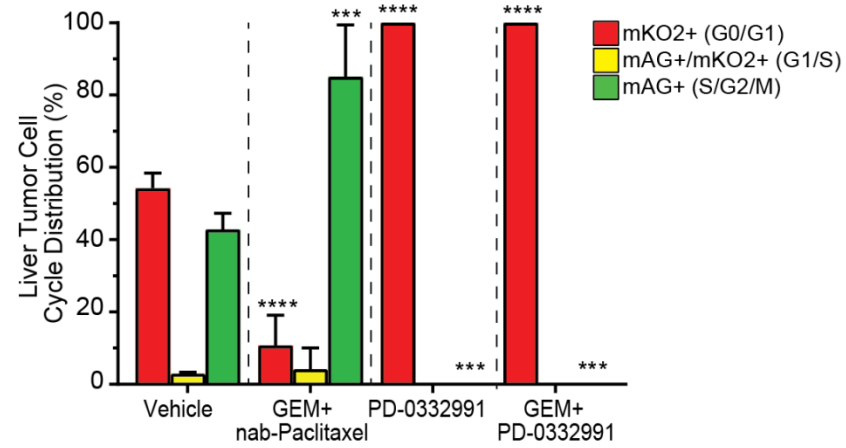
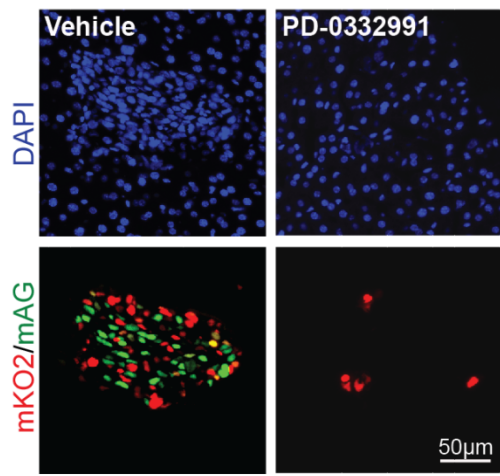
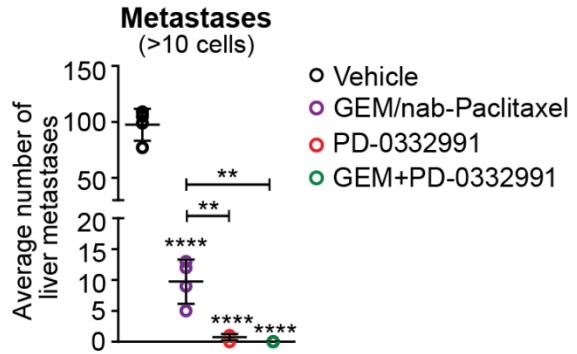
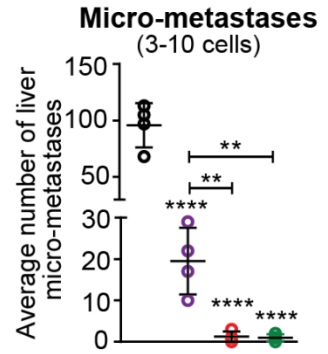
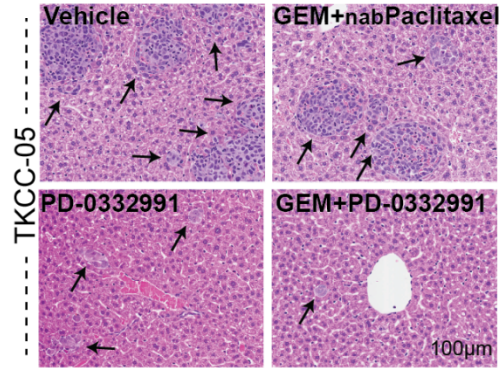
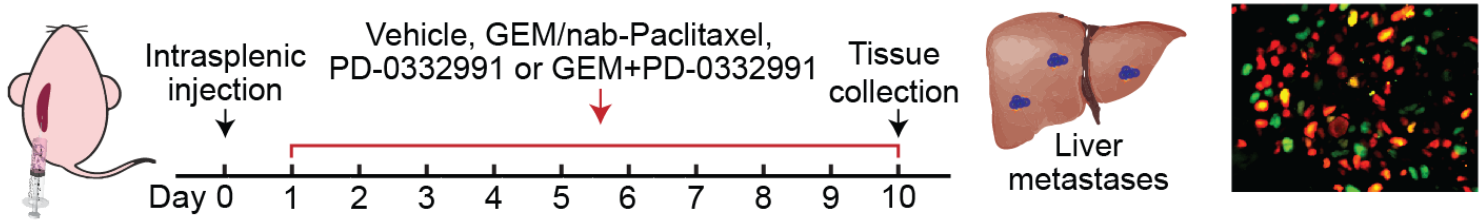
RB-high PDX



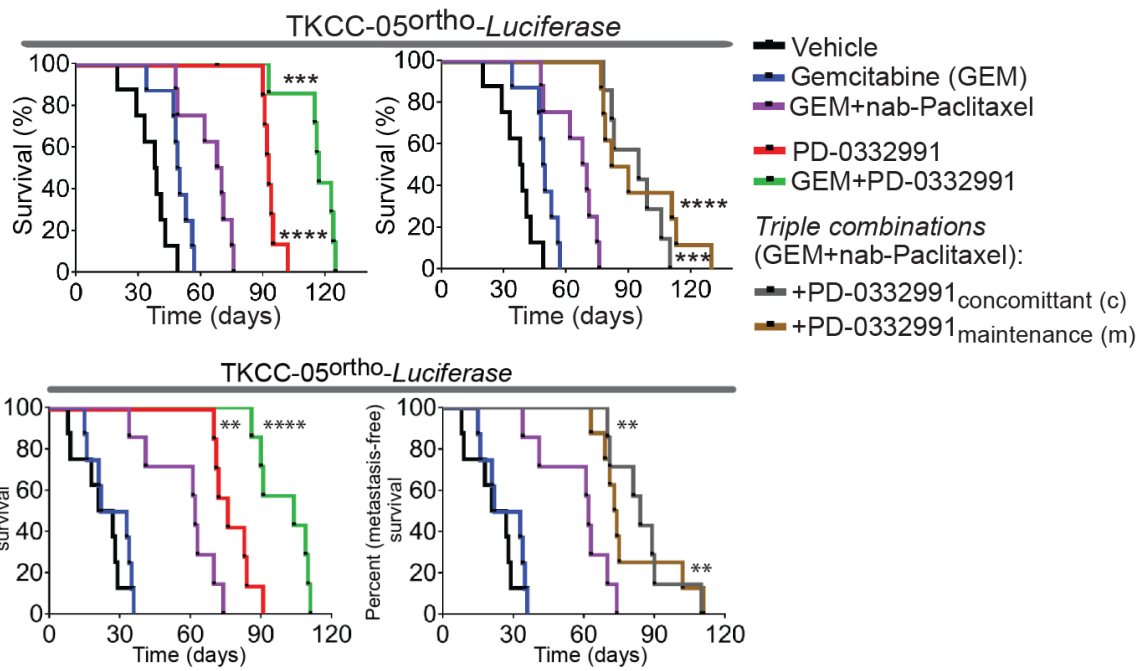
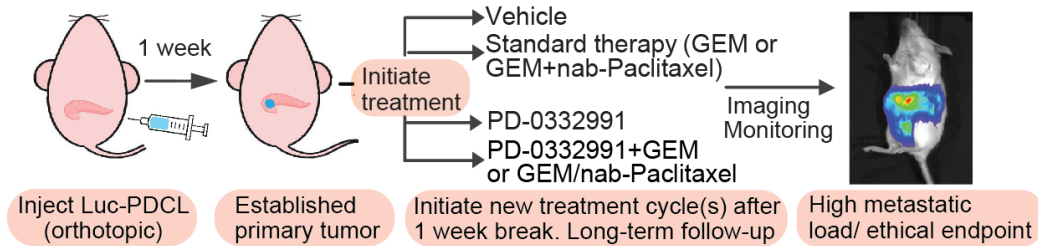
RB - PDX



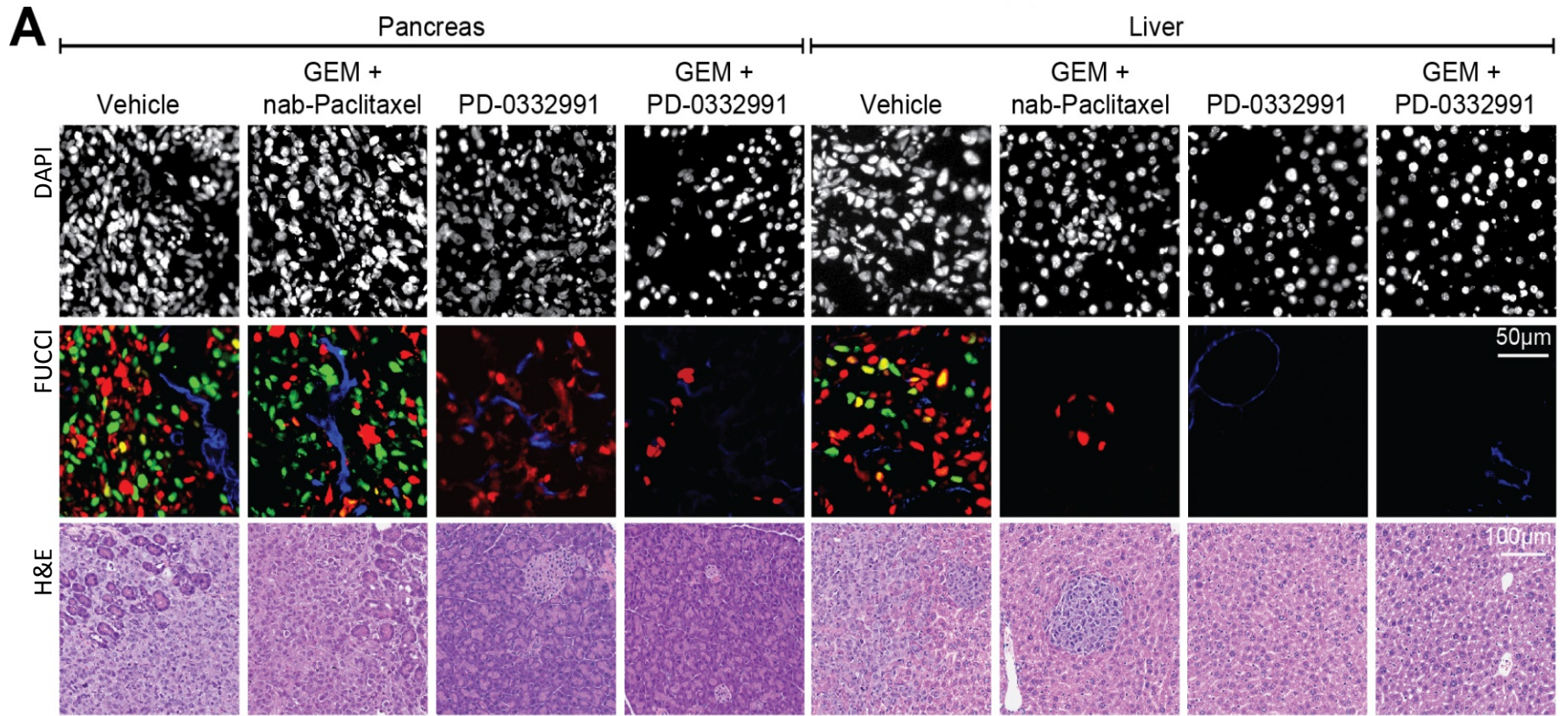
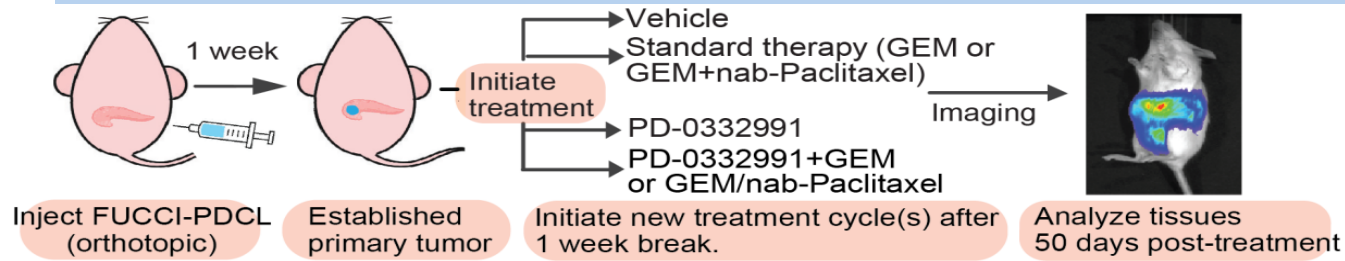
CDK4/6i Therapeutic Interventions Inhibit Spread in the Liver



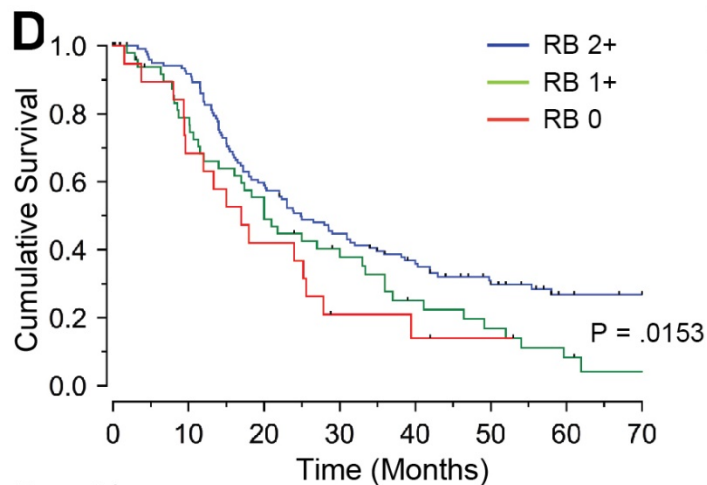
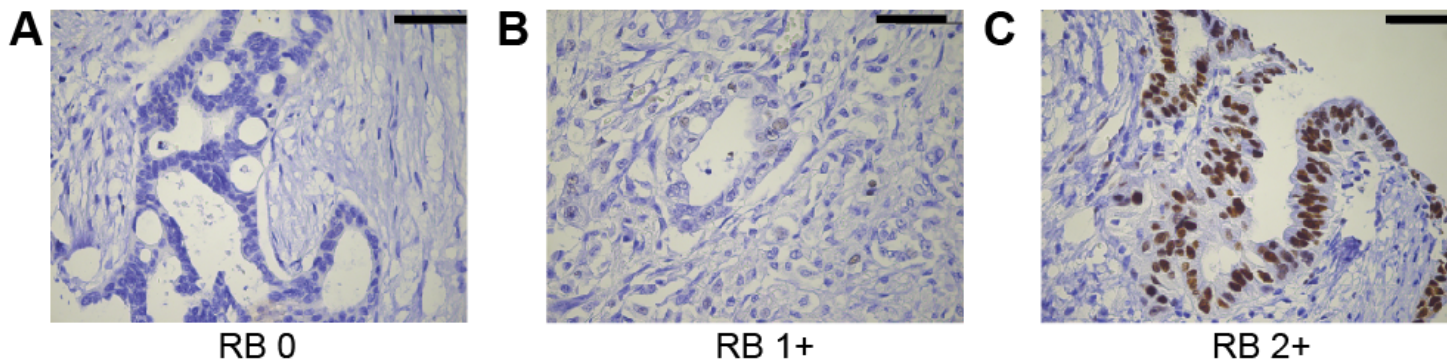
CDK4i-Based Therapy Delays Disease Progression in PDA



CDK4/6i Mono- and Combination Therapy Delays Metastasis in PDA

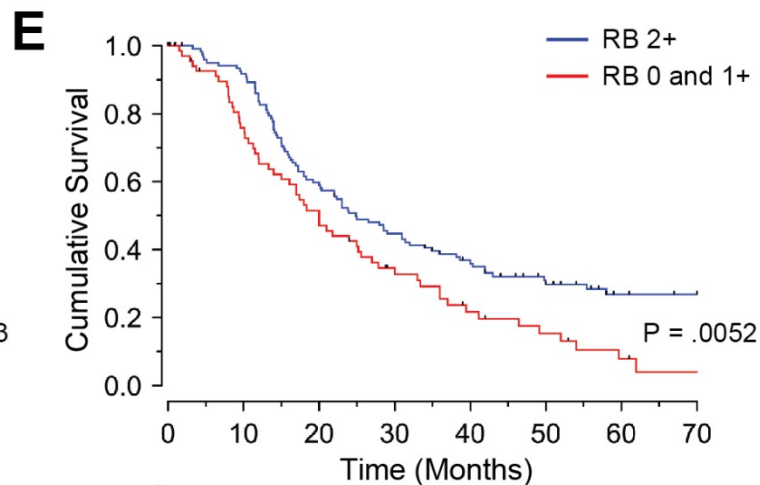


RB is Prevalent in PDA and of Prognostic Value



No. at risk	0	10	20	30	40	50	60	70
RB 2	129	113	73	58	43	30	19	15
RB 1	52	42	28	23	18	15	12	11
RB 0	19	13	8	4	3			

Median survival 17 vs 20 vs 24.9 months



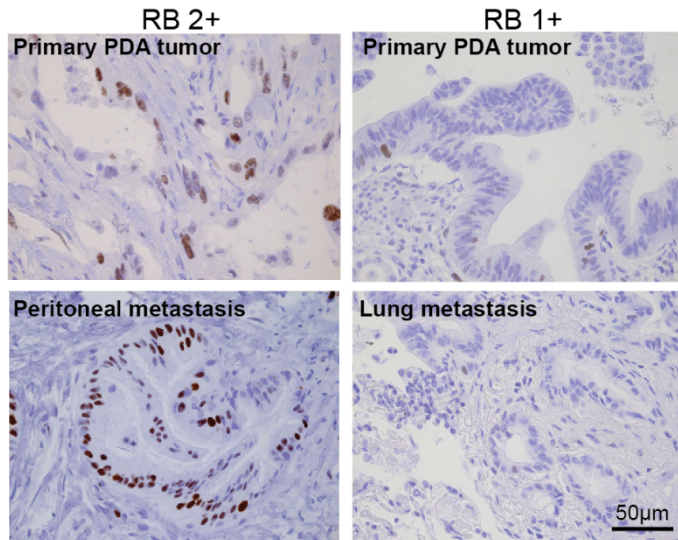
No. at risk	0	10	20	30	40	50	60	70
RB 2	129	113	73	58	43	30	19	15
RB 0/1	71	65	36	27	21	15	12	11

Median survival 20 vs 24.9 months

RB is Prevalent in Metastatic PDA



RNSH Metastatic Cohort		
RB Score	RB prevalence	
	<i>n</i> =54	%
score 2	36	67
score 1	15	27
score 0	3	6



Metastasis RB score	Matched Primary Tumor RB score	
	High (2)	Negative (0/1)
High (2)	9	1
Negative (0/1)	0	2

kappa = 0.750 (SE 0.232; 95% CI 0.296 to 1.000)

CDK4/6-based Therapy in PDA



- RB high phenotype specific
- Subtype-specific efficacy at multiple stages of PDA progression
- Complex mechanism of action (tumour and stroma)
- Where to from here?



Acknowledgements



*Personalised Cancer
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Tim Molloy

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Jas Samra

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Metastasis (Garvan)*

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*Transplantation
Immunology (Garvan)*

Shane Grey

APGI

Lorraine Chantrill

Amber Johns

Sean Grimmond

Andrew Biankin

QIMR

Nicola Waddell



...AND the generous support
of patients,
family members and friends,
members of community



Team Phil
Ms Jane Hemstrich