Microenvironmental control of tumor dissemination and response to therapy

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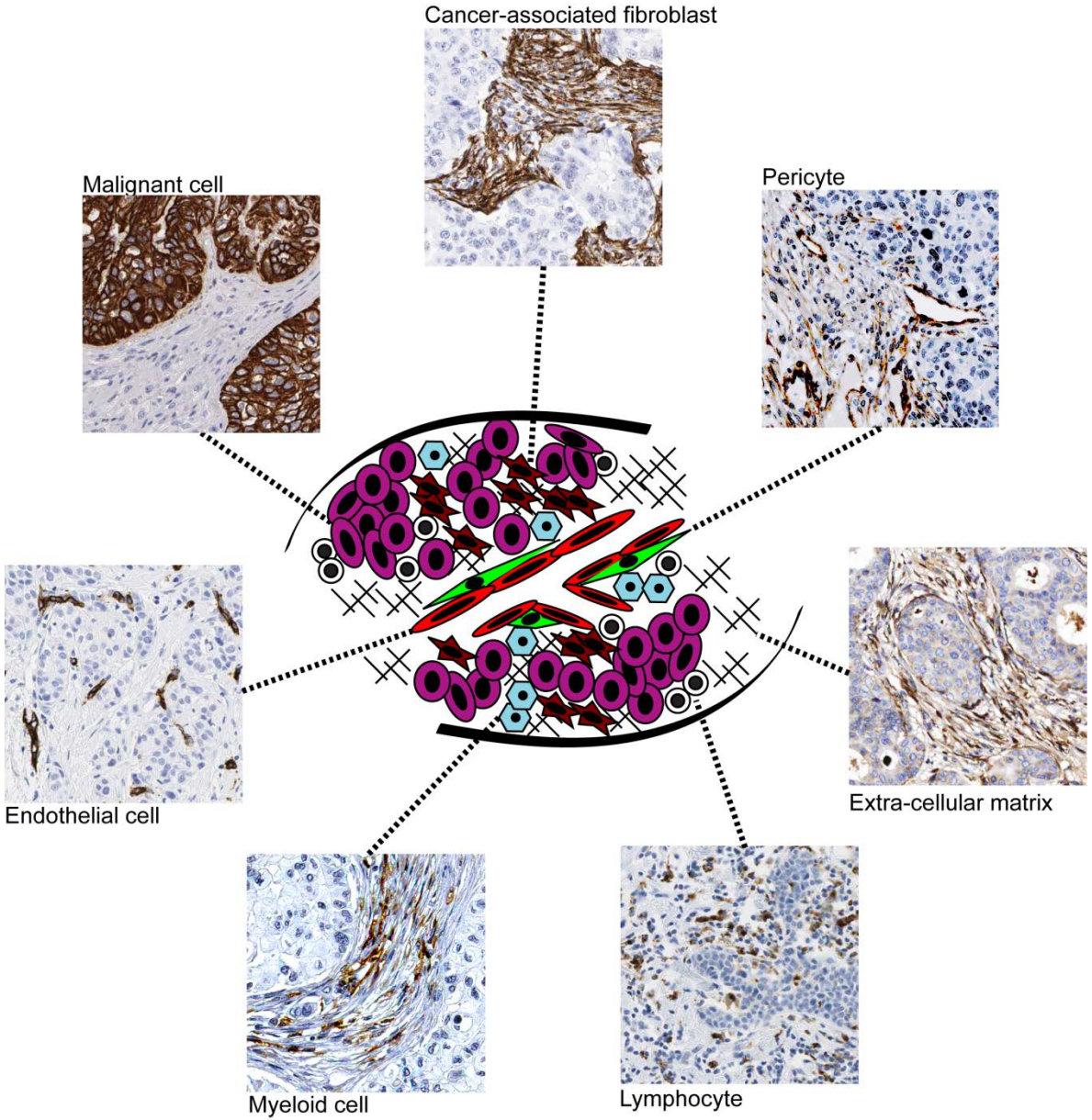
KRISTIAN PIETRAS

GROSSKOPF PROFESSOR OF MOLECULAR MEDICINE

The tumor as a communicating organ



Pietras and Östman, Exp Cell Res, 2010

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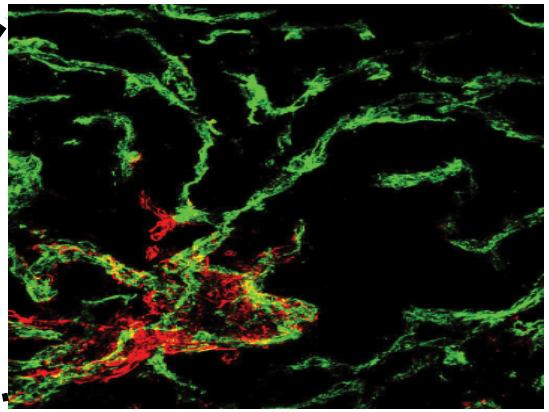
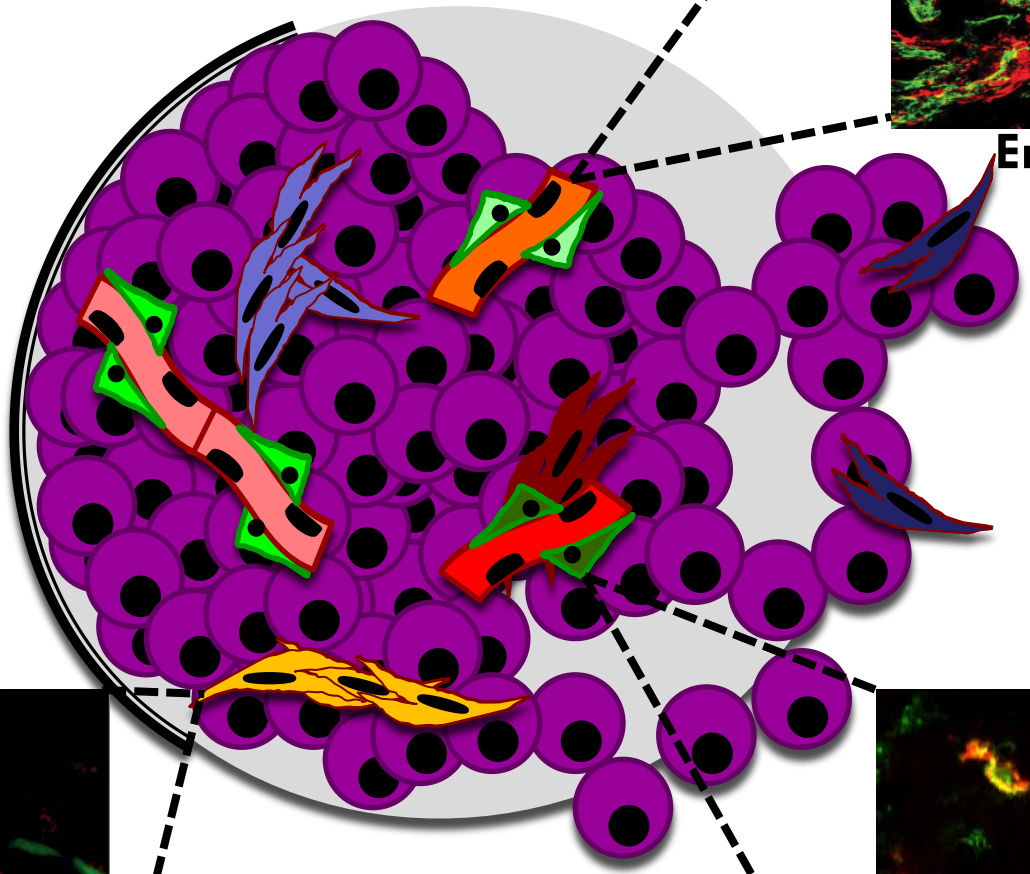
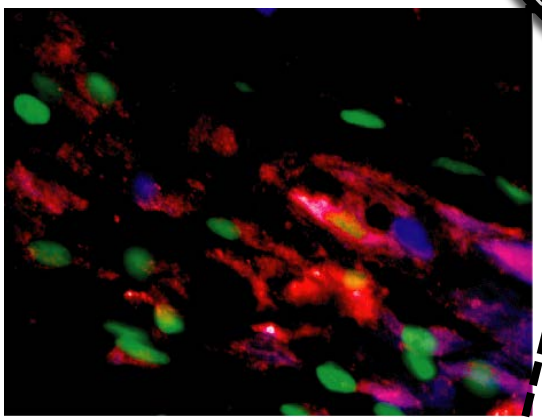
A refined tumor taxonomy



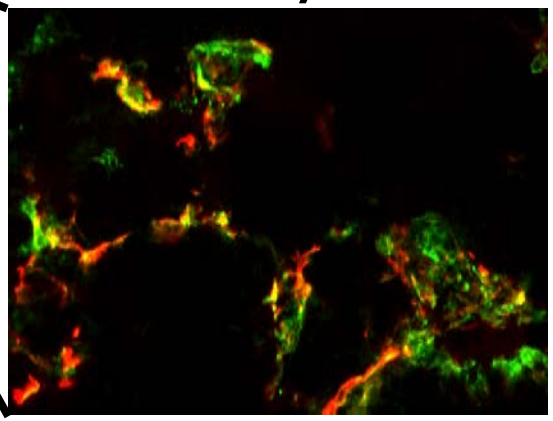
Endothelial subsets



Fibroblast subsets

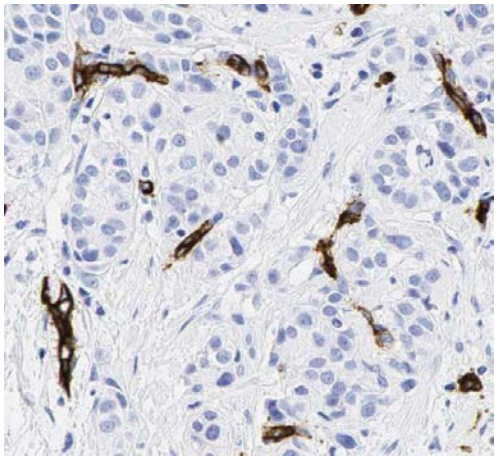


Pericyte subsets

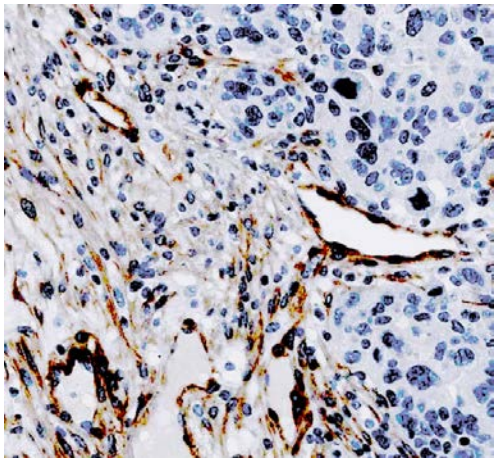


Our focus

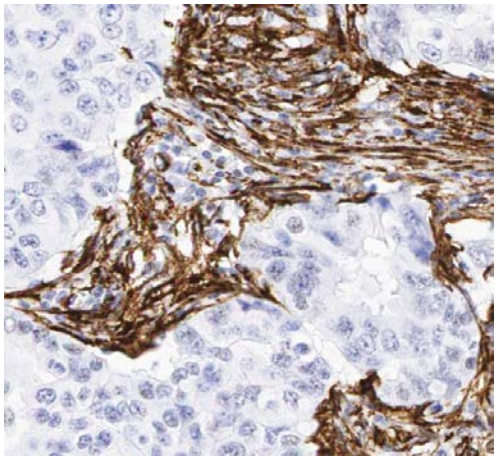
Breast cancer



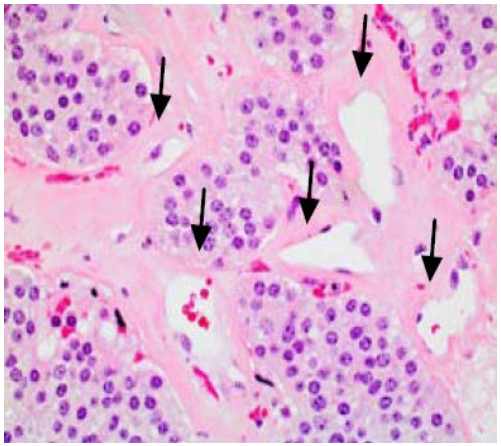
Endothelial cells

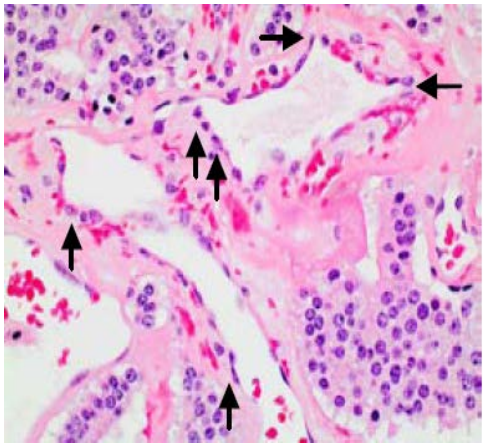


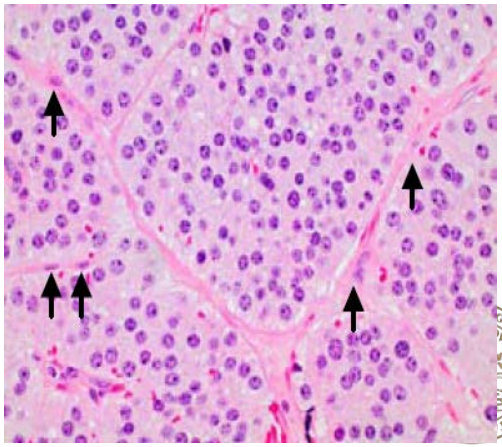
Pericytes



Cancer-associated fibroblasts







Pancreatic neuroendocrine tumors

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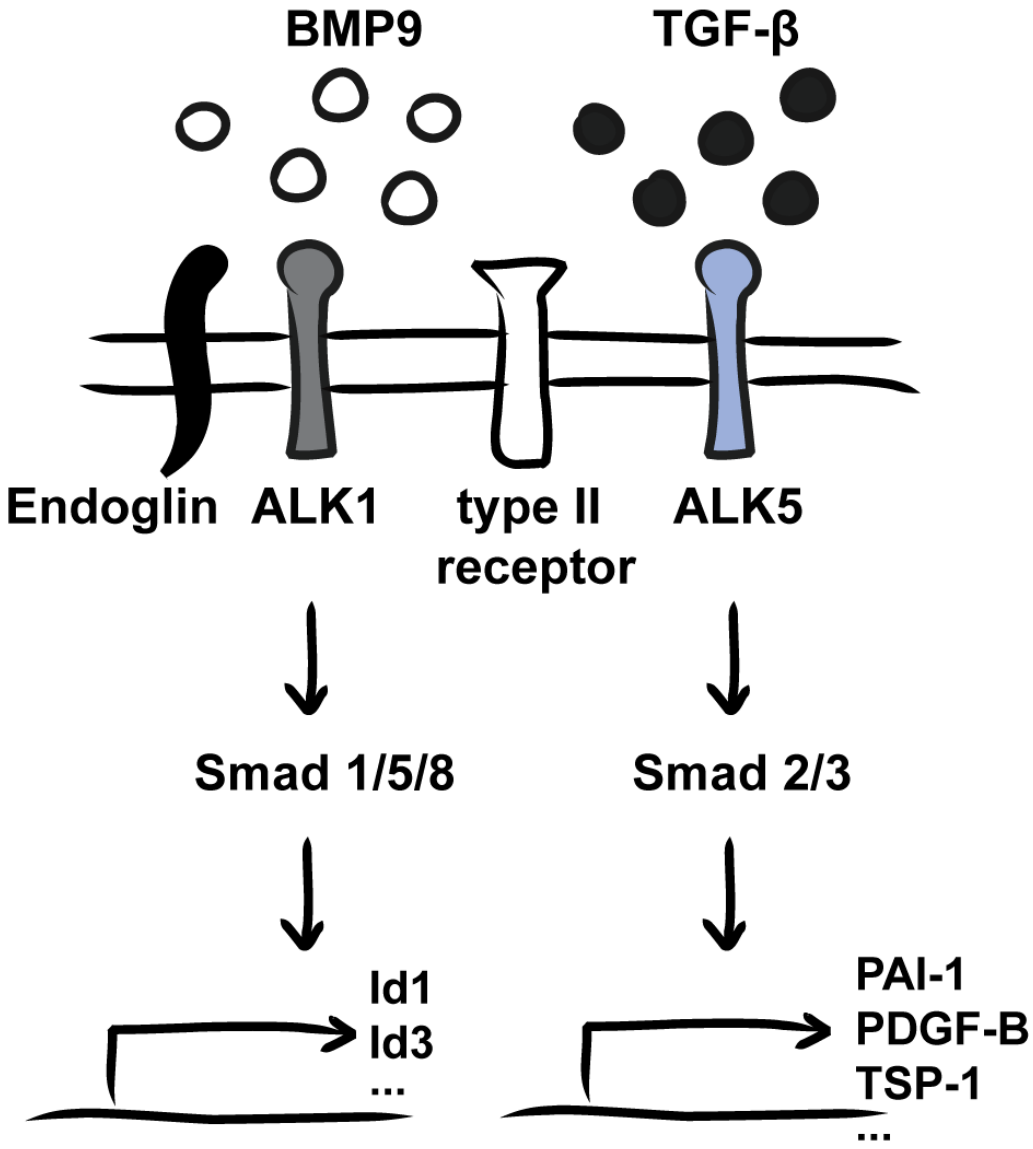
Simplified TGF-β family signaling in endothelial cells



Cunha and Pietras, Blood, 2011

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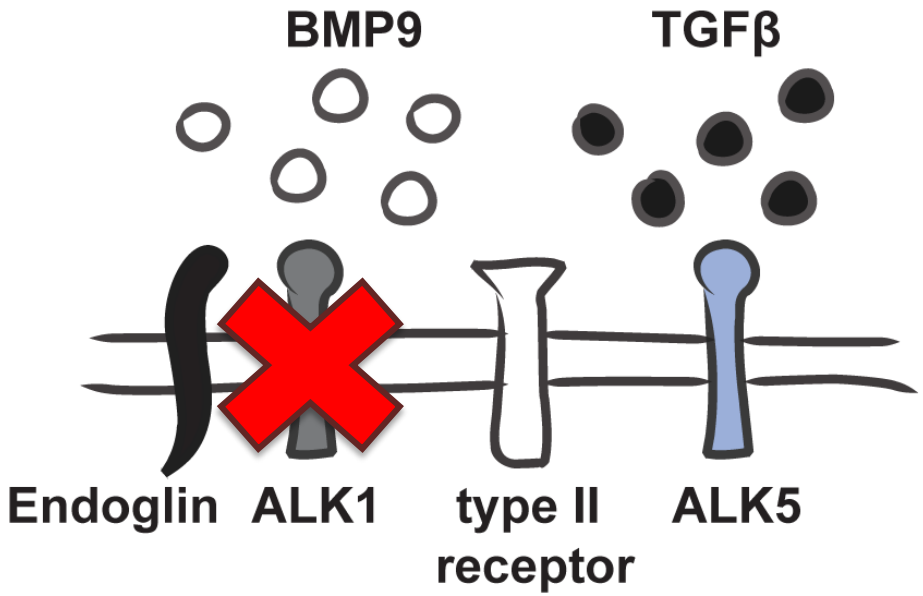
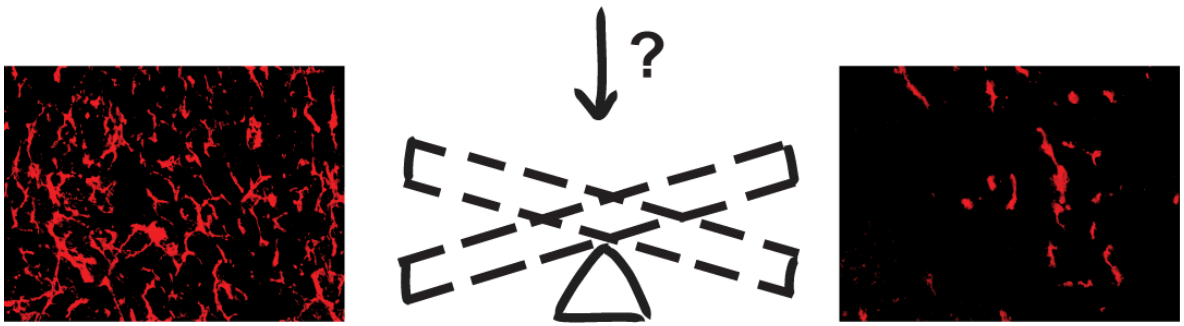
Simplified TGF-β family signaling in endothelial cells





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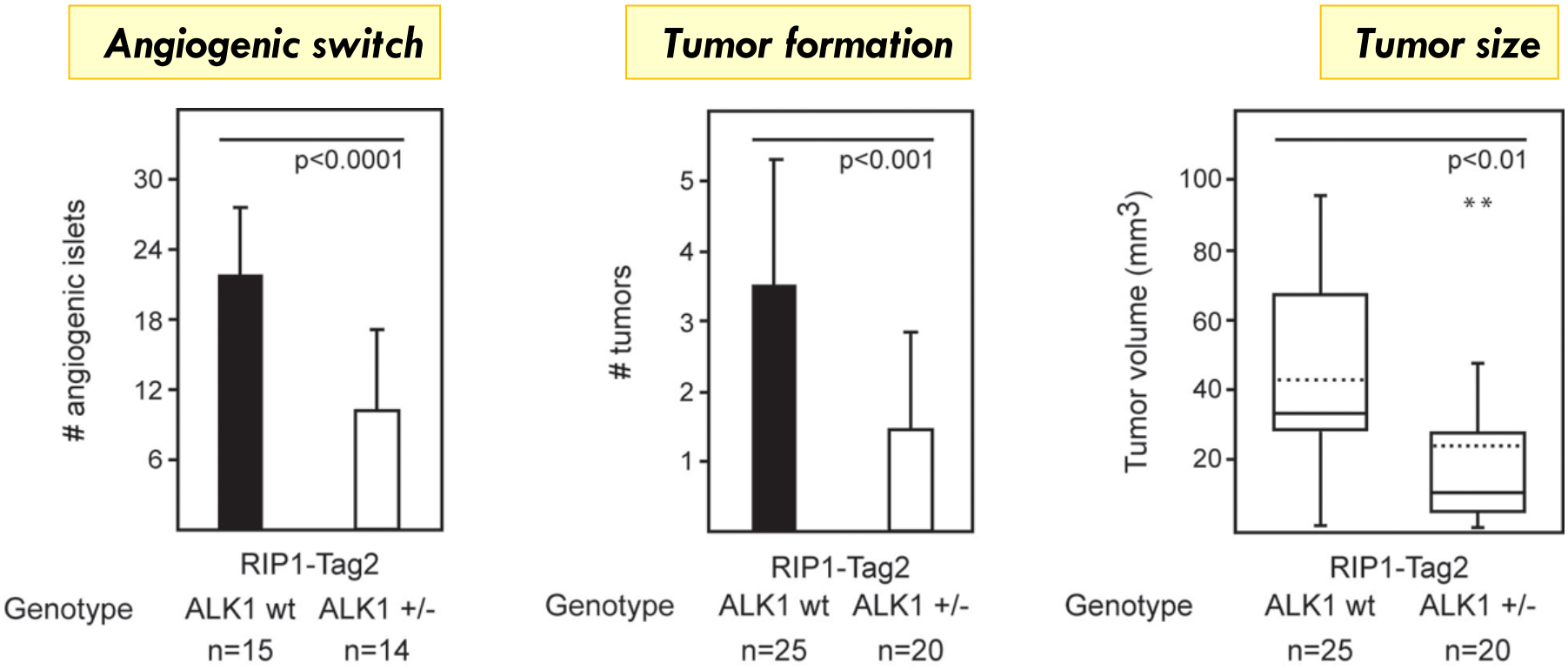
Genetically impaired ALK1 signaling retards tumor progression in RIP1-Tag2 mice



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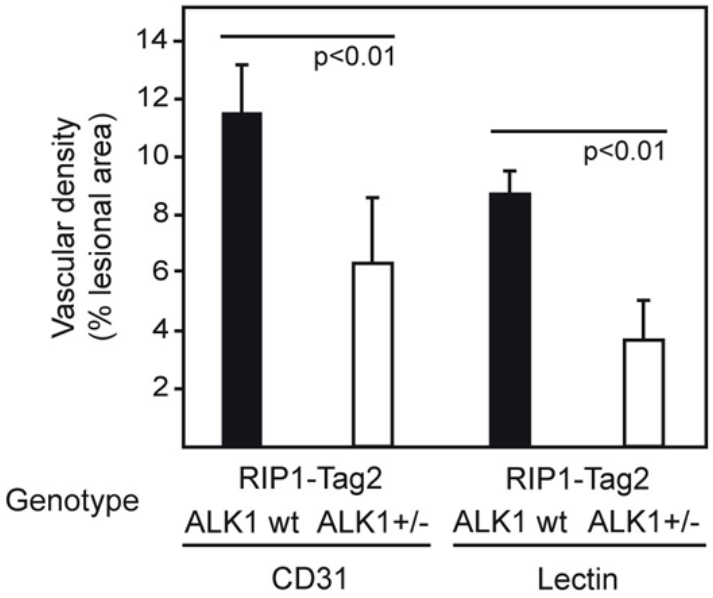
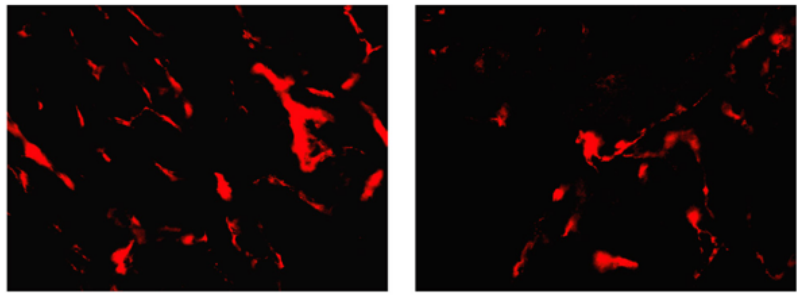
Genetically impaired ALK1 signaling hampers tumor angiogenesis



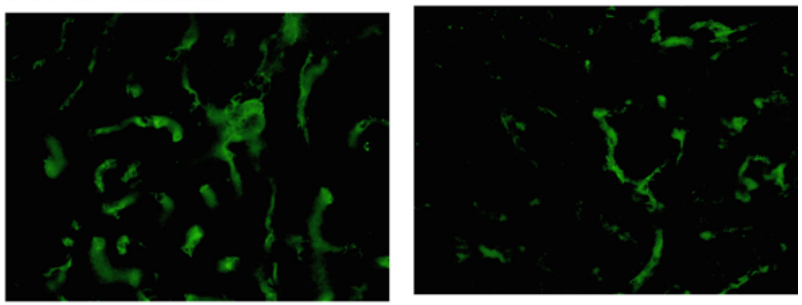
CD31



RIP1-Tag2
ALK1 wt

RIP1-Tag2
ALK1 +/-

FITC-Lectin



RIP1-Tag2
ALK1 wt

RIP1-Tag2
ALK1 +/-

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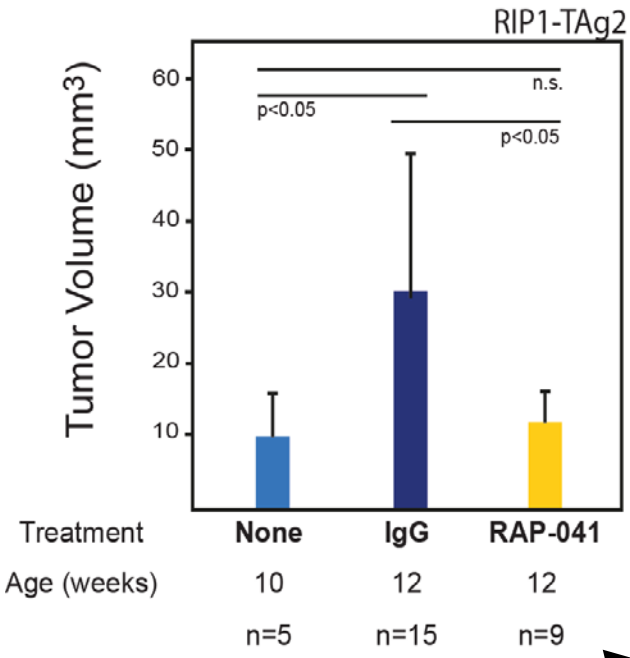
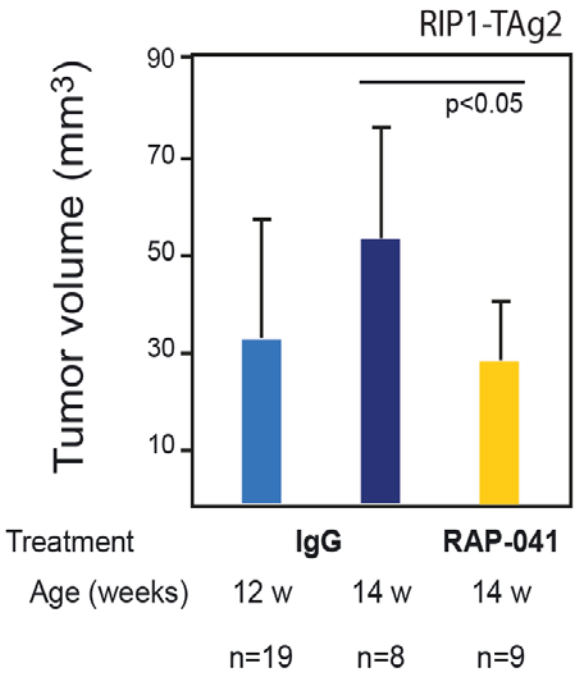
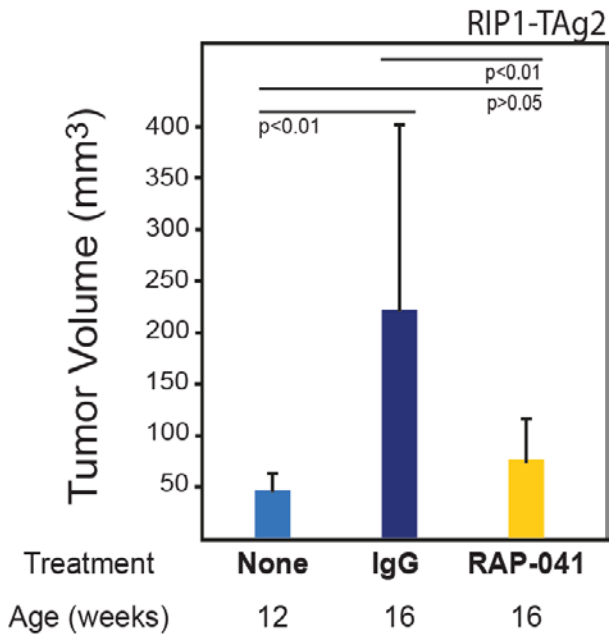
Therapeutic trials in RIP1-Tag2 mice







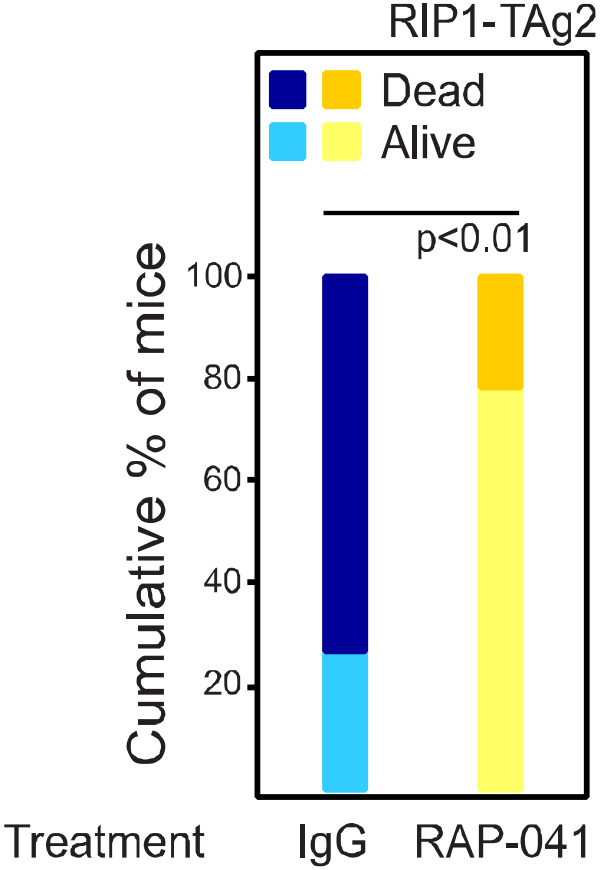
Intervention Trial (10-12 w.)

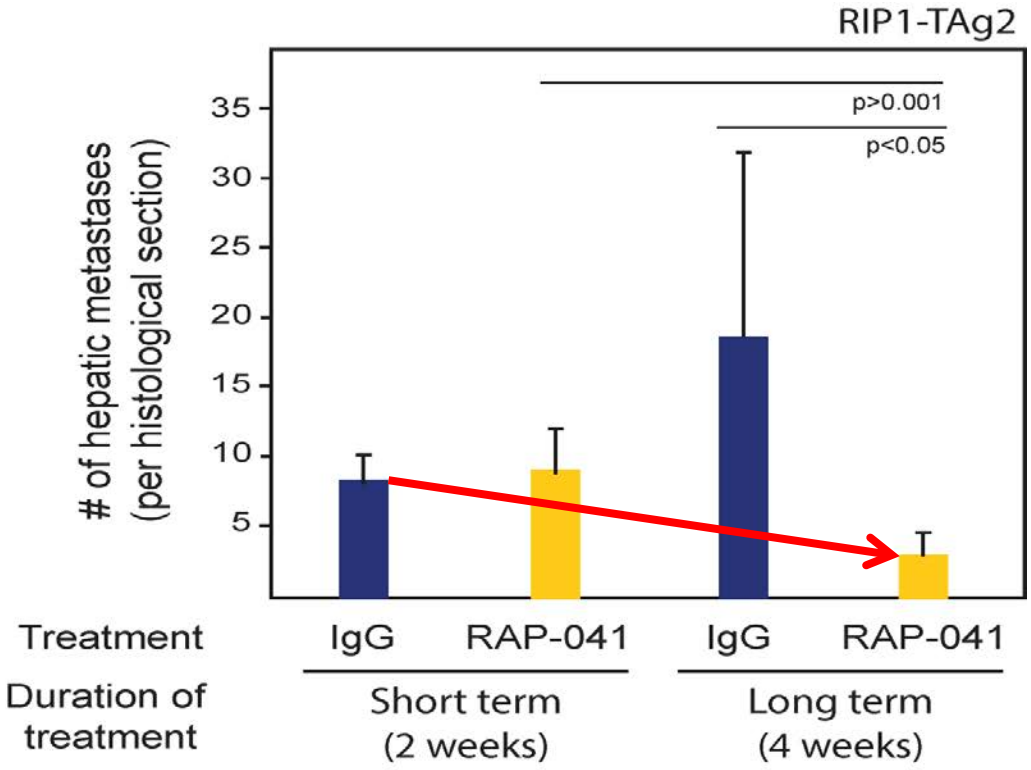
Regression Trial (12-14 w.)

Regression Trial (12-16 w.)

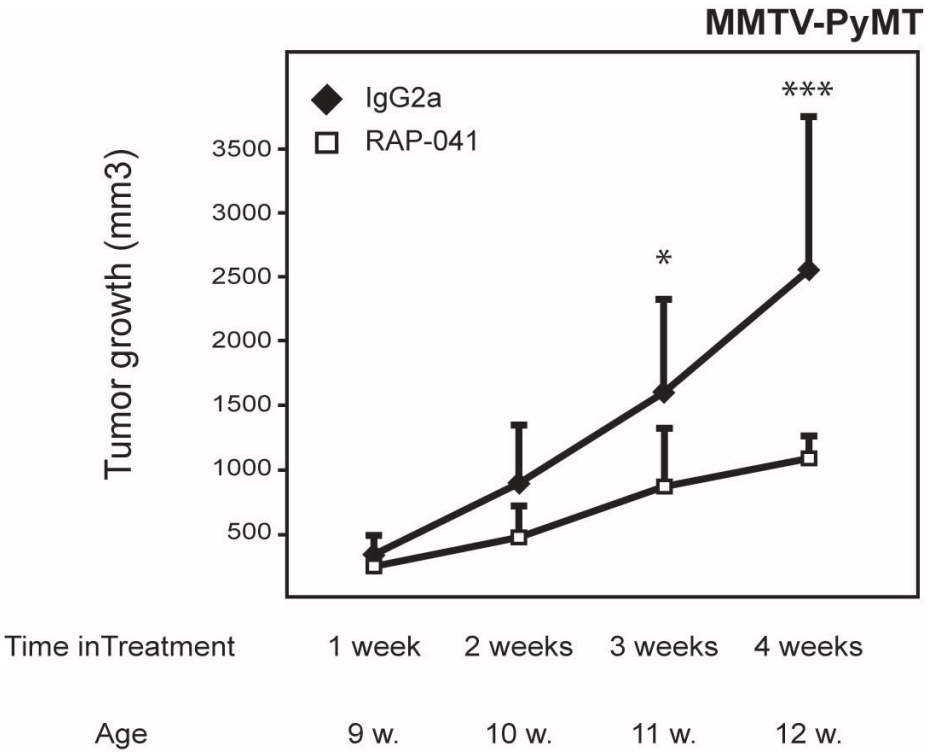
Cunha et al, Cancer Res, 2015 (in press)

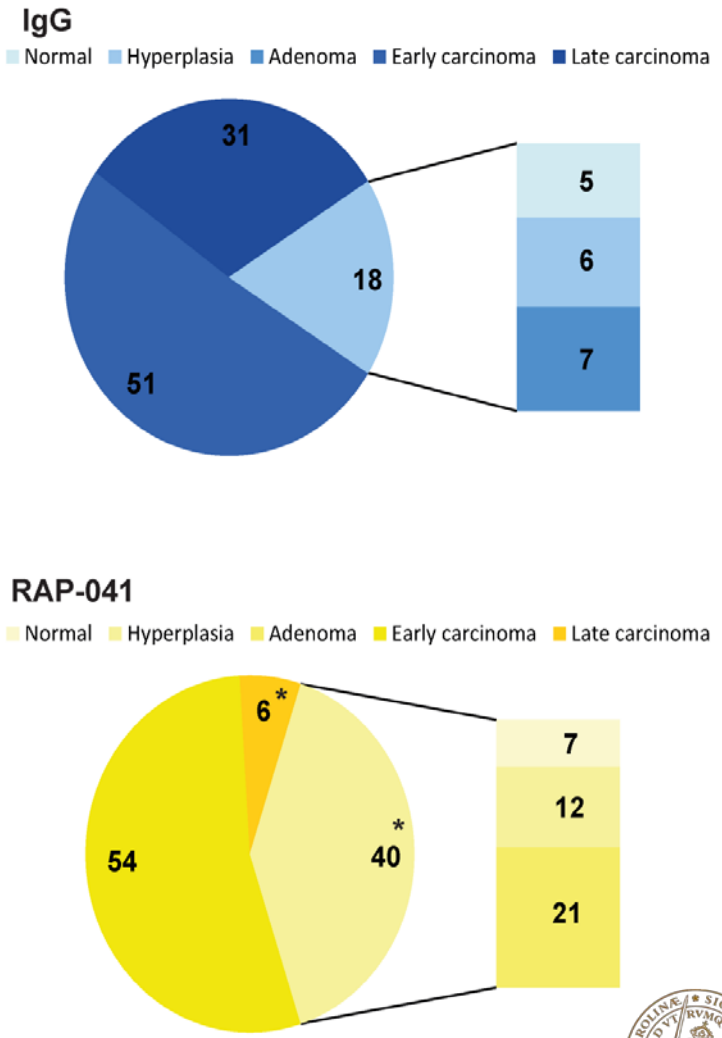
Prolonged treatment with an ALK1 inhibitor causes regression of metastatic lesions





ALK1 inhibition delays the progression of mammary carcinomas





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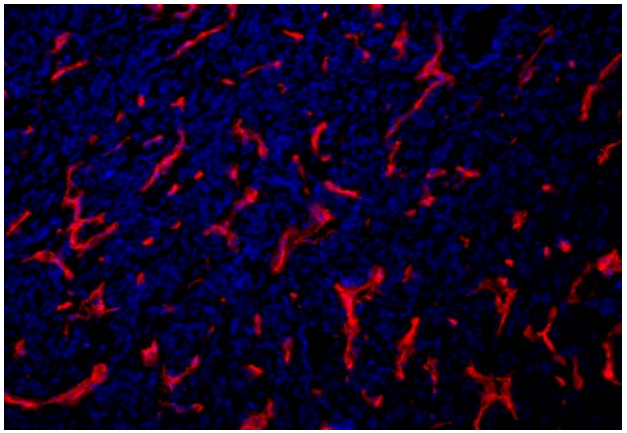
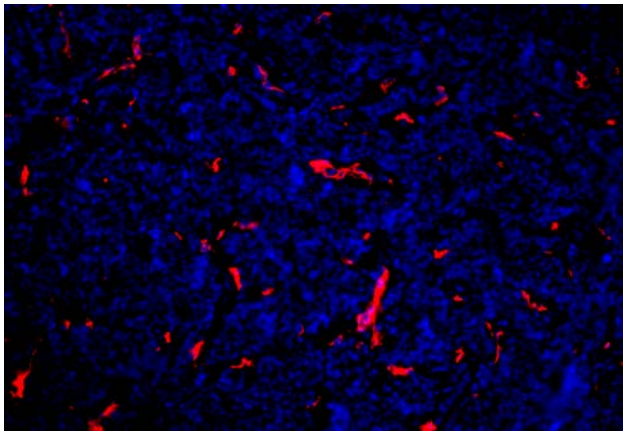
ALK1 inhibition reduces angiogenesis and metastatic spread of mammary carcinomas

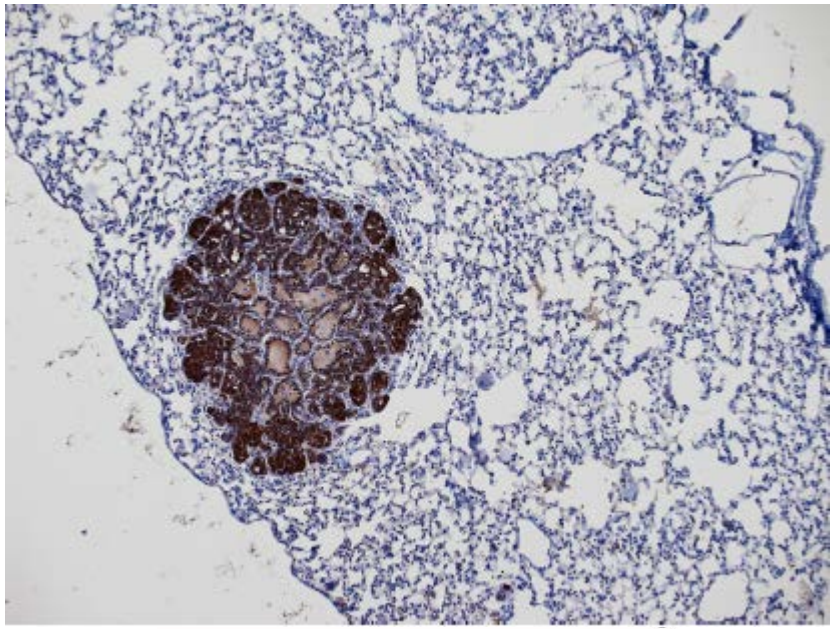
CD31 DAPI

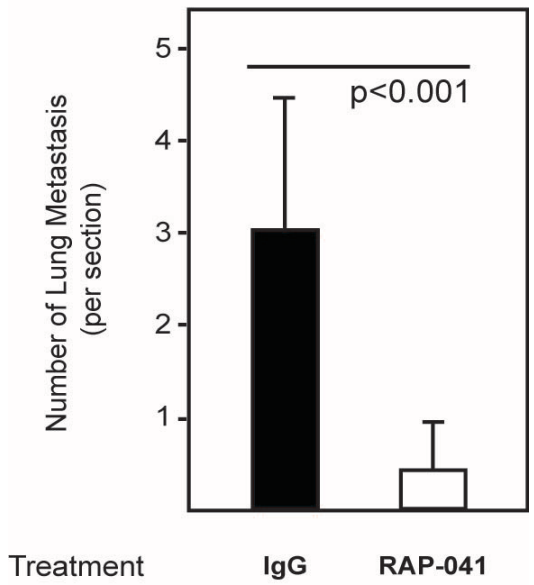
IgG2a



RAP-041







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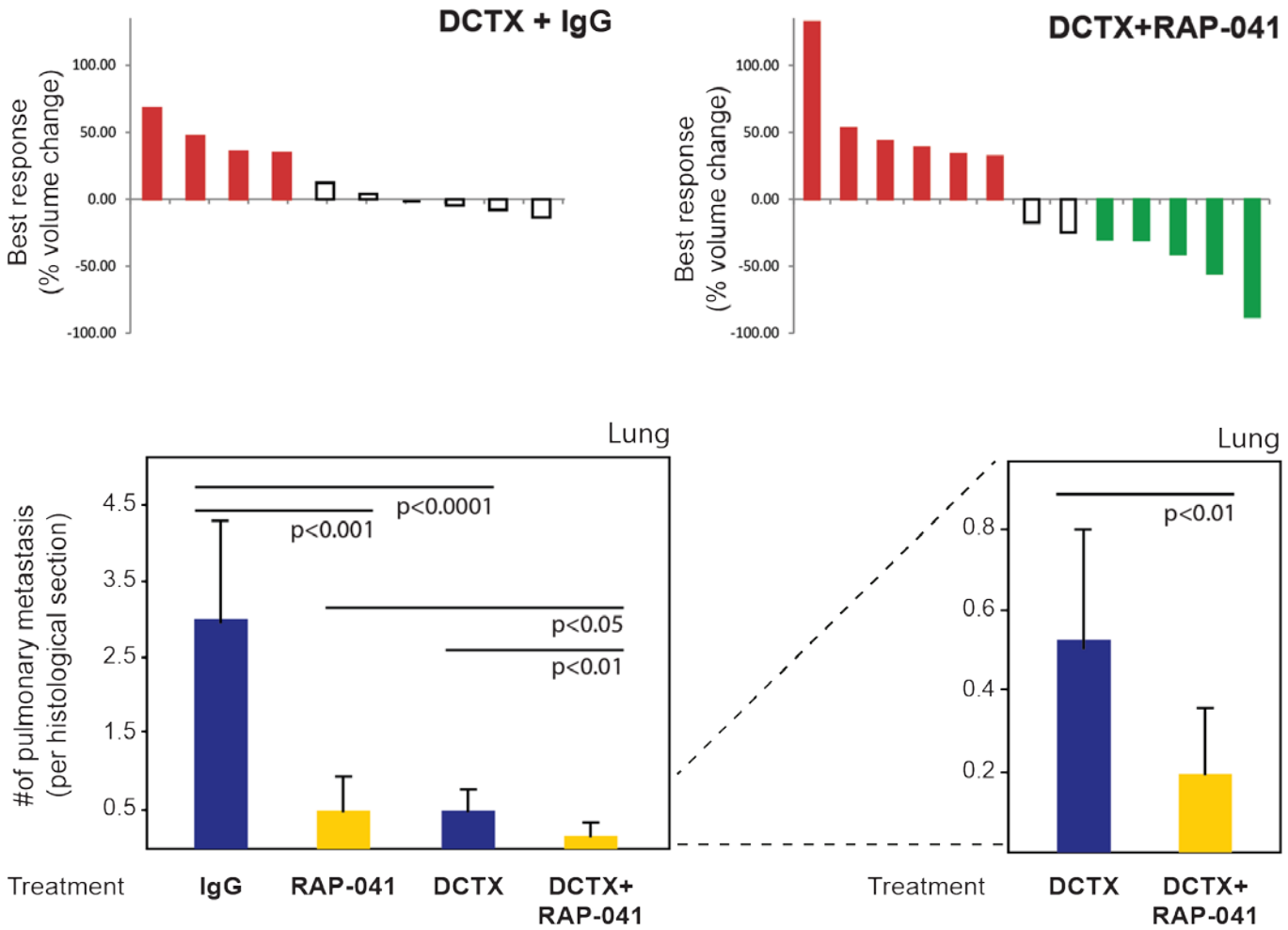
ALK1 inhibition combined with chemotherapy effectively reduces angiogenesis and metastatic spread of mammary carcinomas



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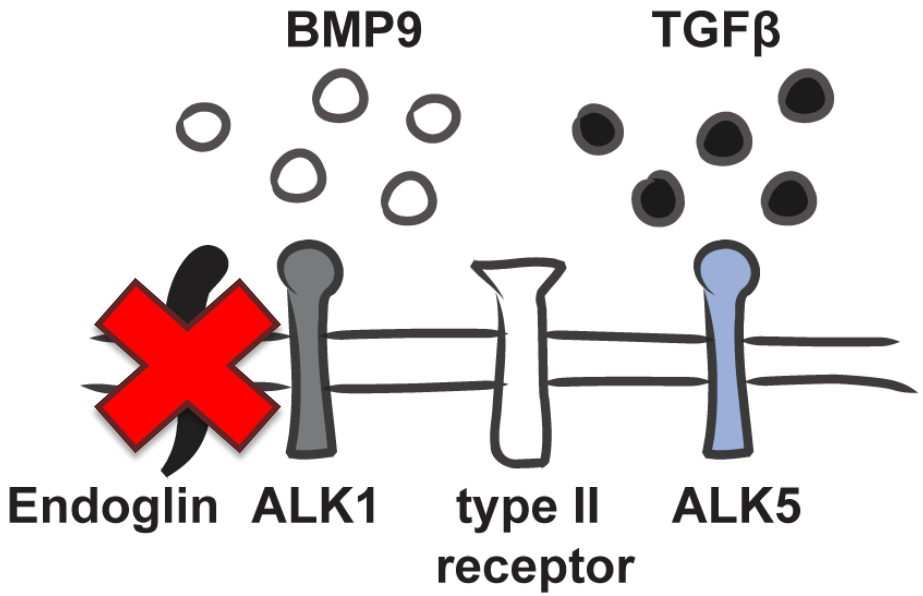
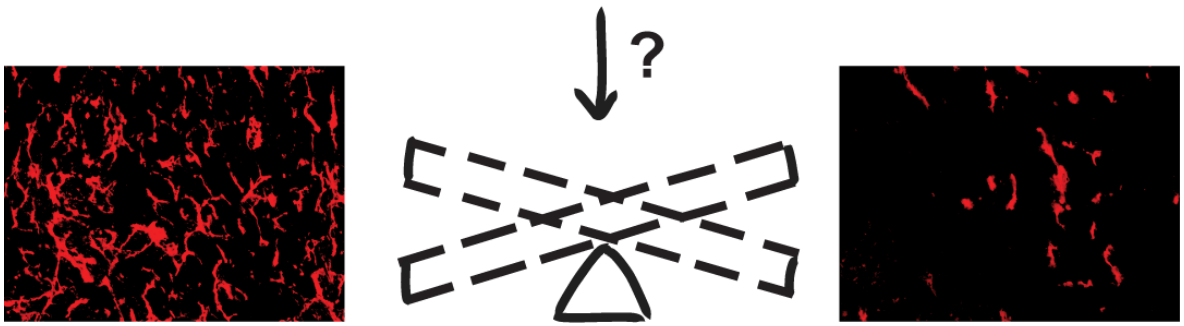
TGF-β family signaling in endothelial cells revealed





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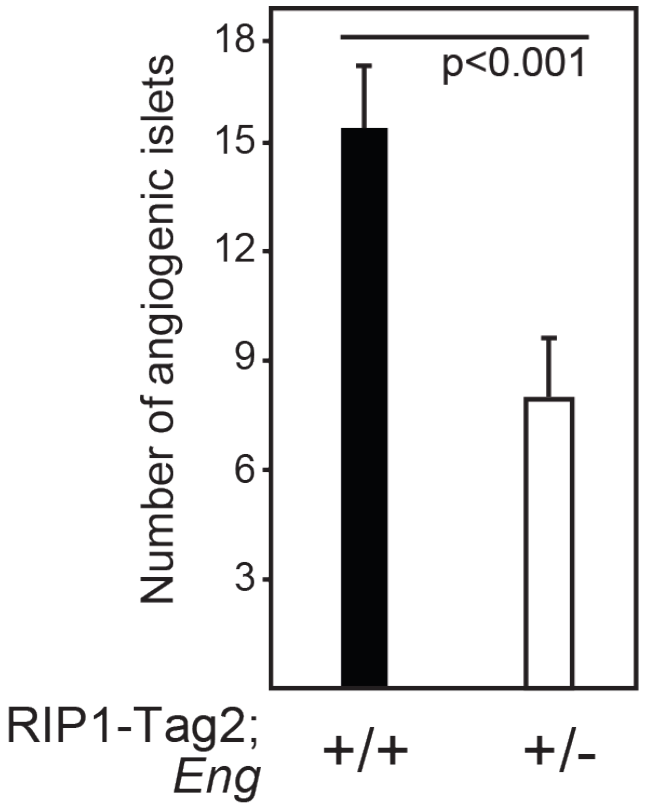
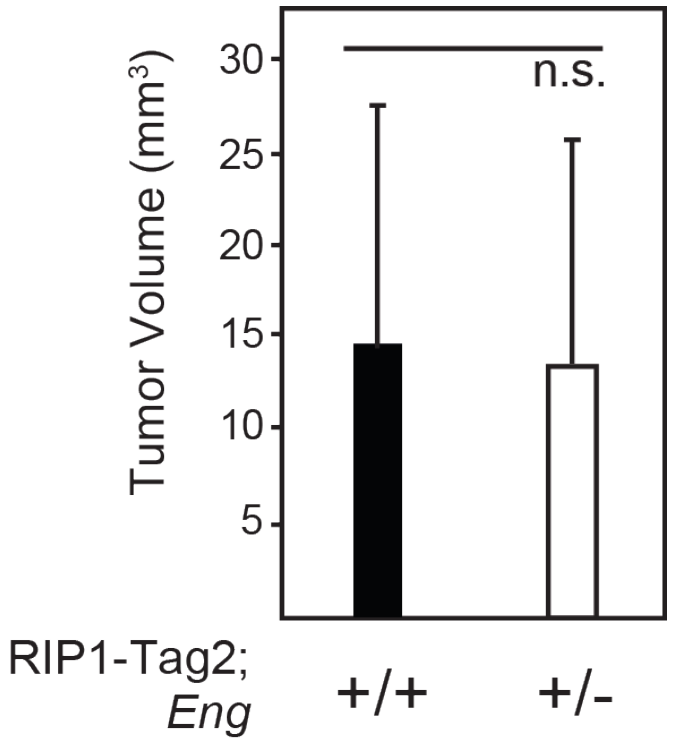
Delayed angiogenic switching in endoglin deficient mice is rescued at later stages

Angiogenic islets @ 9 weeks



Tumors @ 12 weeks



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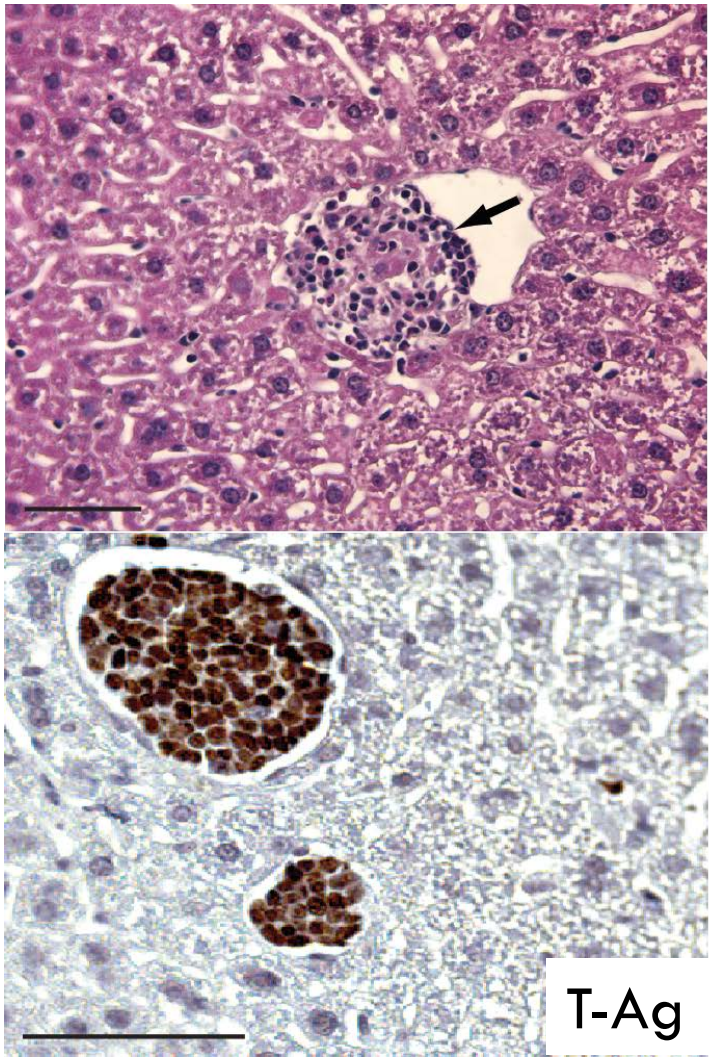
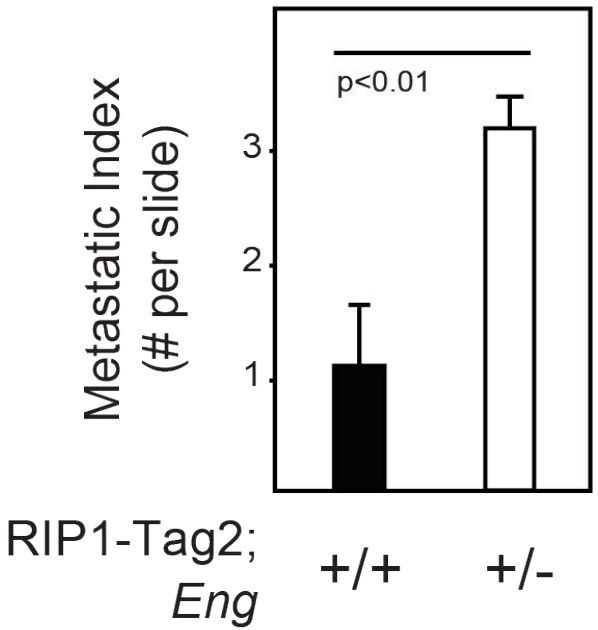
Endoglin-deficient mice present with an increased number of metastatic lesions





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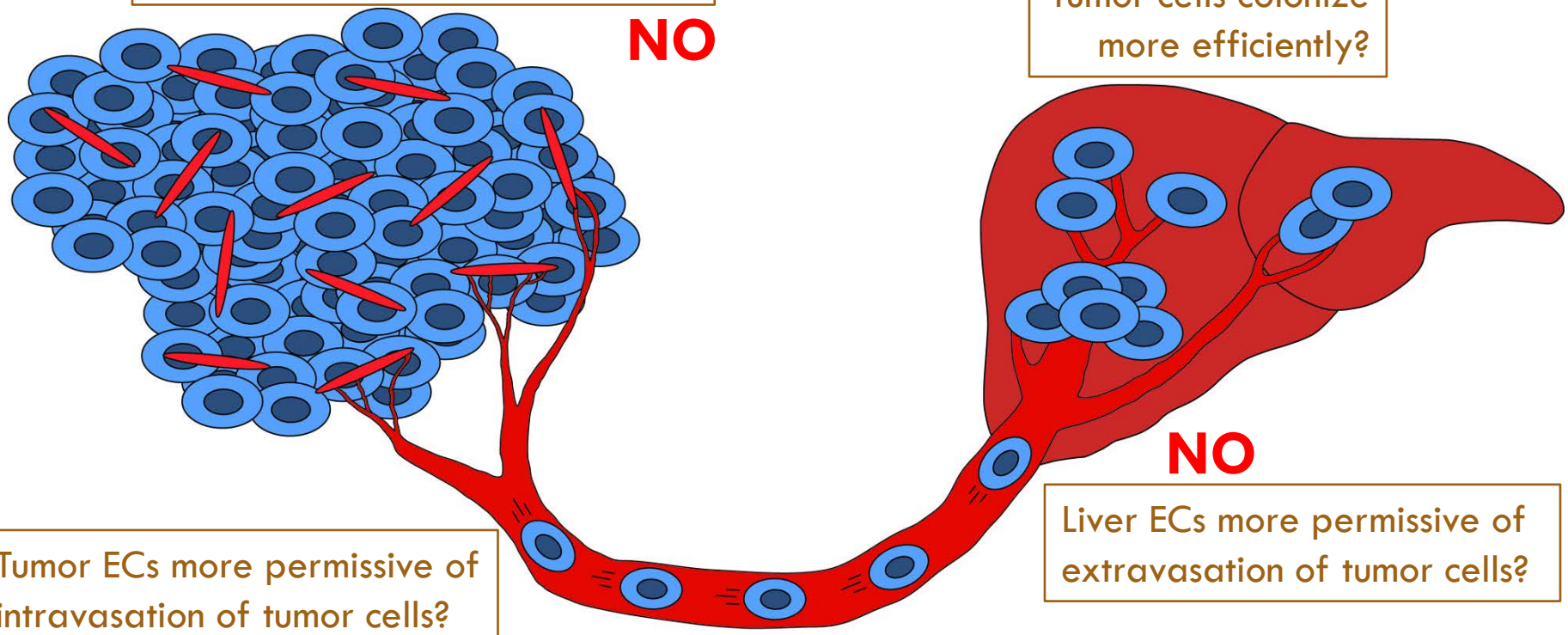
Why more metastases in endoglin-deficient mice?



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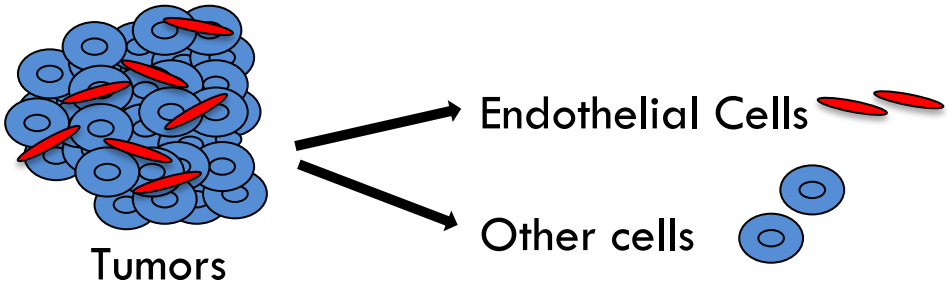
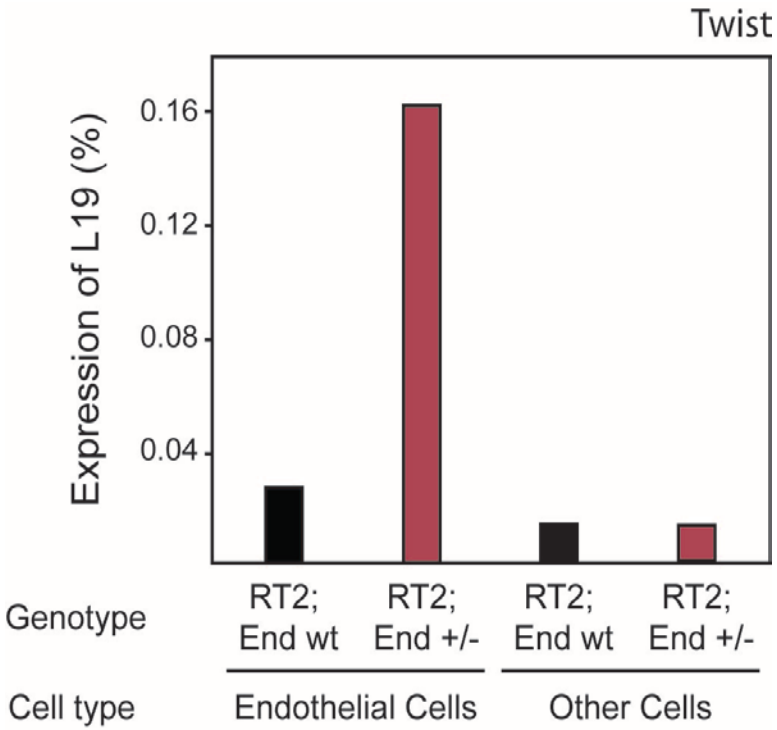
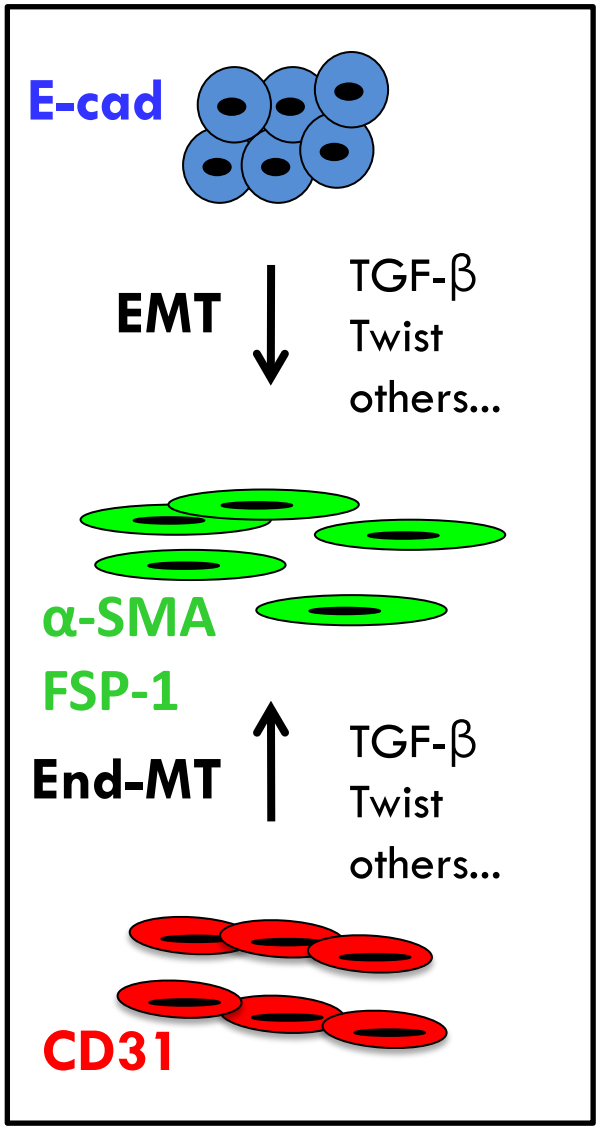
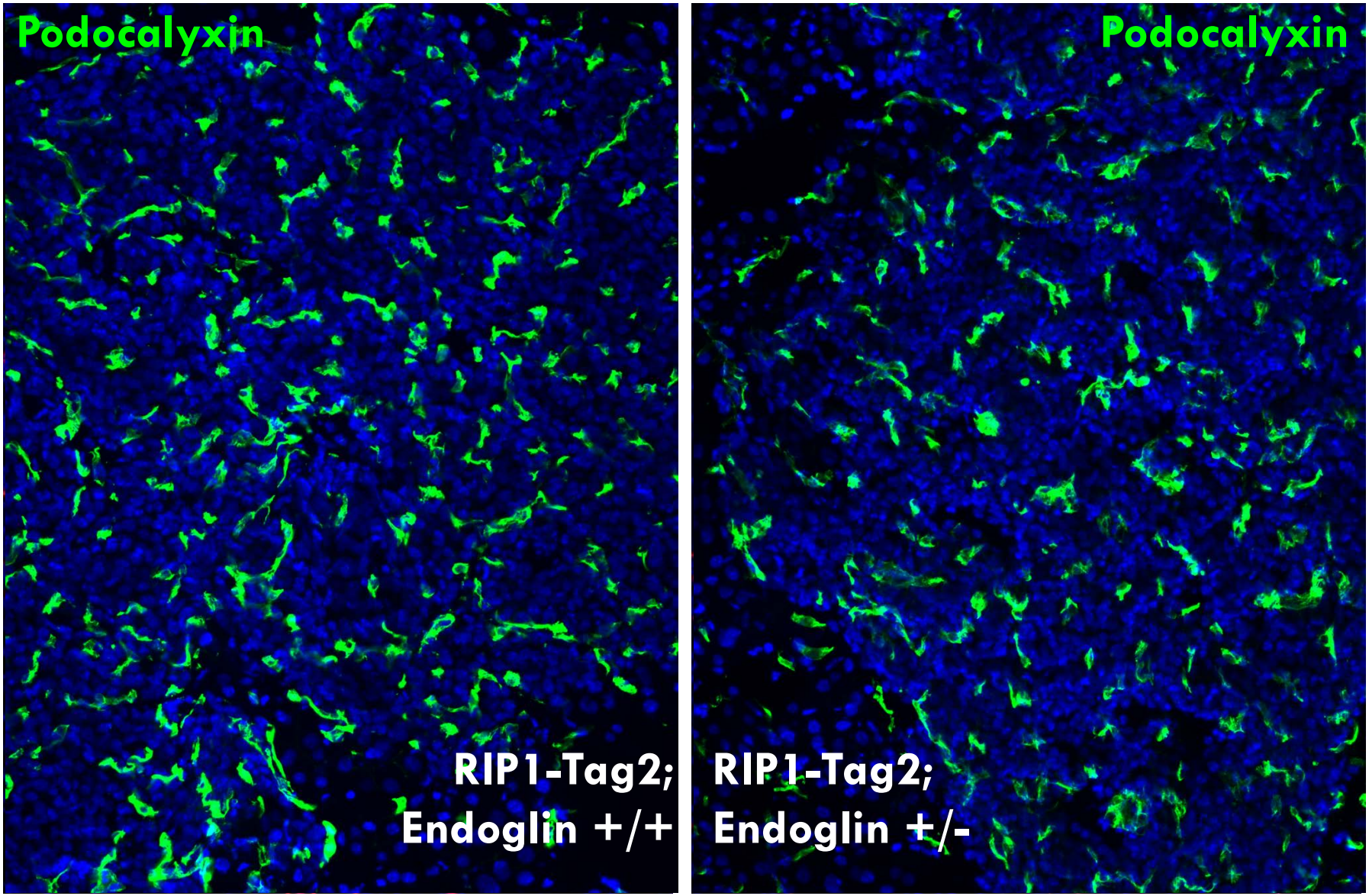
Twist is selectively upregulated in tumor endothelial cells from endoglin-deficient mice







Endoglin-deficient endothelial cells gain mesenchymal markers



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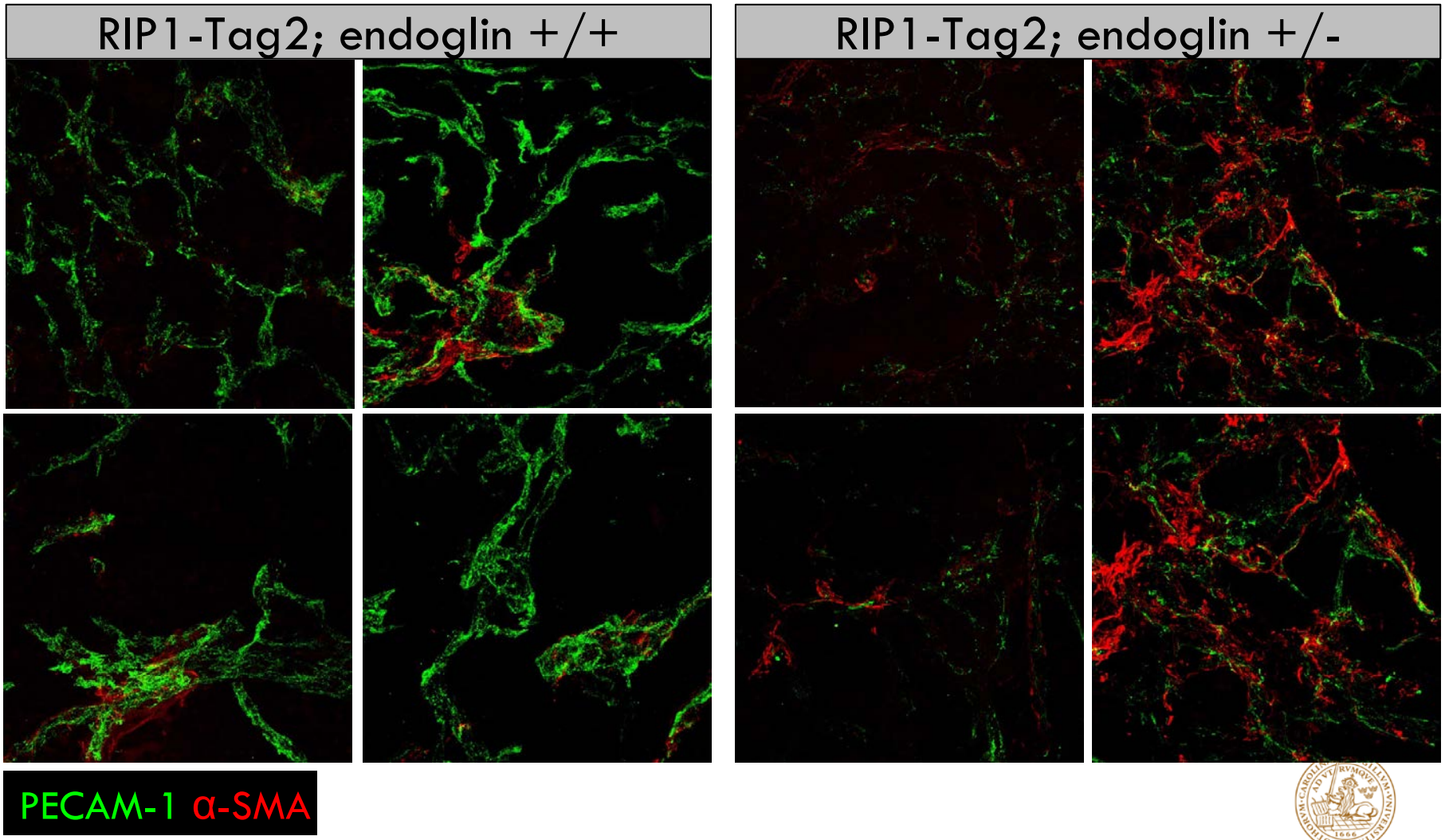

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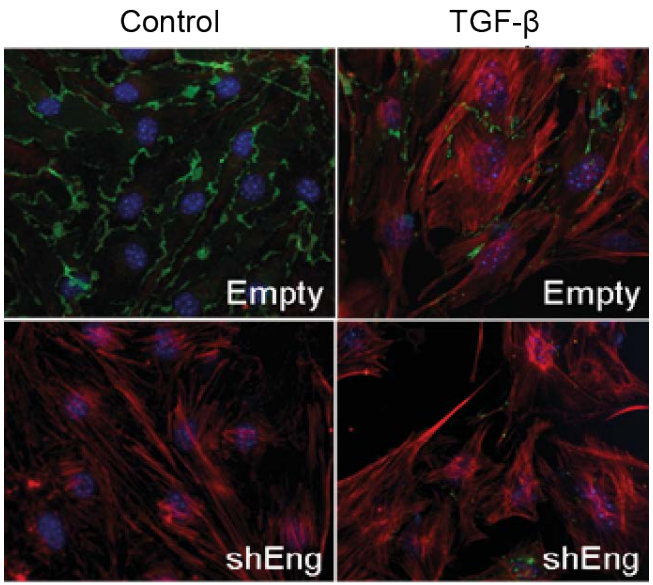
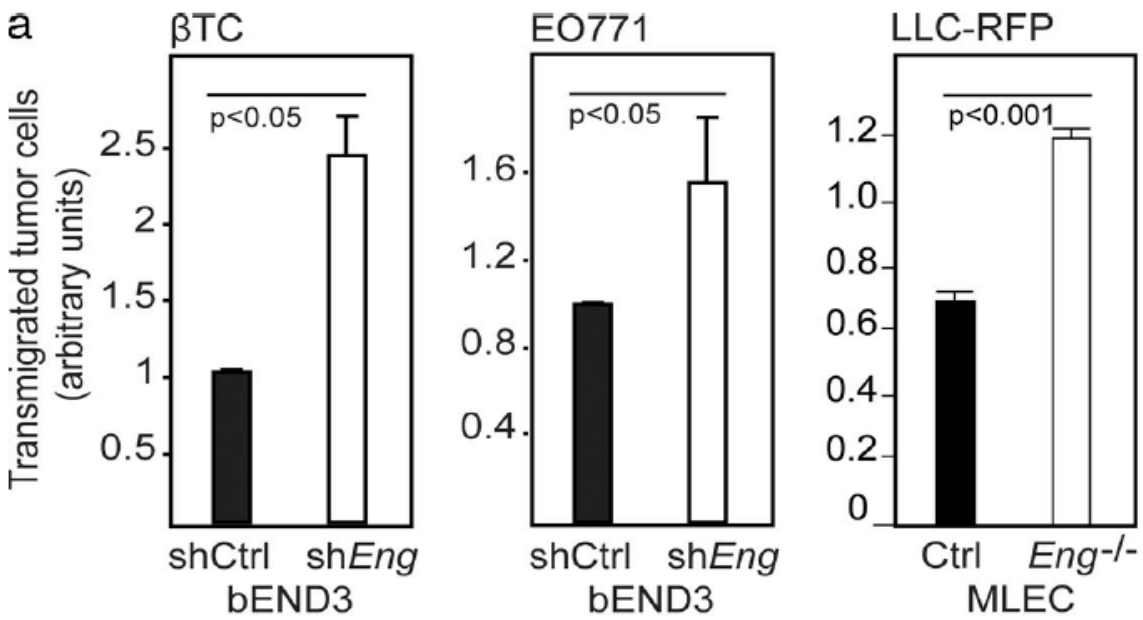
TGF-β induced EndMT weakens the endothelial barrier to tumor cell transmigration





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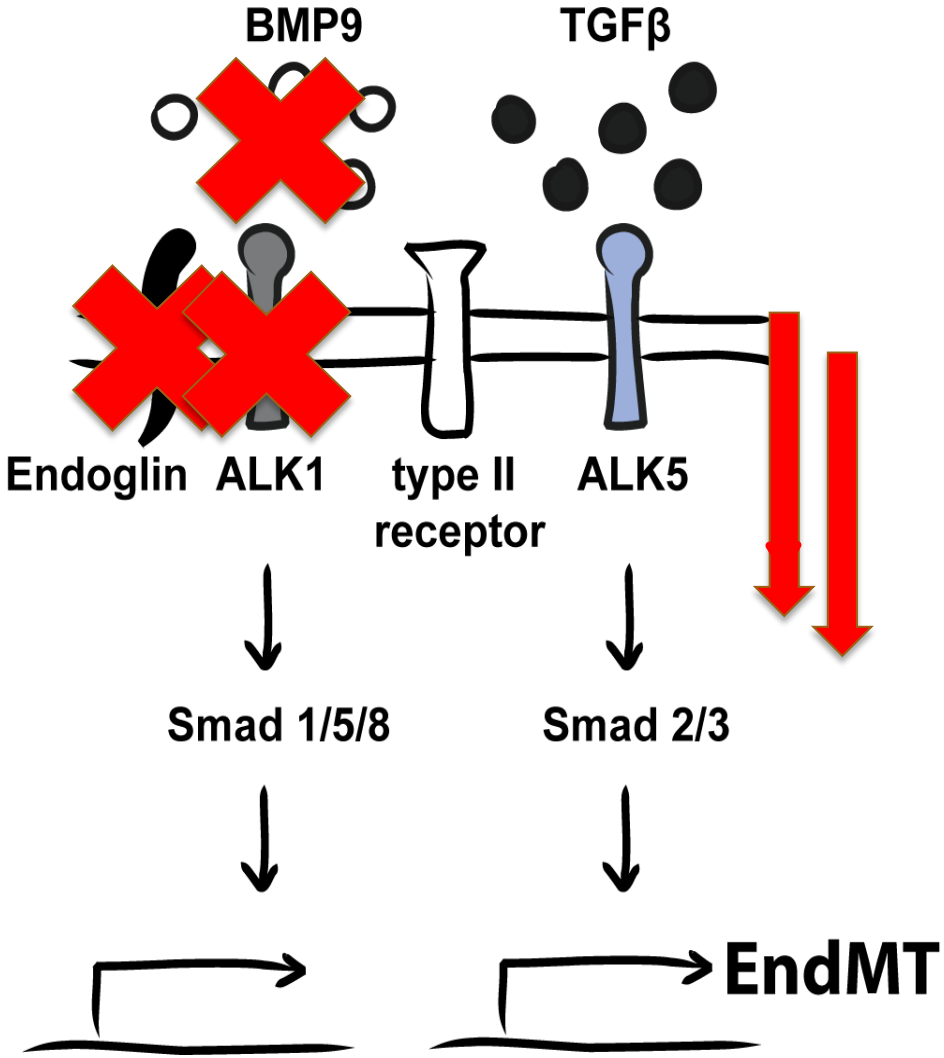
Our model



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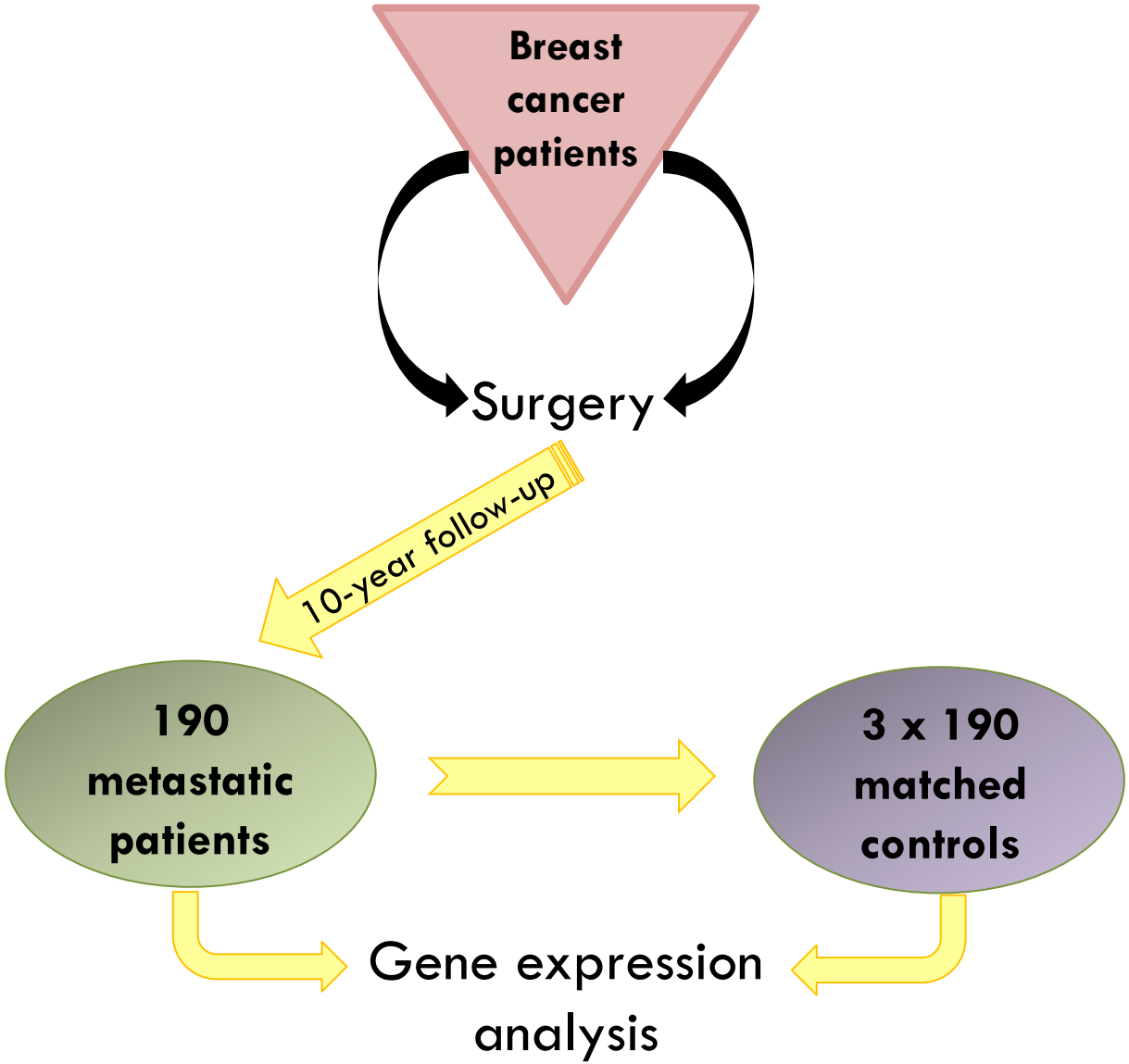
A nested case-control study to assess risk factors for metastatic disease in breast cancer



John Lövrot, Linda Lindström, Jonas Bergh

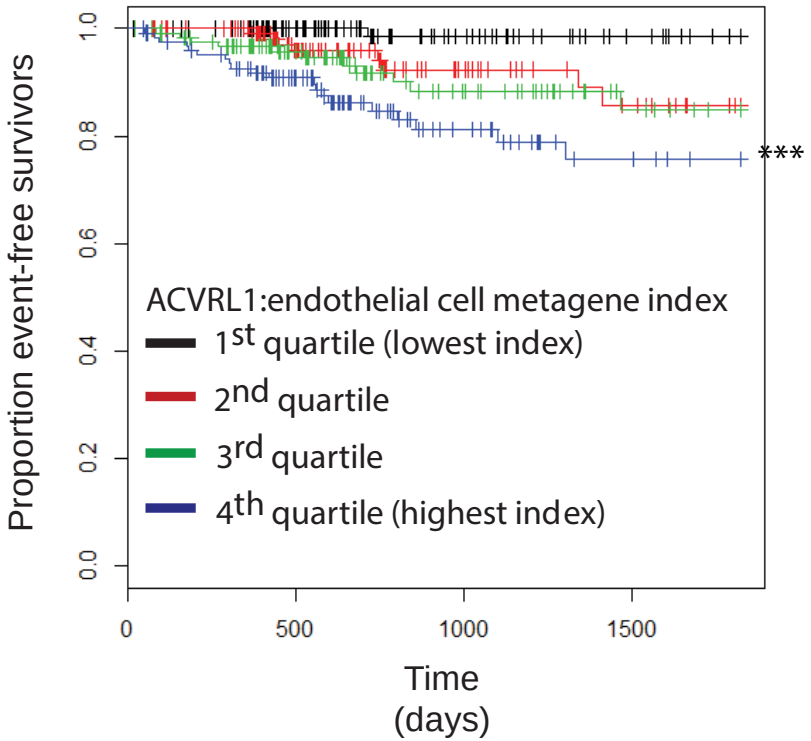
Population-based nested case-control study of prognostic factors for metastatic relapse of breast cancer

Variable*	n	Univariate models HR†	95% CI	*P*	Multivariable model A HR†	95% CI	*P*	Multivariable model B HR†	95% CI	*P*
Lymph node status				< .001			.046			.052
Negative	304	1 (ref.)			1 (ref.)			1 (ref.)		
Positive	442	2.52	1.69 to 3.77		1.77	1.13 to 2.78		1.73	1.11 to 2.70	
Unknown	22	1.11	0.36 to 3.41		1.44	0.36 to 5.73		1.44	0.38 to 5.50	
Tumor size, mm				.008			.023			.048
≤ 20	354	1 (ref.)			1 (ref.)			1 (ref.)		
> 20	398	1.73	1.22 to 2.44		1.76	1.18 to 2.63		1.65	1.11 to 2.46	
Unknown	16	0.98	0.27 to 3.59		1.15	0.23 to 5.84		1.16	0.24 to 5.48	
HER2 status				< .001			.004			< .001
Negative	519	1 (ref.)			1 (ref.)			1 (ref.)		
Positive	145	2.60	1.74 to 3.88		2.10	1.31 to 3.36		2.37	1.49 to 3.76	
Unknown	104	0.75	0.44 to 1.31		0.80	0.44 to 1.48		0.83	0.46 to 1.52	

Prognostic significance of ALK1 expression in human breast cancer

TCGA, event-free survival, multi-variate analysis

Parameter	Hazard ratio	95% CI	p-value
ACVRL1	2.35	1.34-4.09	0.0027
Endothelial index (CD31, CD34, CDH5)	0.46	0.28-0.74	0.0017



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Michael Bartoschek
Sebastian Braun
Hideki Miyazaki
Eugenia Cordero
Jonas Sjölund
Christina Möller

Karolinska Institutet

Jonas Bergh
John Lövrot
Linda Lindström

Leiden University

Peter ten Dijke

Newcastle University

Helen Arthur
Jason Zhai

Tokyo University

Kohei Miyazono
Tetsuro Watabe

Acceleron Pharma

Scott Pearsall
Ravi Kumar

BioCARE

Göran & Birgitta Grosskopf

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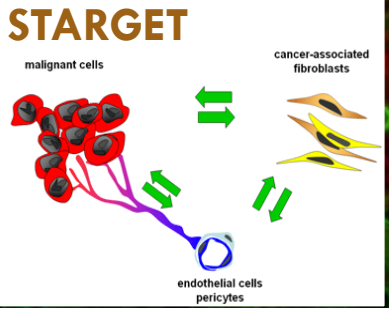
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