Reprograming the Tumor Microenvironment to Improve Responses to Therapy

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SITC-Workshop

April 17th, 2018

Washington University in St. Louis

SITEMAN CANCER CENTER

BARNES-JEWISH HOSPITAL • WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Disclosures

I have no financial disclosures relevant to this talk

Pancreas Cancer Outcomes

Type	Deaths/year	% 5 year Survival All	% 5 year Survival Local
Lung	158,040	17%	45%
Colon	49,700	65%	90%
Breast	40,730	89%	99%
Pancreas	40,560	7%	26%
Prostate	27,540	99%	>99%

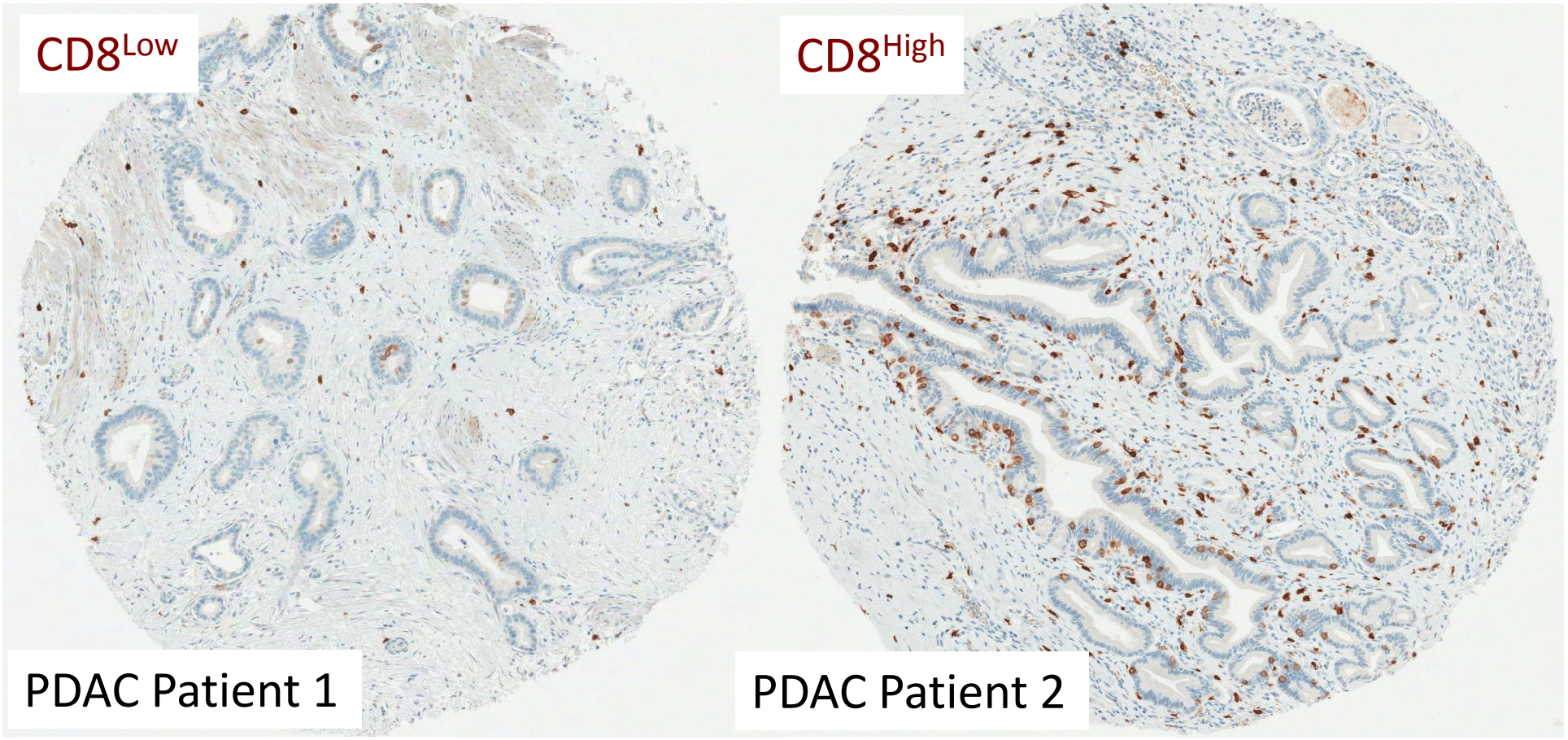
Completed Trials

Immunotherapy	Response Rate (Stable Disease)
Checkpoint Blockade	
• Anti-CTLA4 (Ipilimumab)	0%
• Ipilimumab + Gemcitabine	0%
• Ipilimumab + GVAX (vaccination strategy)	0%
• Anti-PD-1 (Pembrolizumab)	0% (+ in MSI^{High})
• Pembro + Gemcitabine	0%
• Anti-PD-L1 (BMS-936559)	0%

Ma, Y. *et al. Cancer Res. Front.* (2016) Kunk, P. R., *et al. J. Immunother. Cancer* (2016)

SEER.Cancer.Gov Report (2007-2013)

Diverse Immune Responses Impact Patient Outcomes



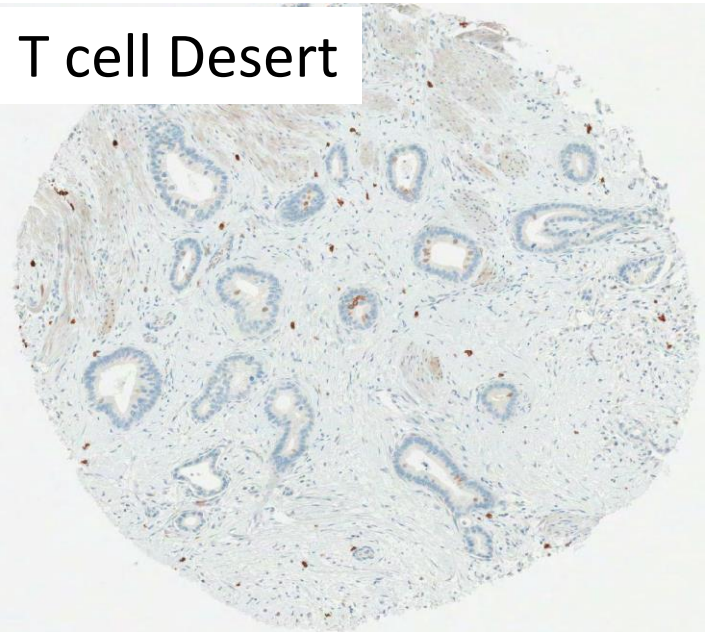
Survival <6 months

Survival >3 years

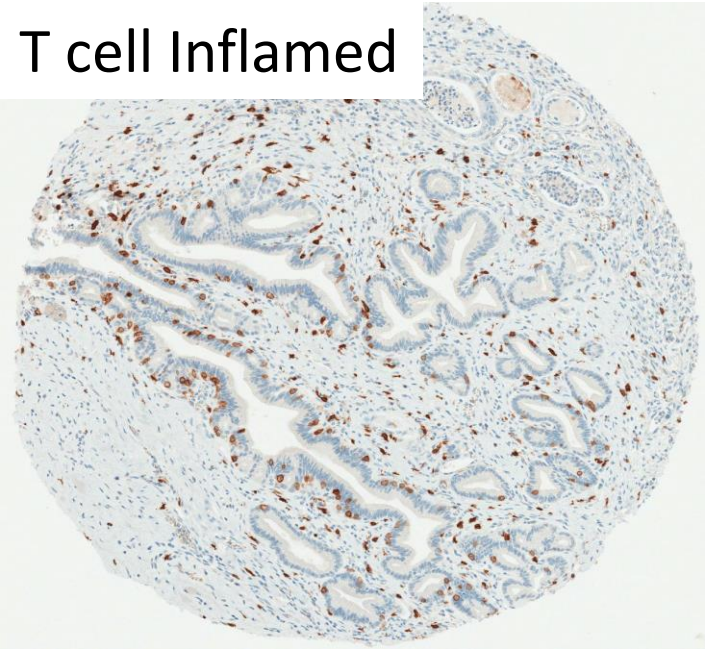
Mitchem et al., Cancer Research 2013
DeNardo et al Cancer Discovery 2011

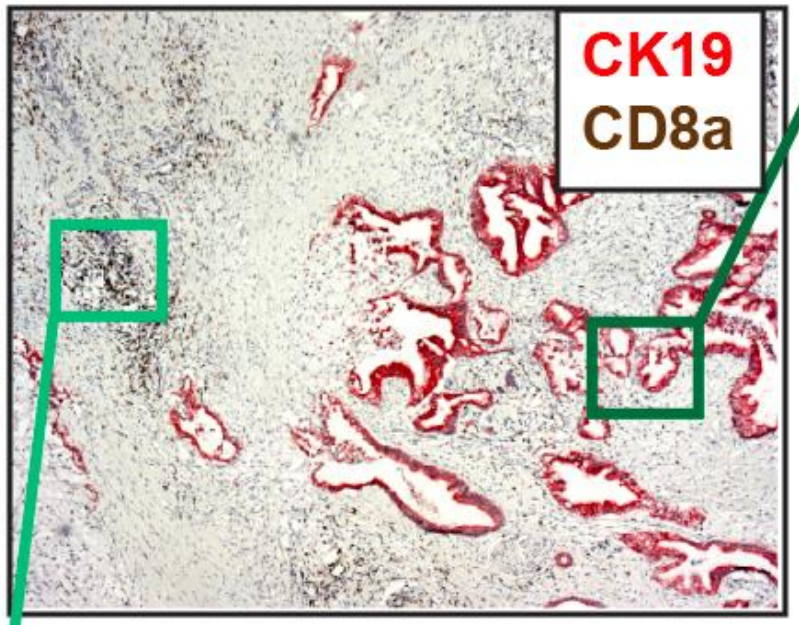
Diverse Immune Responses Impact Patient Outcomes

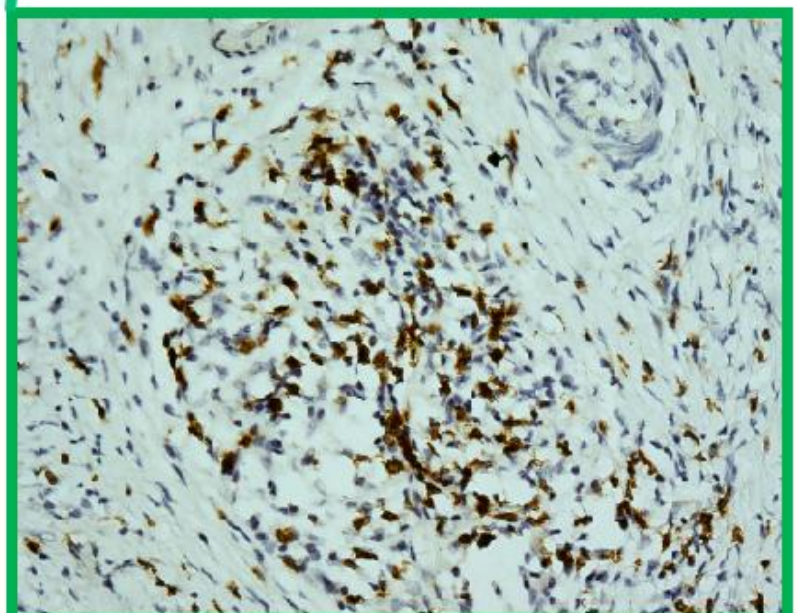
T cell Desert

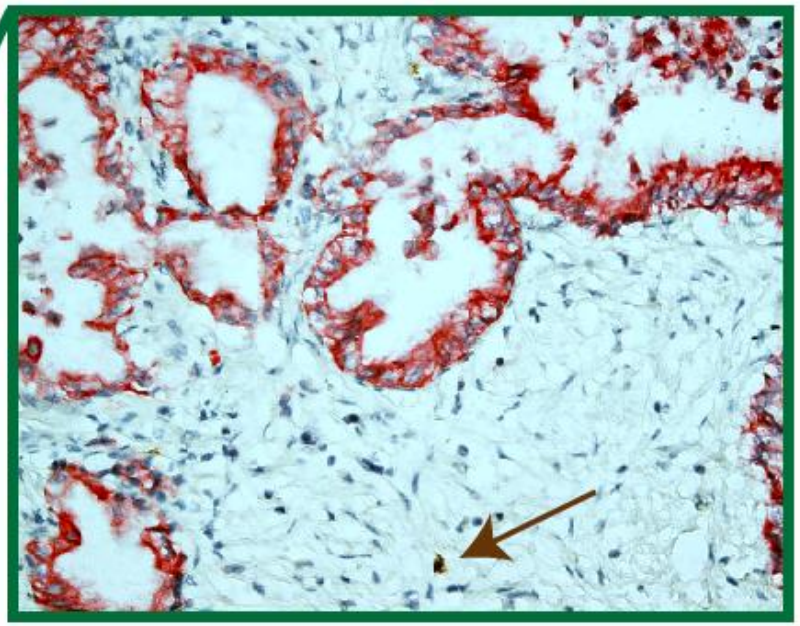


T cell Inflamed

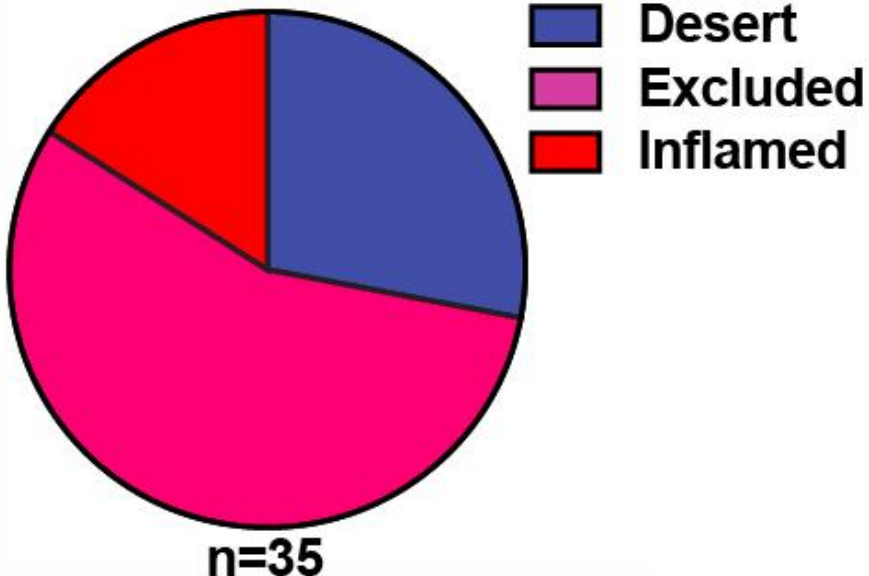




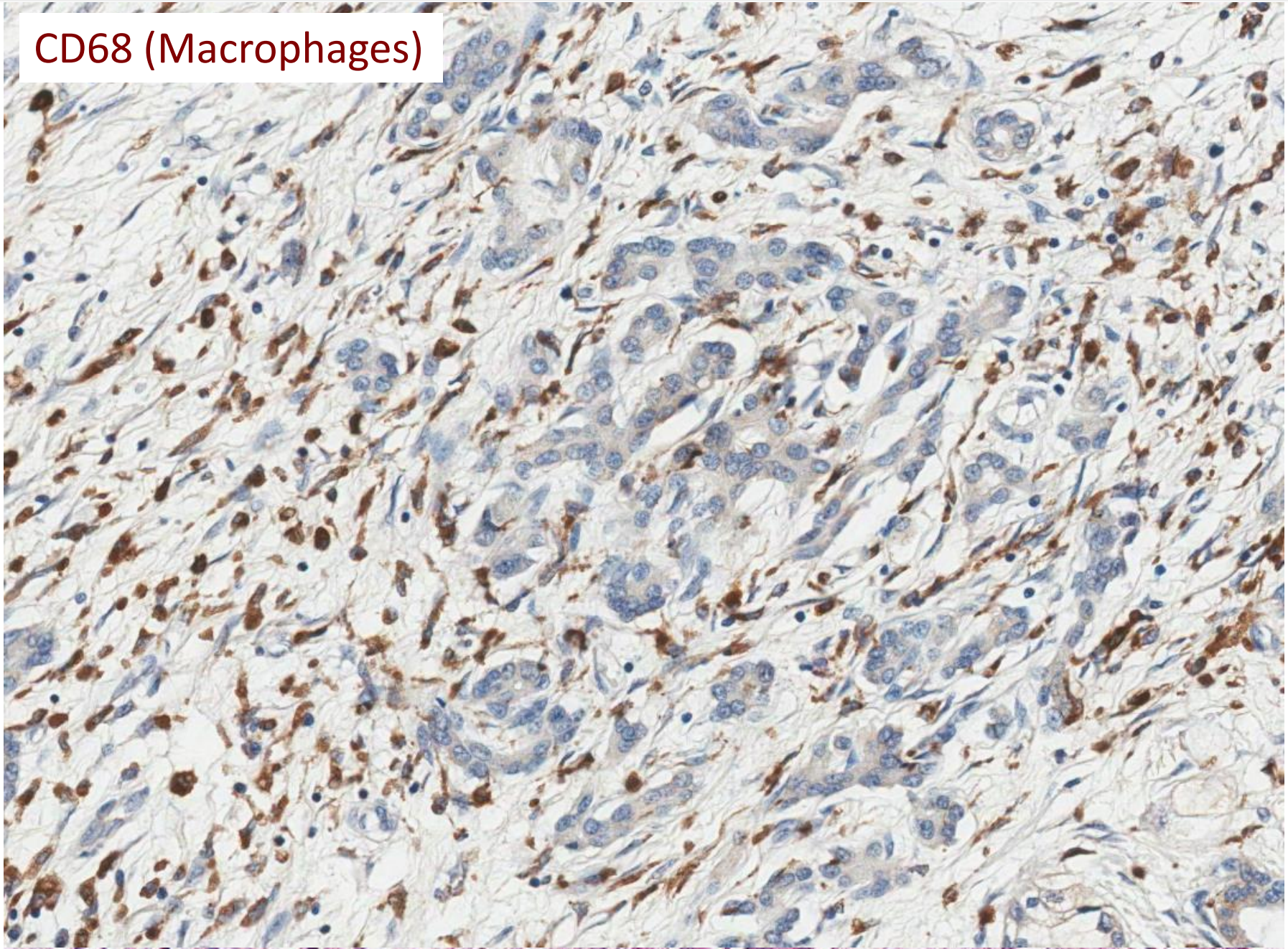




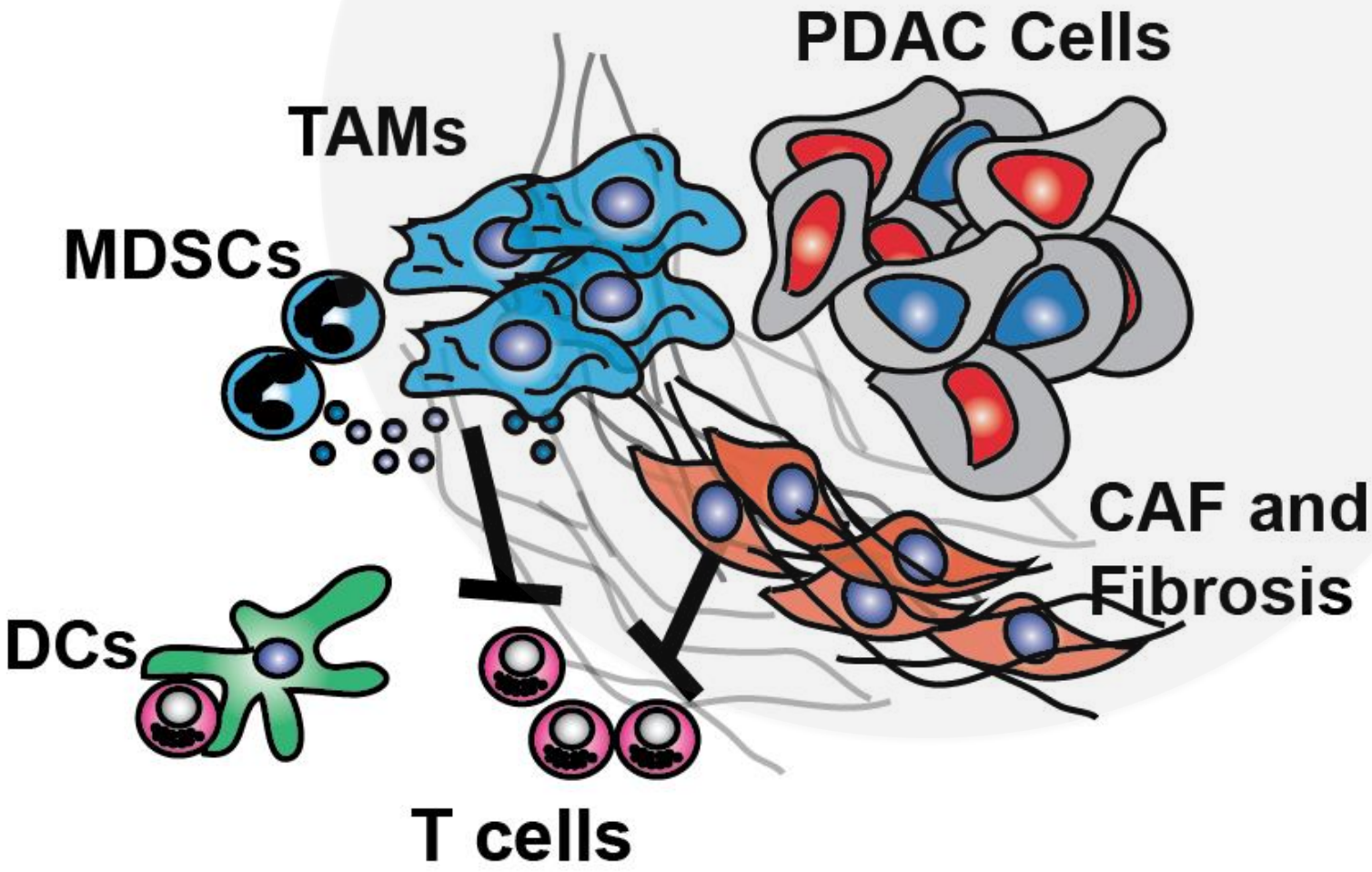
T Cell Phenotype



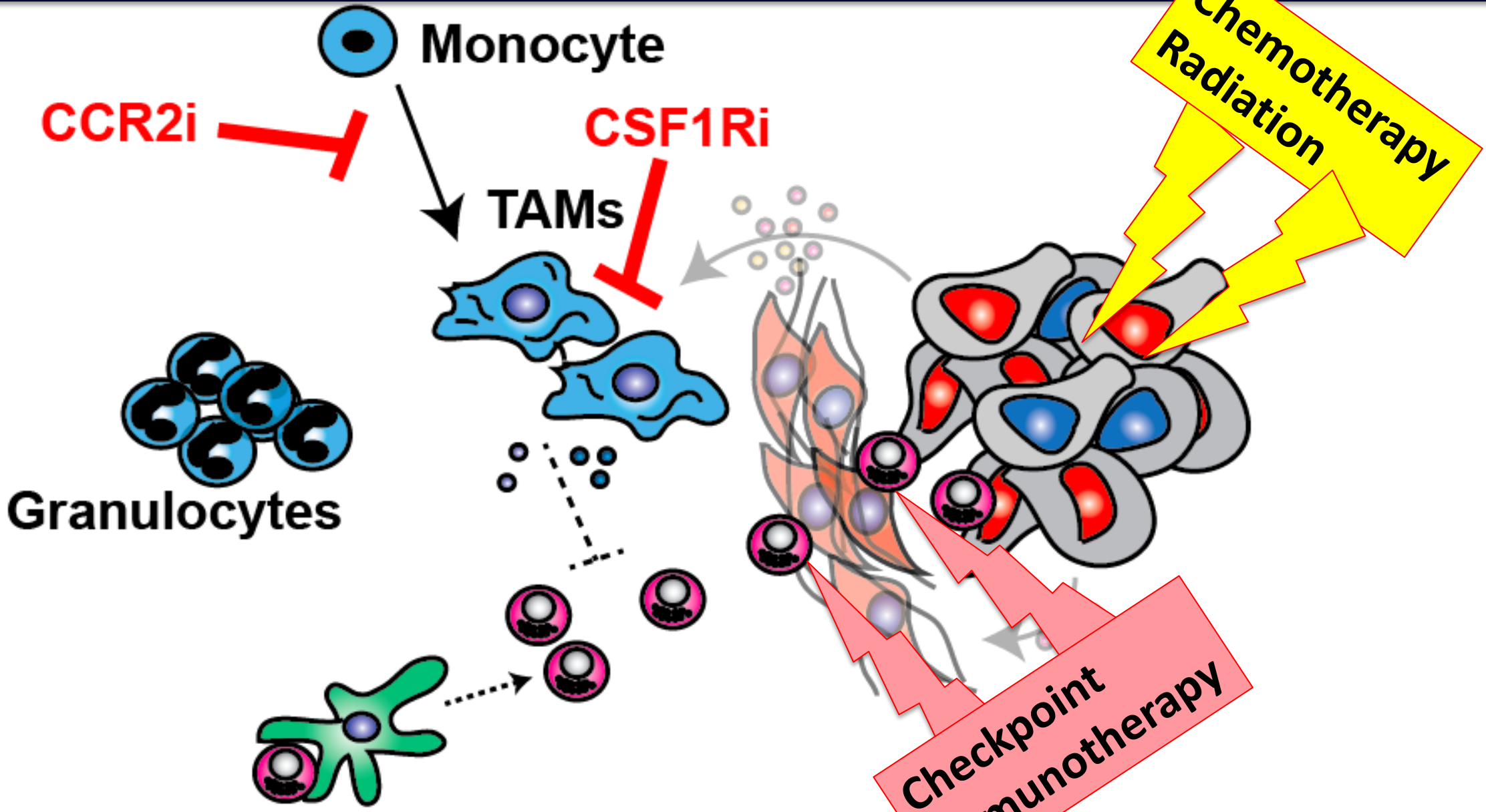
Pancreas Cancer Is Not Melanoma



Targeting PDAC Microenvironment

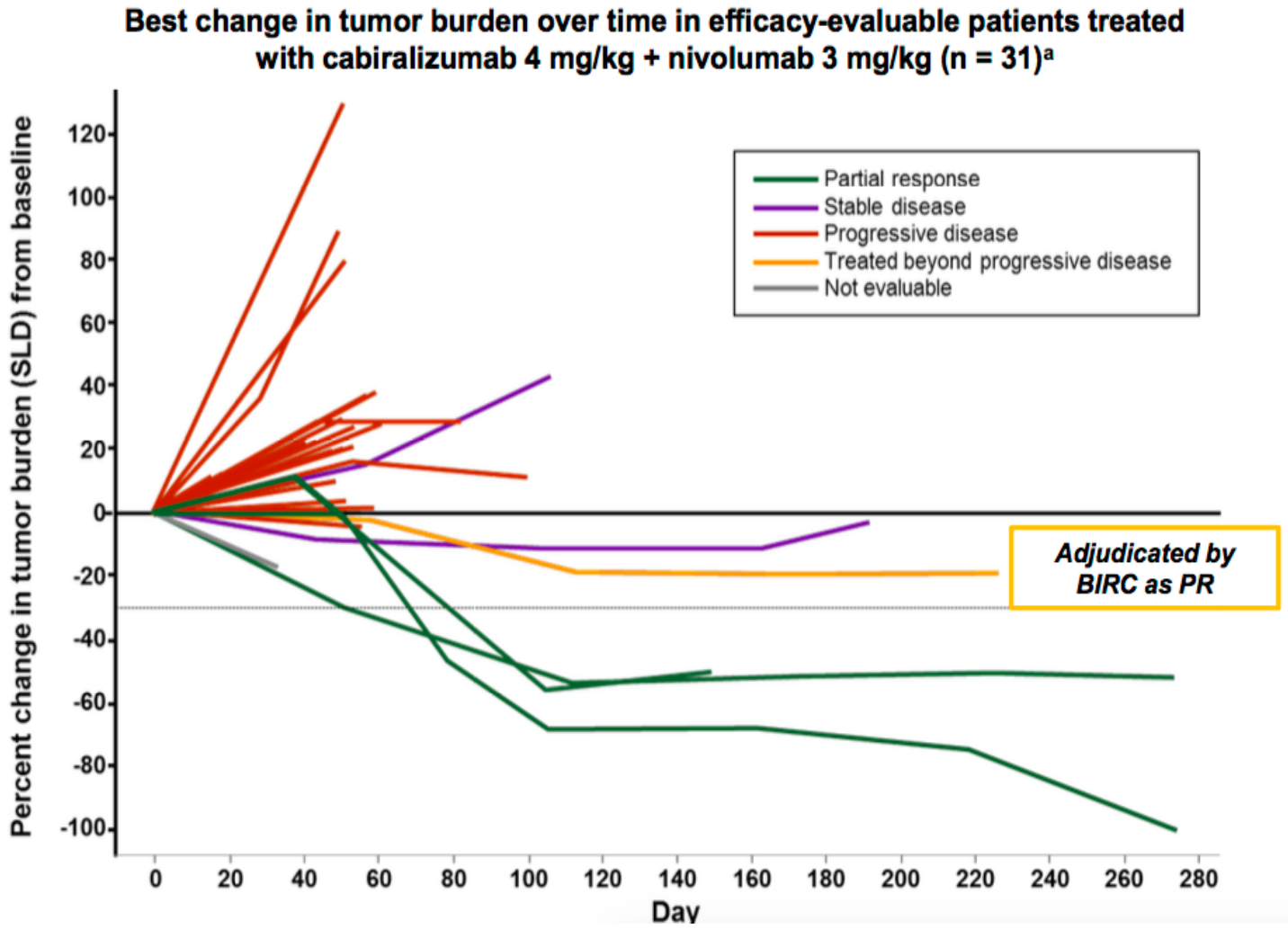


Targeting Macrophages To Improve Response to Therapy



Mitchem et al 2013, Stanford et al 2013, Xu et al 2013, Zhu et al 2014, Nywening et al 2017 (and [illegible]oups outside of pancreas)

CSF1R Inhibition in Combination with PD1 Checkpoint in PDAC



- In this heavily pretreated population, durable clinical benefit was observed in **5 patients (16%)**

  Confirmed ORR = 10%
  (Updated confirmed ORR = 13%)

  Duration of treatment for responders = 275+, 168+, 258, and 247+ days

- All 4 confirmed responses were observed in patients with MSS disease, who historically have not shown benefit with anti–PD-1/L1 therapy[1,2]

- Responses were accompanied by steep declines in levels of the pancreatic tumor marker CA19-9 over baseline

SITC Late-Breaker Oral Presentation, November 2017 Wainberg Z, et al.

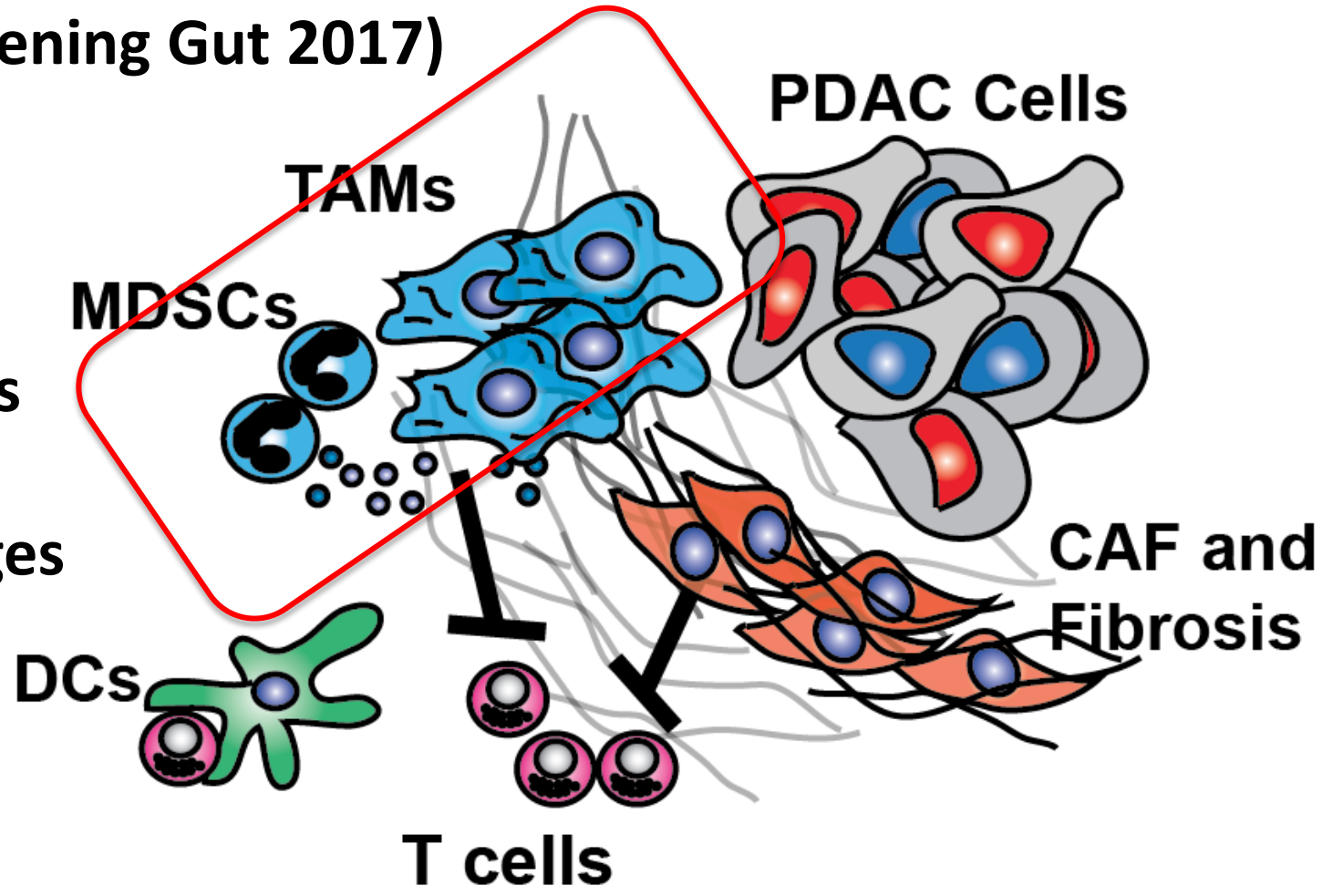
Targeting PDAC Microenvironment

Problem

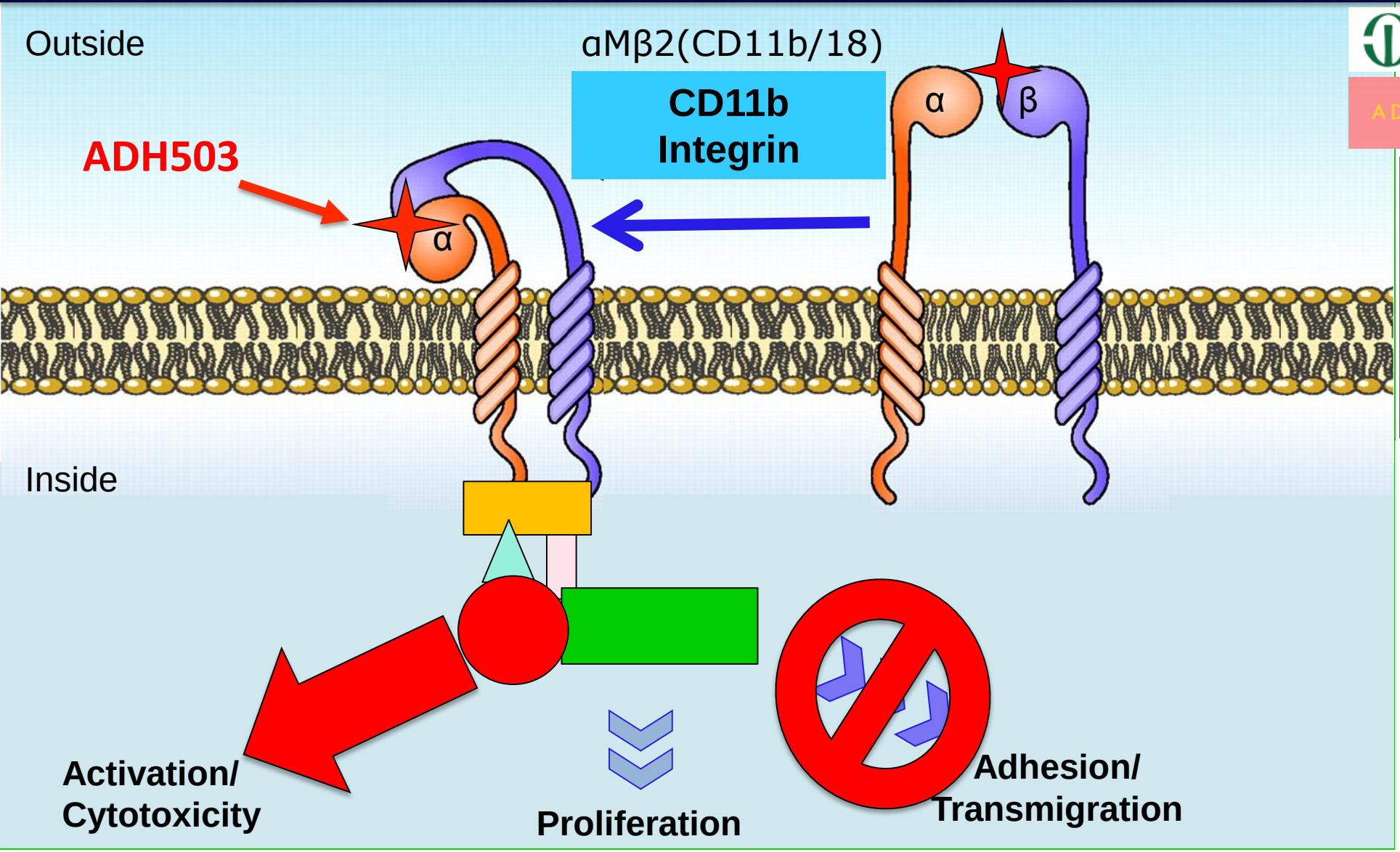
- **Myeloid Compensation**
  (Kumar Cancer Cell 2018, Nywening Gut 2017)

Hypothetical Goals

- **Target Multiple Myeloid Subsets**
- **Repolarize Resident Macrophages**
- **Don’t Impair T cell Priming**

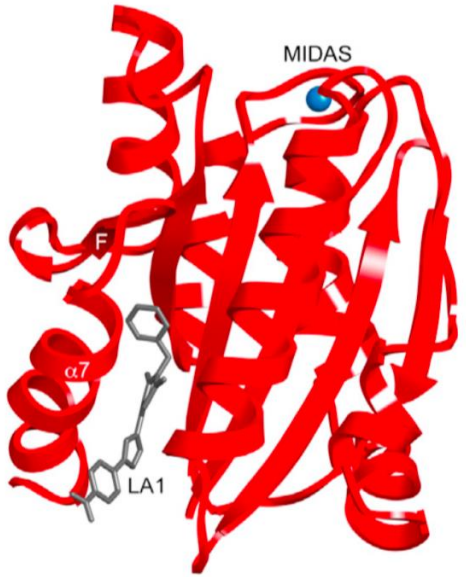


Teaching an Old Dog New Tricks (Targeting CD11b)



RUSH UNIVERSITY

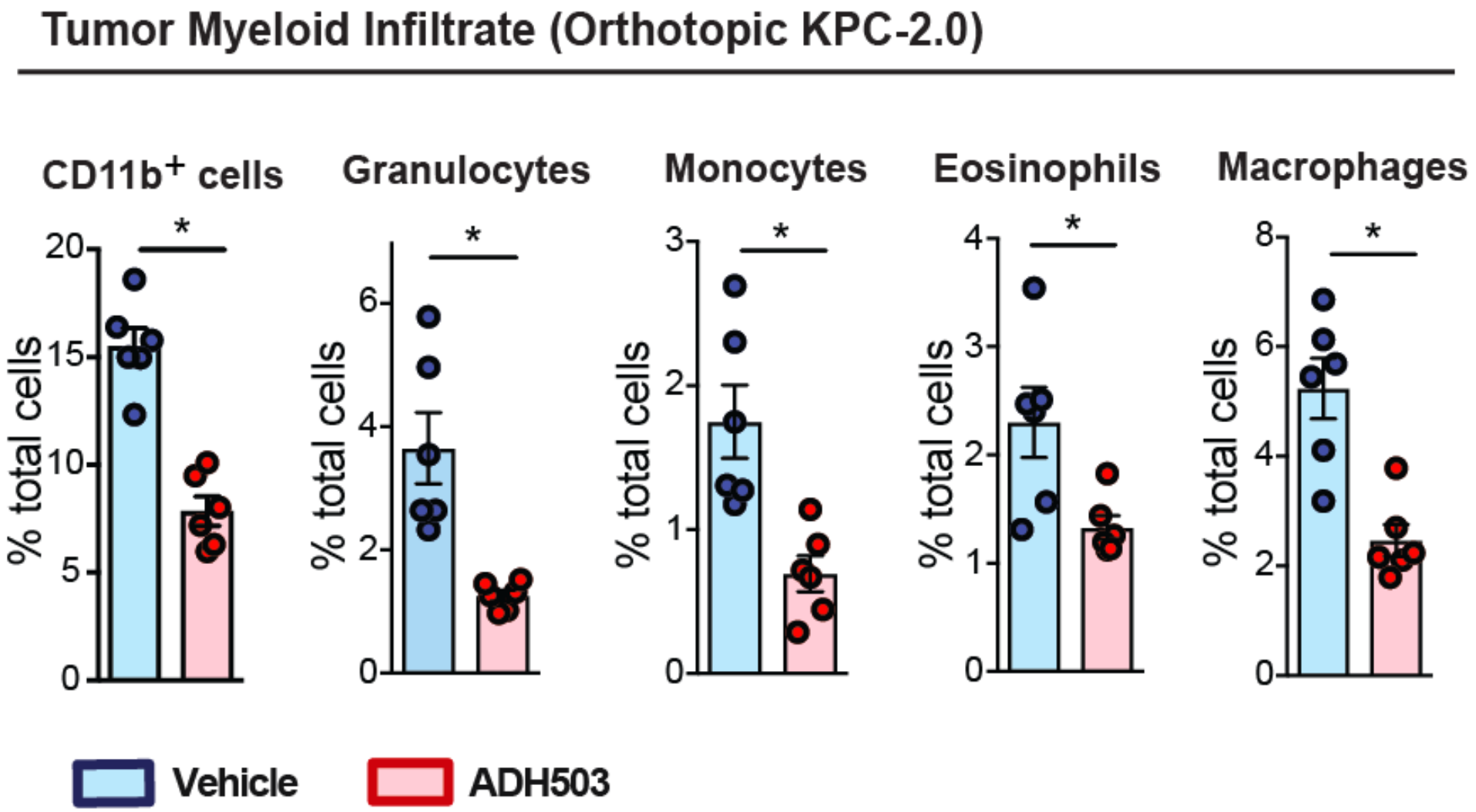
ADHAERE PHARMACEUTICALS, INC.



Harlan J Crit Care Med May, 2002
Jagarapu J. Am J Respir Cell Mol Biol. Dec, 2015
Faridi M Biochim Biophys Acta. Jun, 2013
Celik E. Biophys J. Dec, 2013

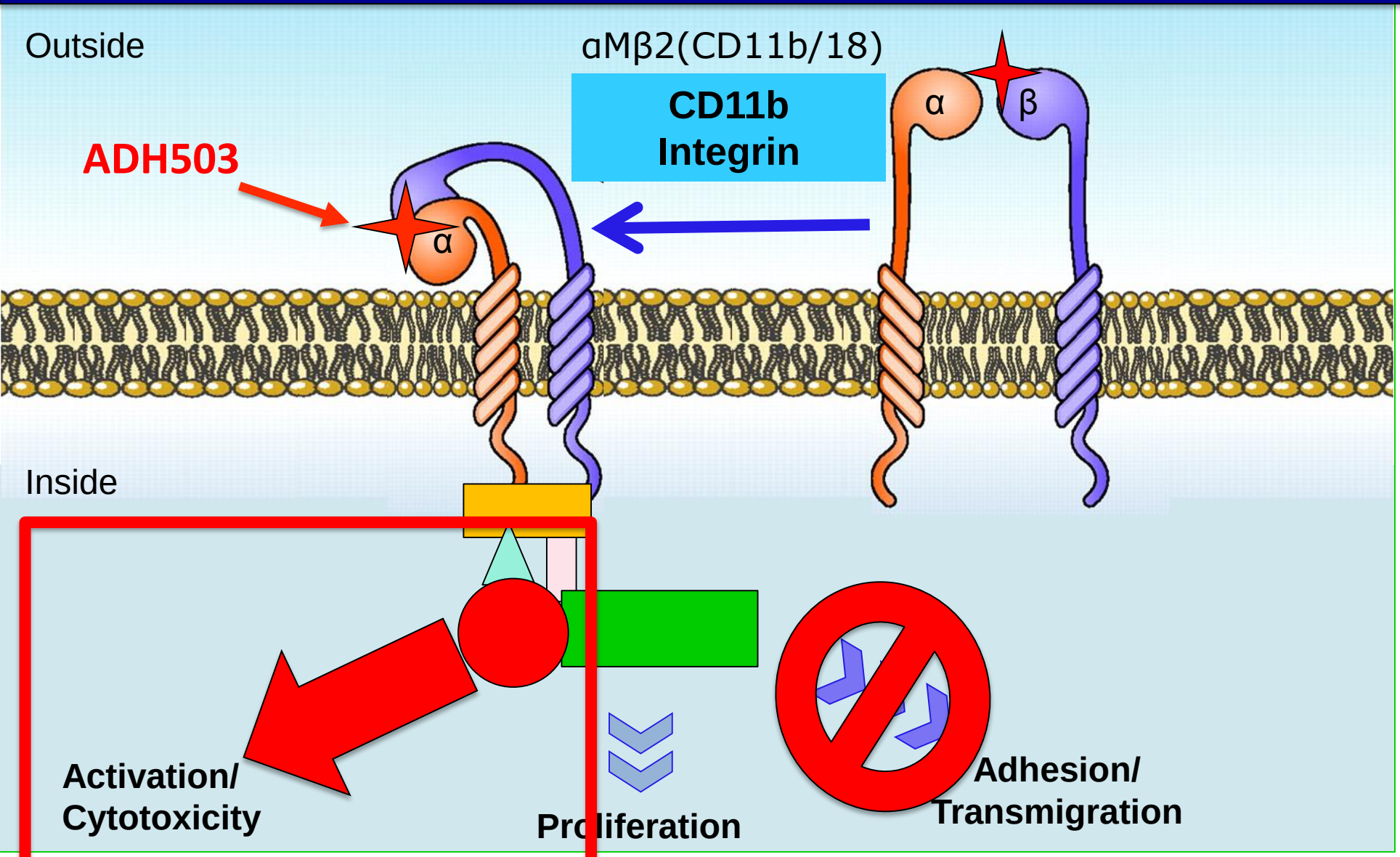
ADH503 Disrupts Multiple Myeloid Cell Populations

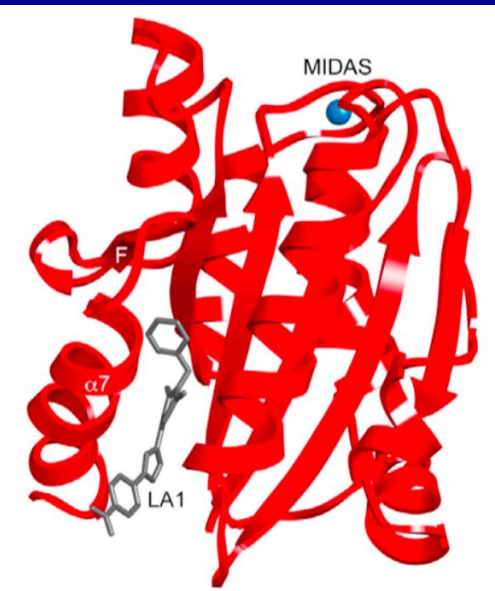
Orthotopic PDAC (KP2)



Consistent Across Three PDAC Models

Teaching an Old Dog New Tricks (Targeting CD11b)





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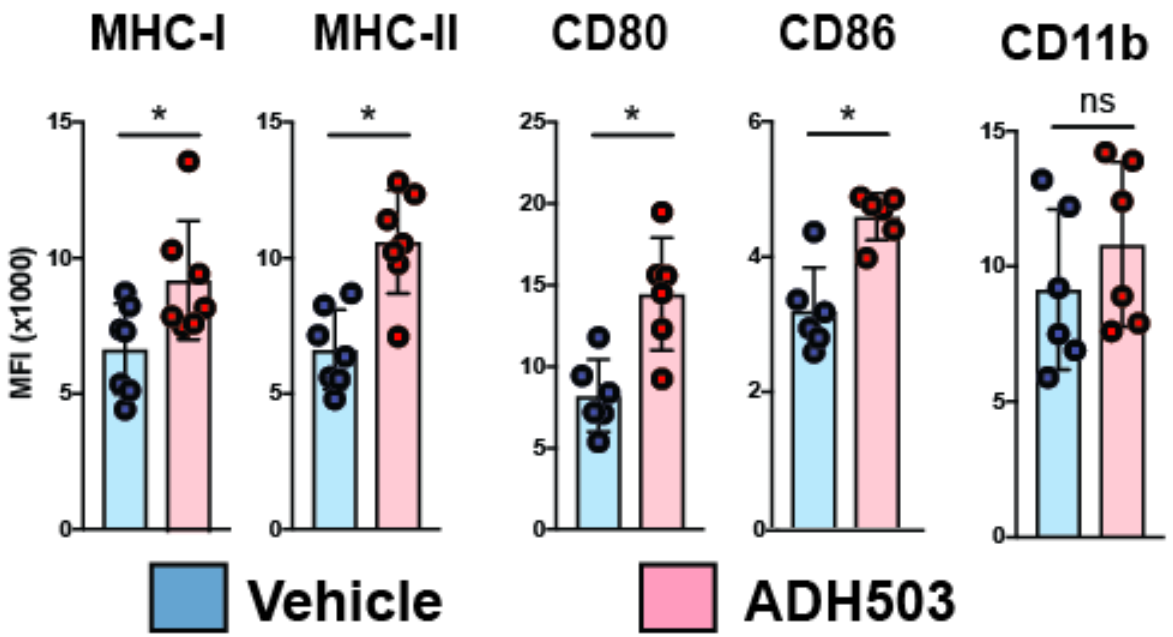
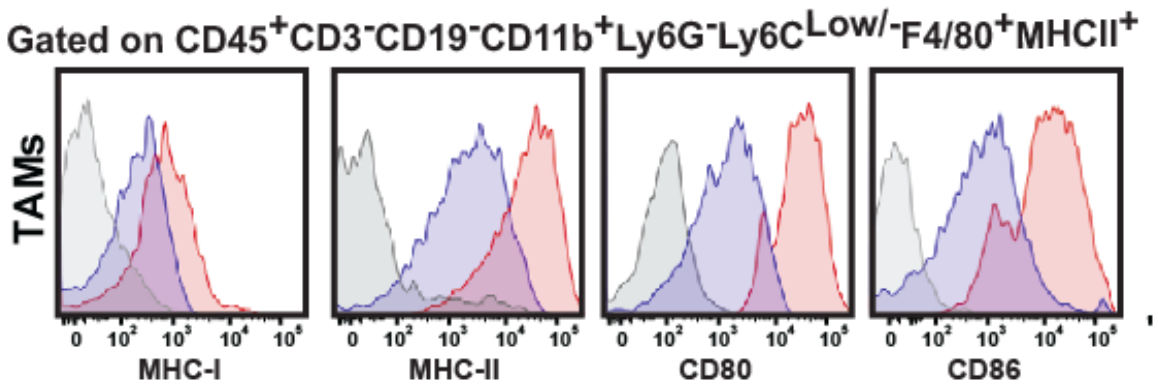
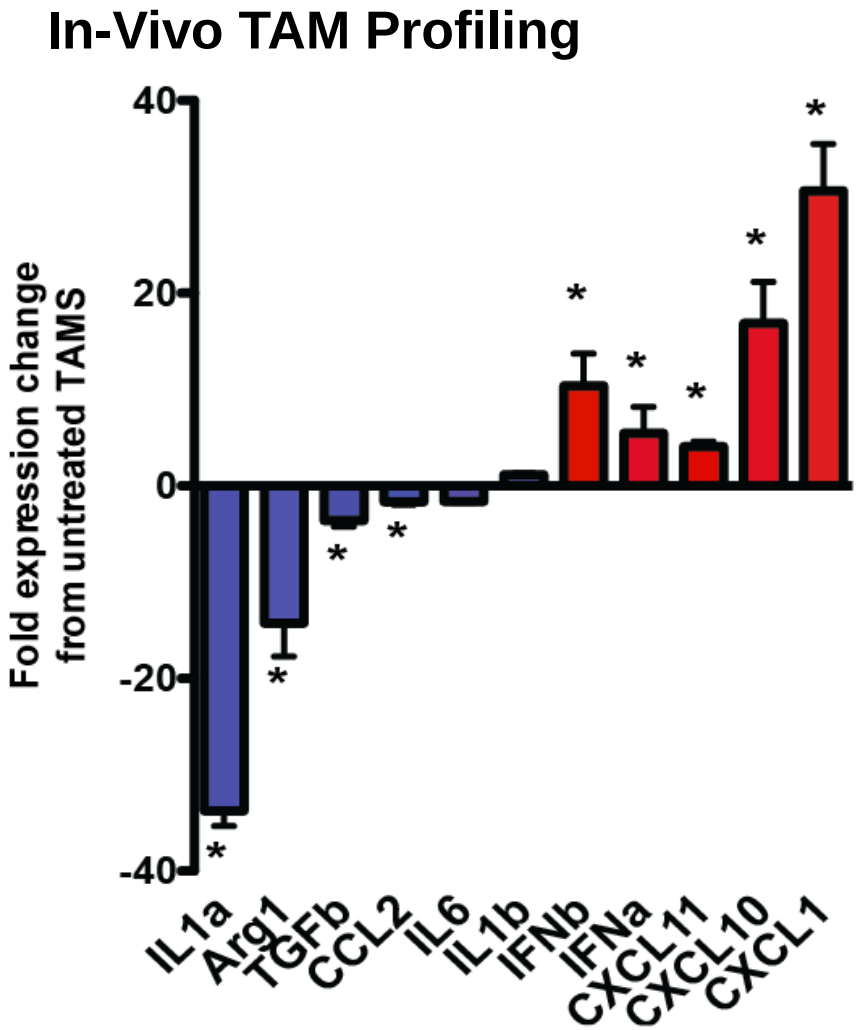
Celik E. Biophys J. Dec, 2013

CD11-Agonists Re-polarize Macrophages

Orthotopic PDAC (KP2)

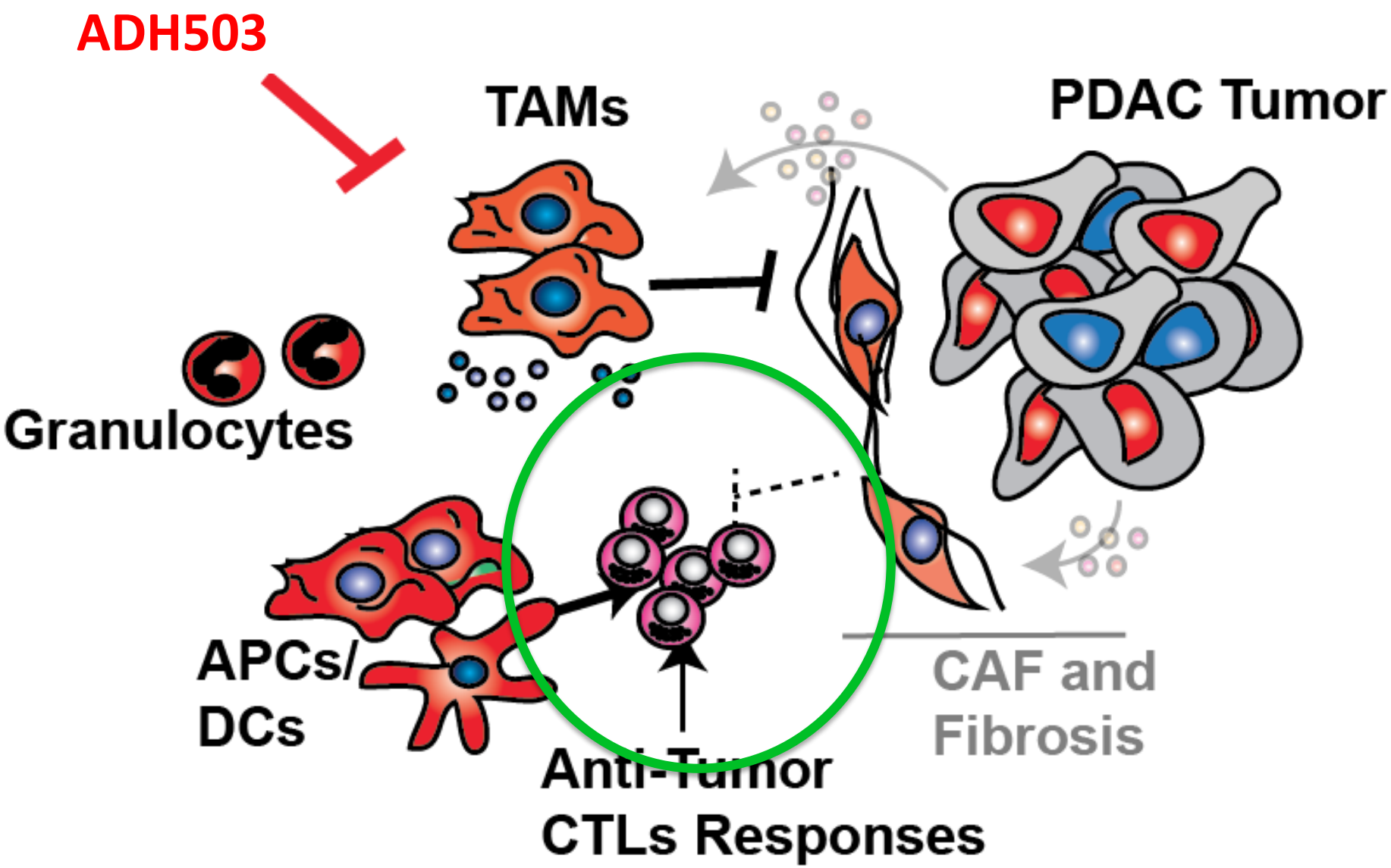




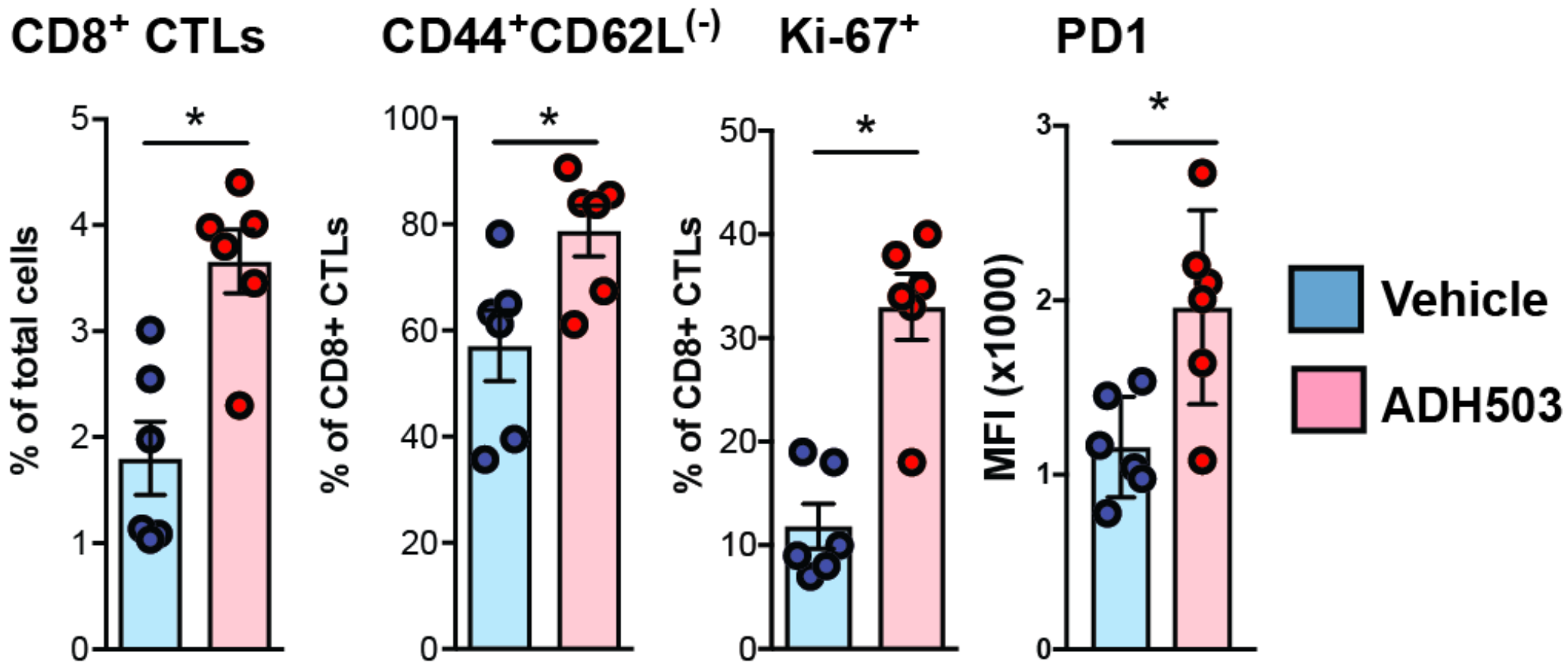


Consistent Across Two PDAC Models

Targeting Myeloid Cells



CD11B-Agonists Invigorate T cell Responses

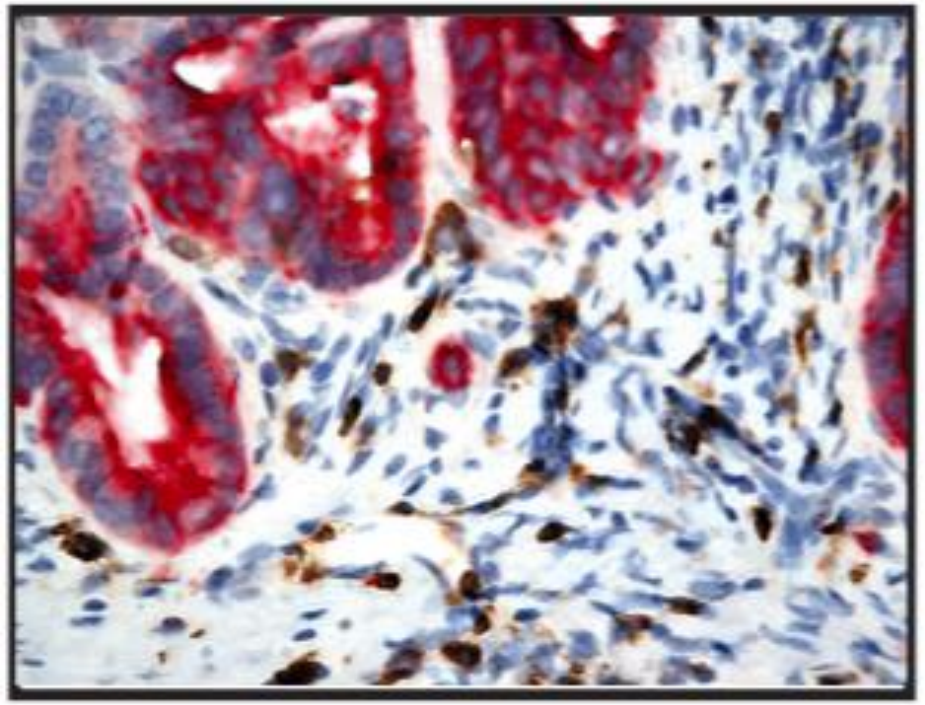


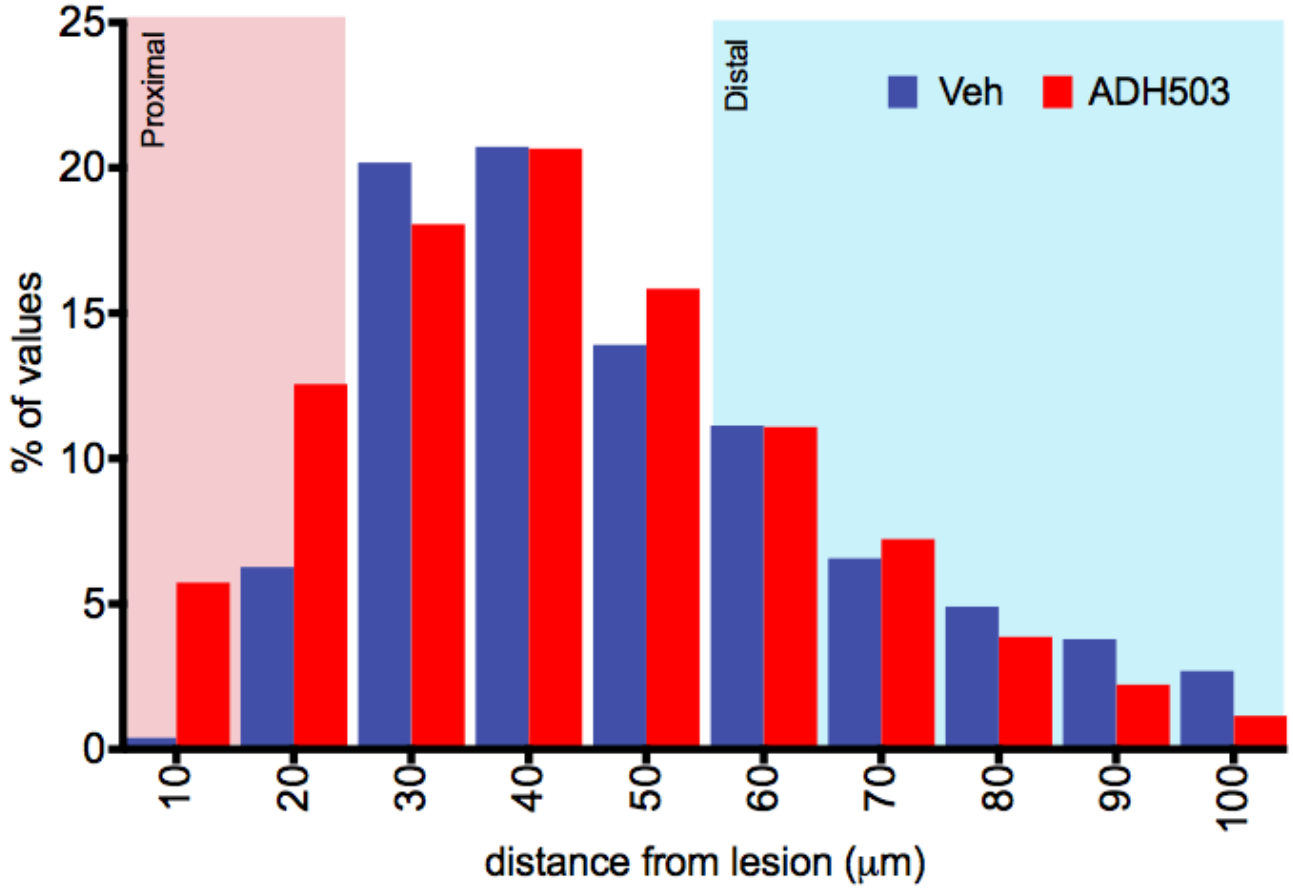
Consistent Across Three PDAC Models

ADH503 Restrains Tumor Progression

KPC GEMM

CD8a CK19





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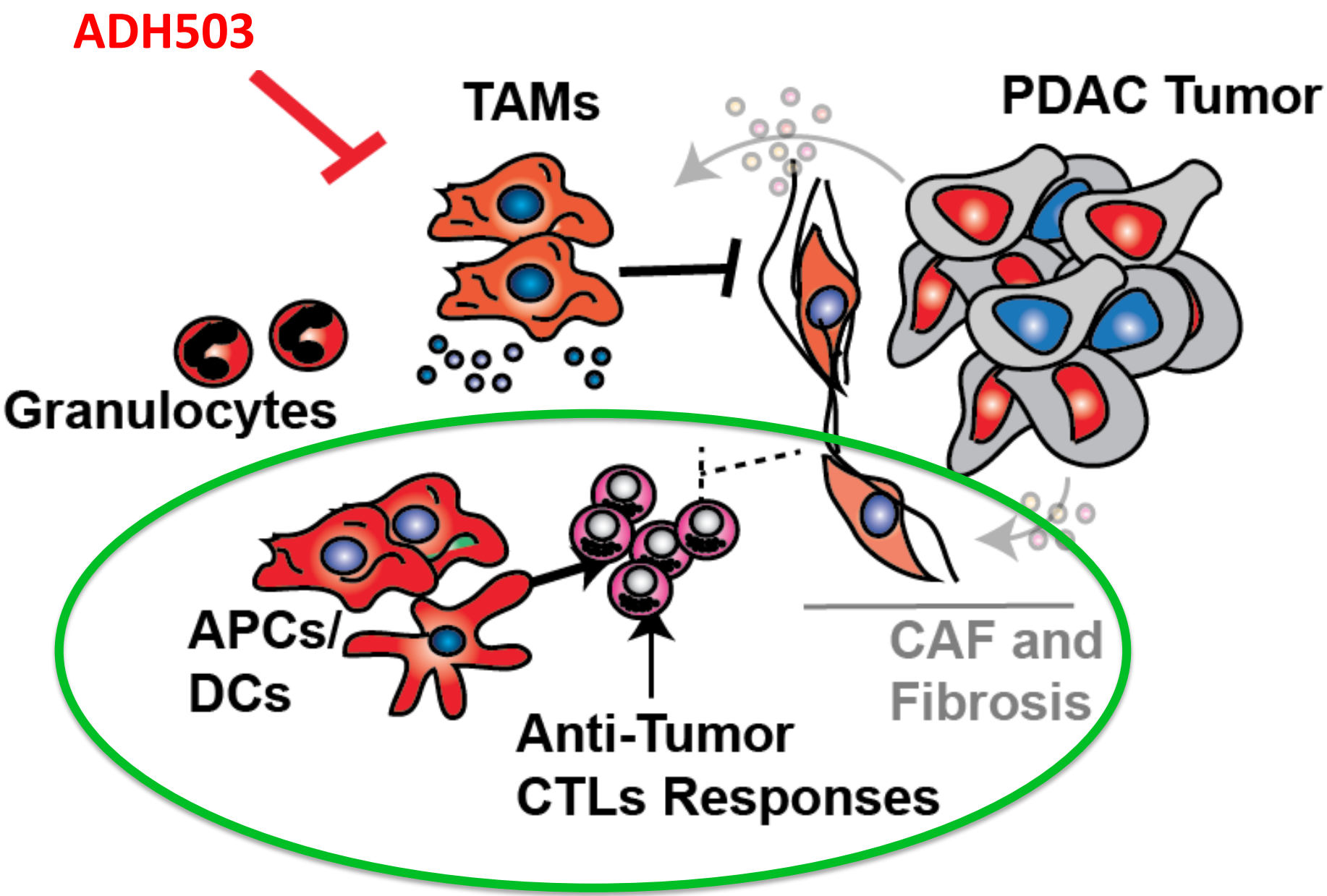
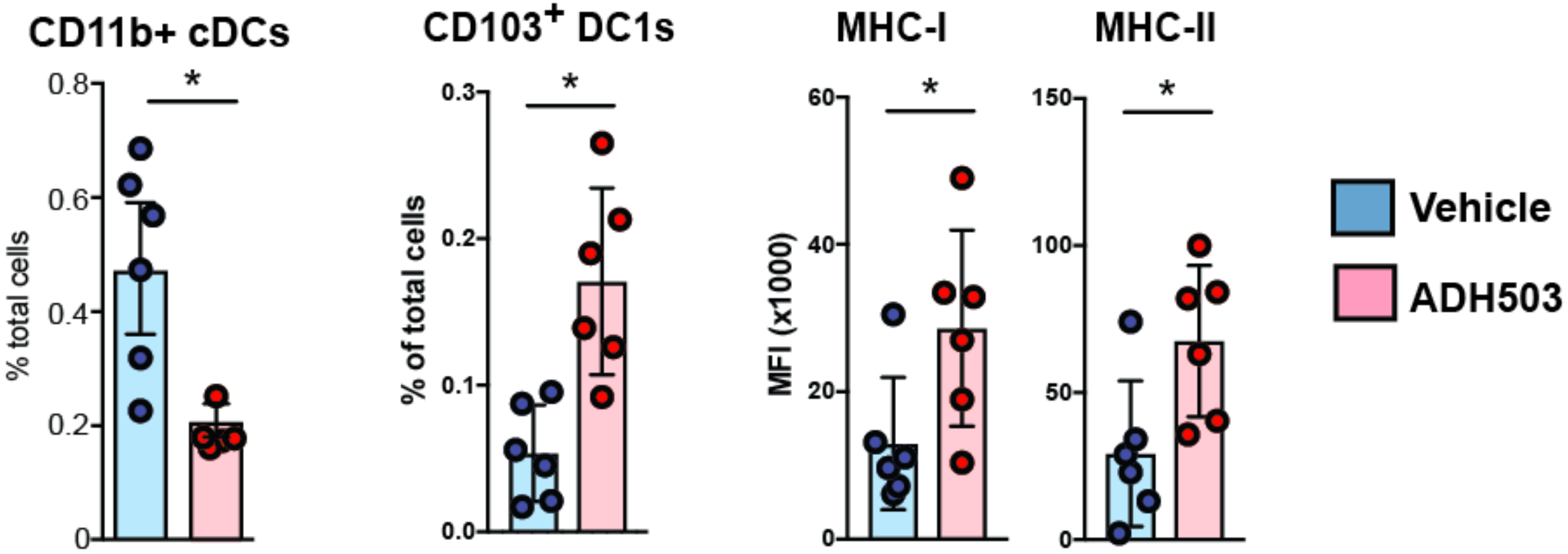


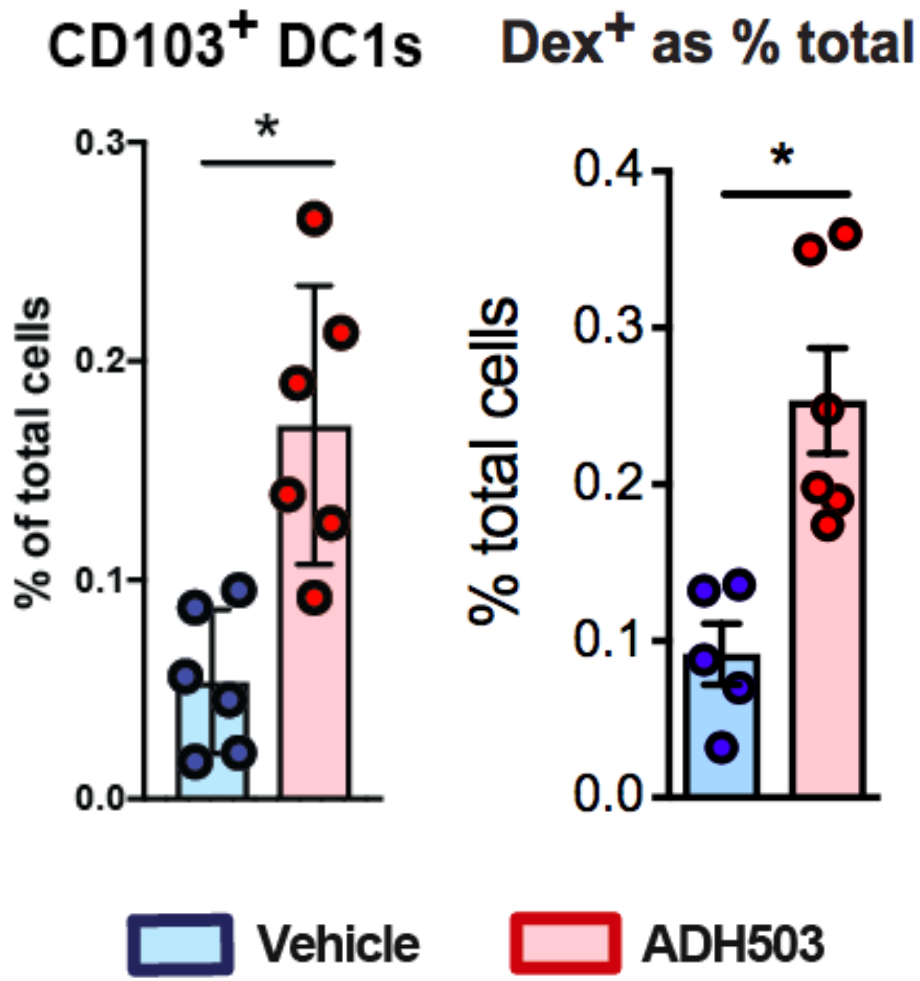
What about Dendritic Cells?



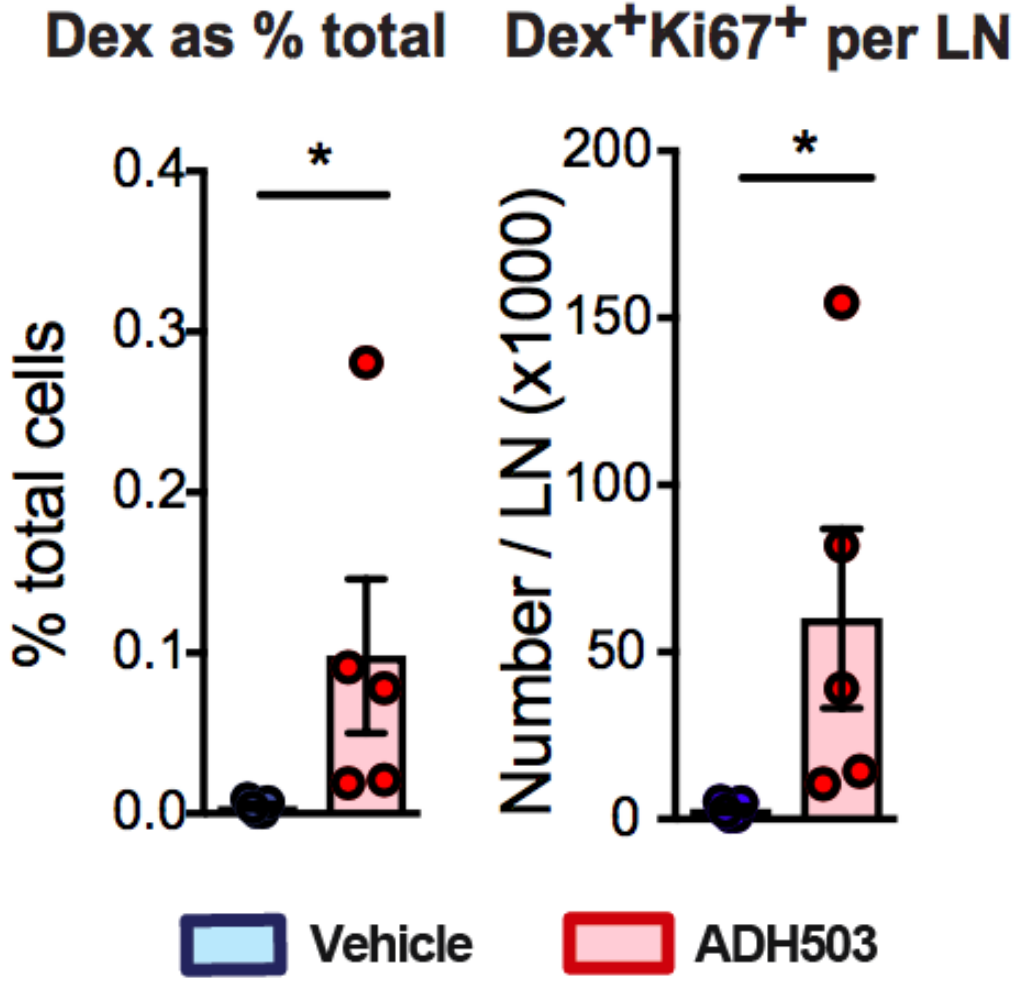
Consistent Across Three PDAC Models

What about Dendritic Cells?

Tumor Tissue



Tumor Draining Lymph-node

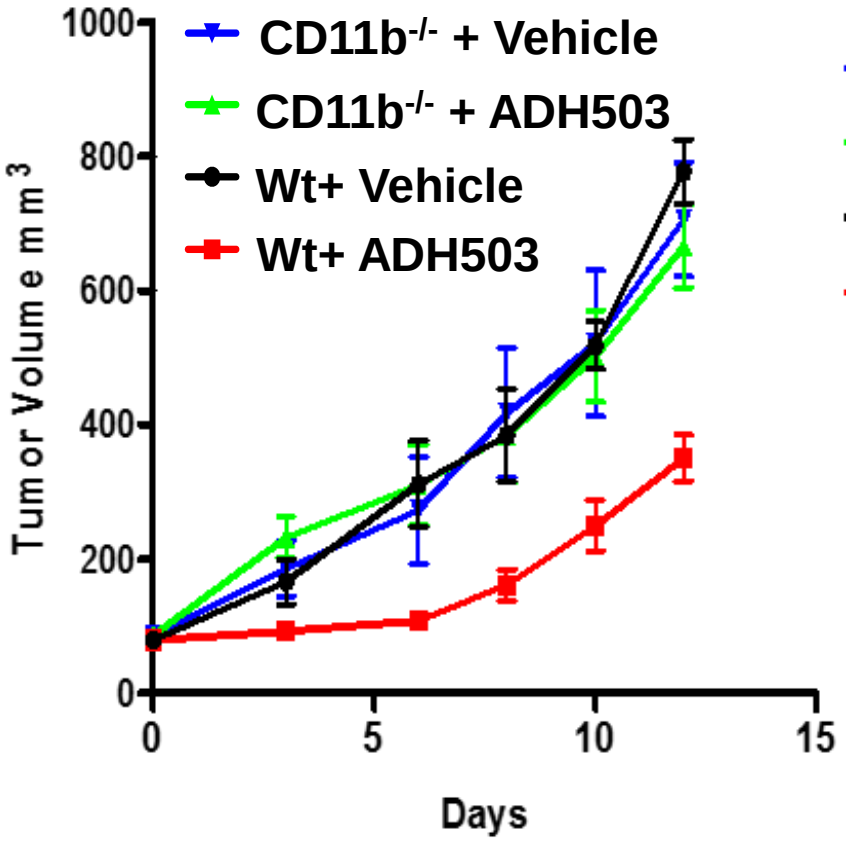


Consistent Across Three PDAC Models

ADH503 Restrains Tumor Progression

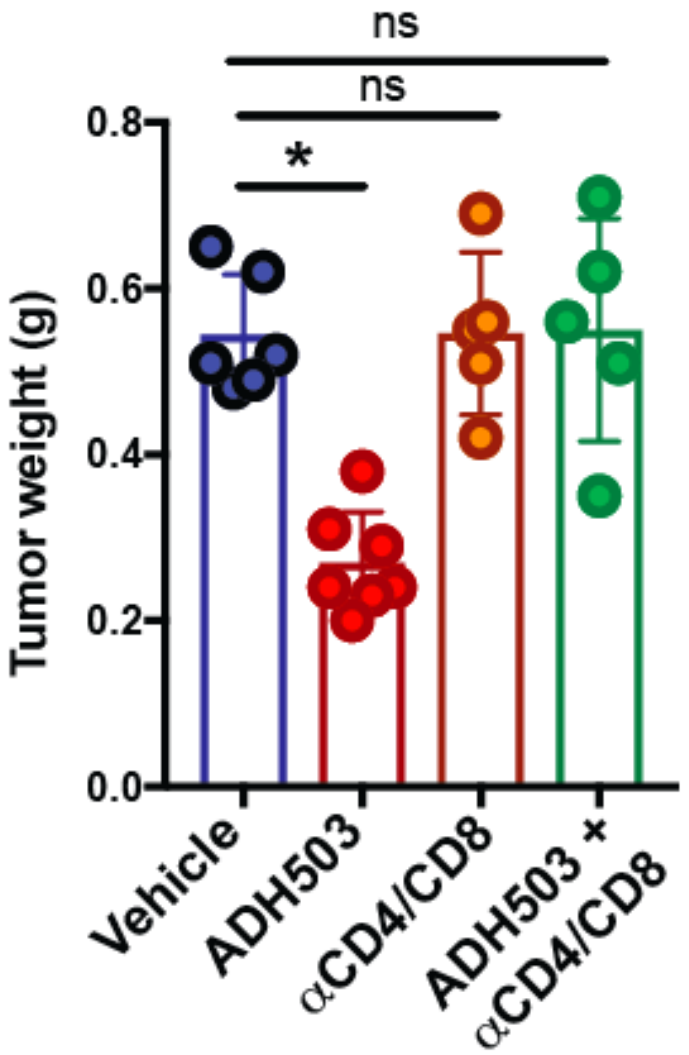
CD11B-DEPENDENT

SubQ PDAC (KP2)



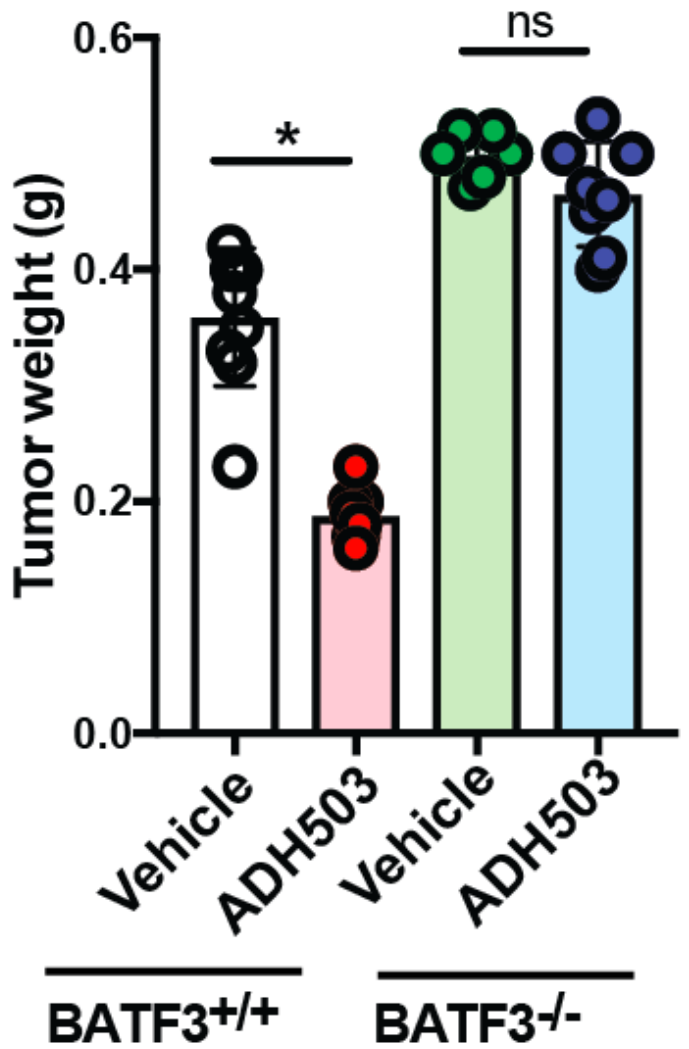
T-CELL-DEPENDENT

Orthotopic PDAC (KP2)



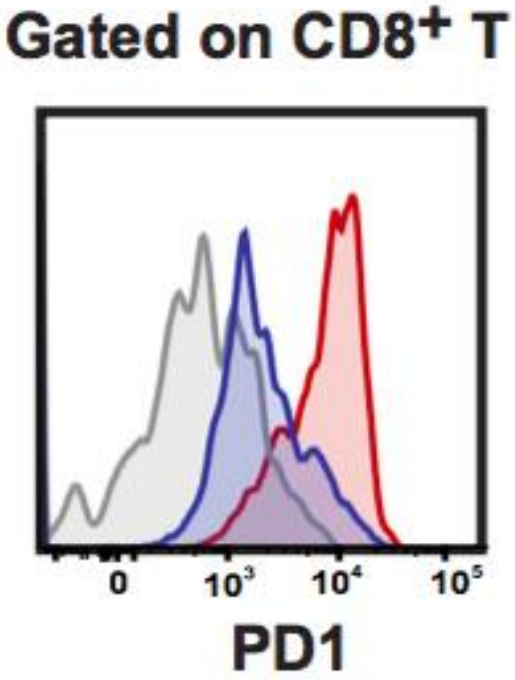
cDC1-DEPENDENT

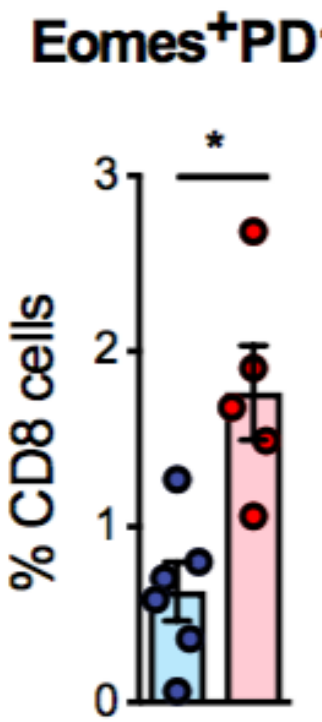
Orthotopic PDAC (KP2)

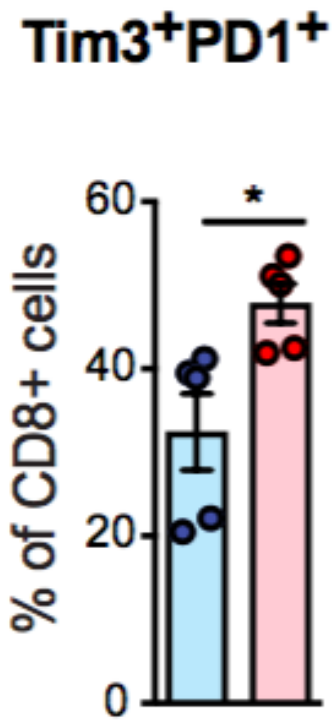


ADH503 Results in Checkpoint Engadgement

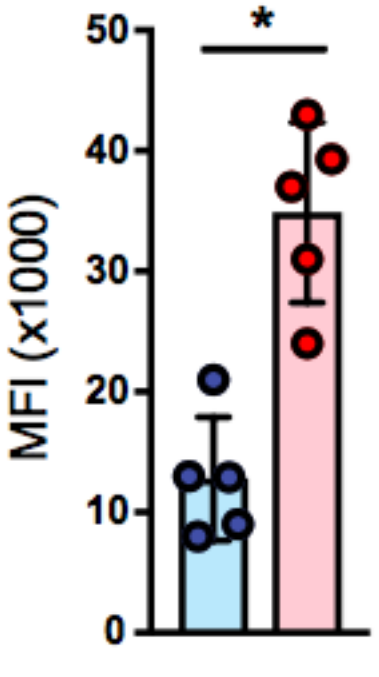
T cells

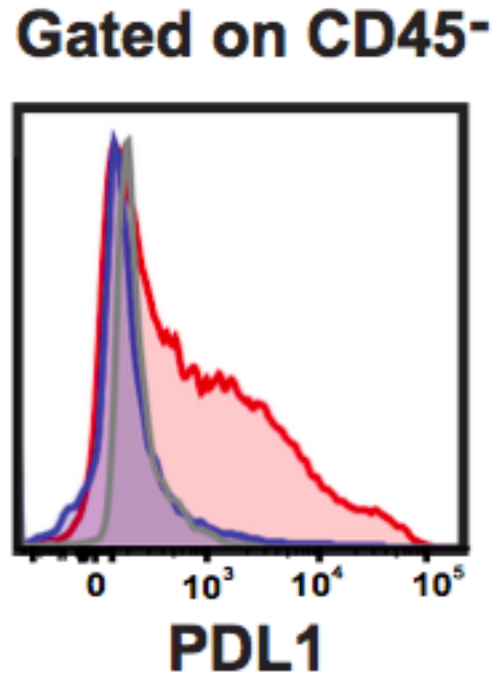






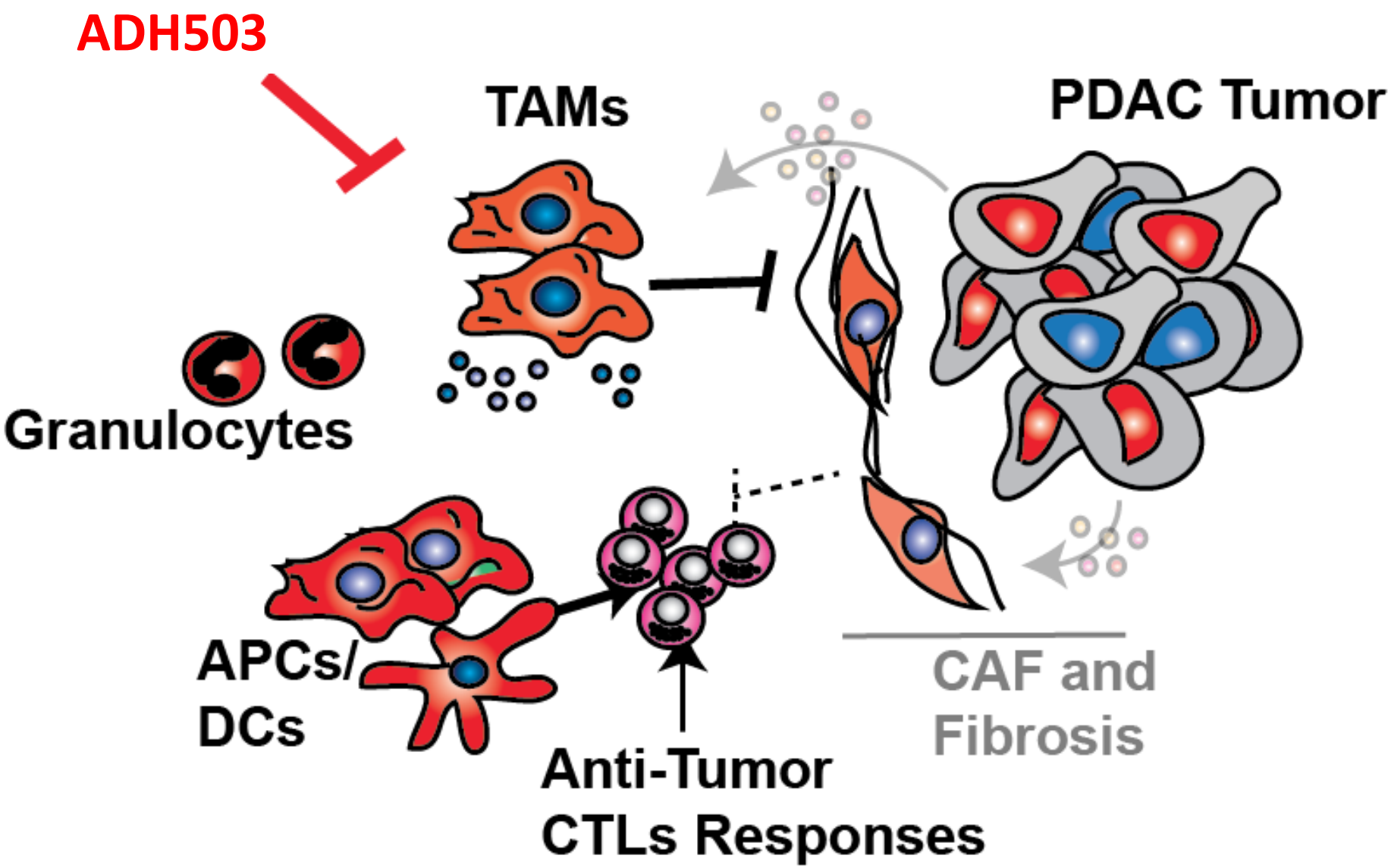
PDAC Cells



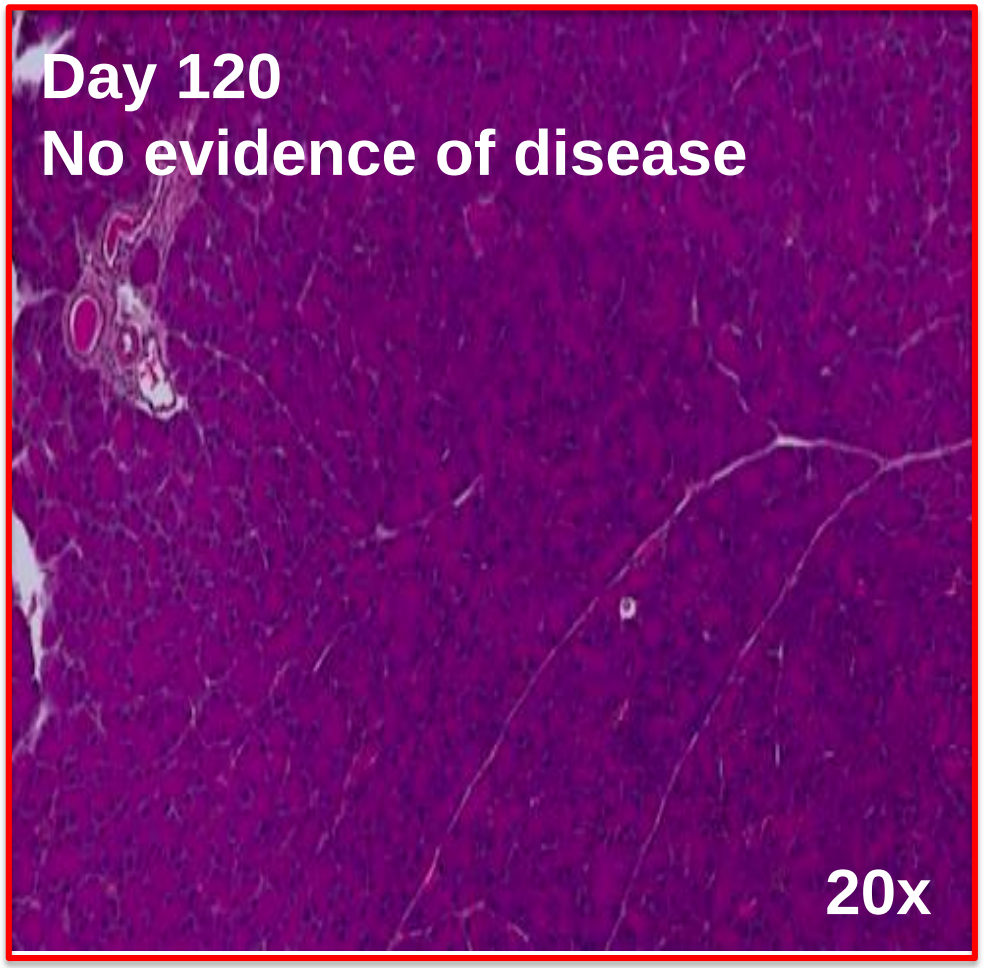


Consistent Across Two PDAC Models

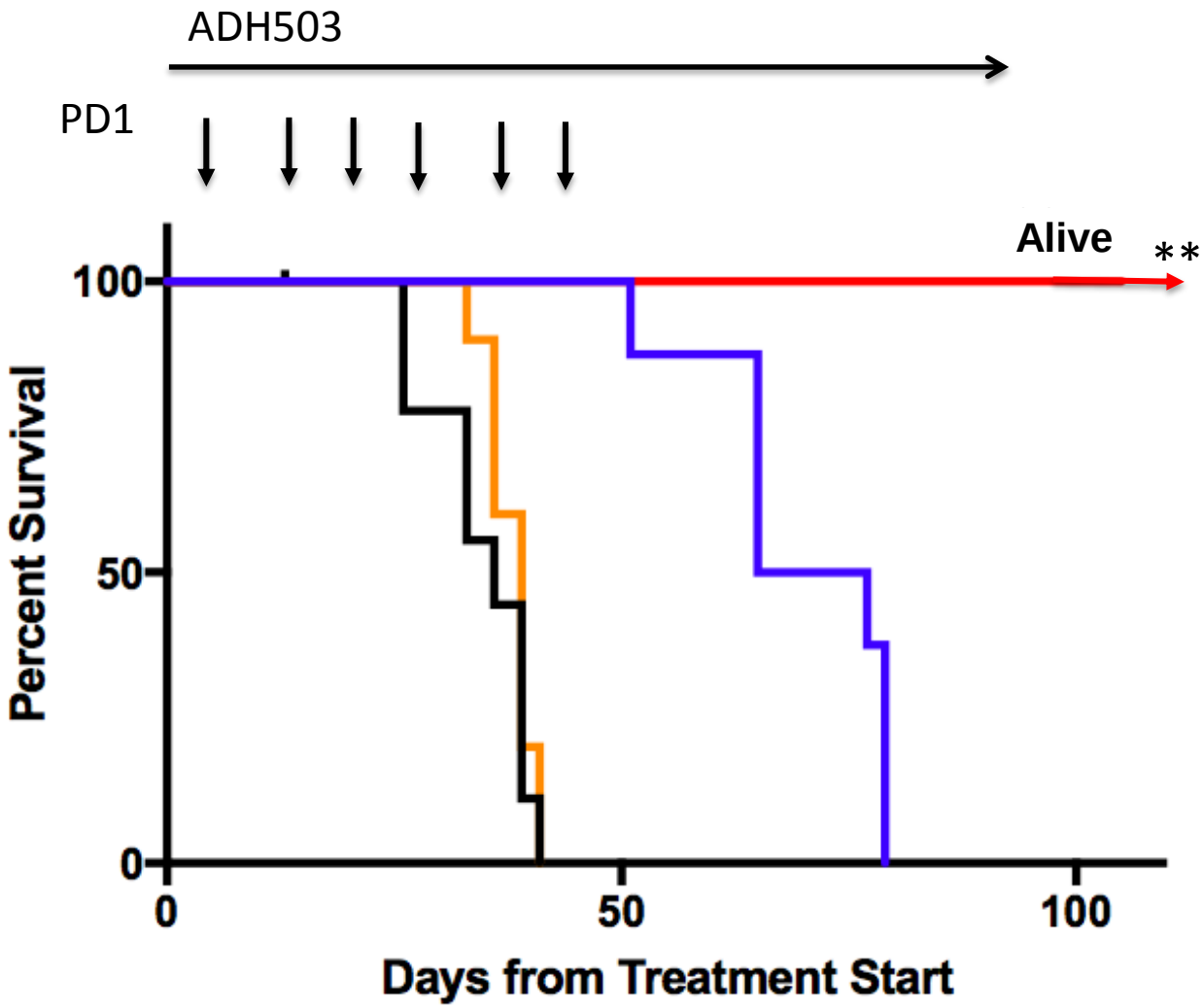
Targeting Myeloid Cells



ADH503 improves checkpoint immunotherapy

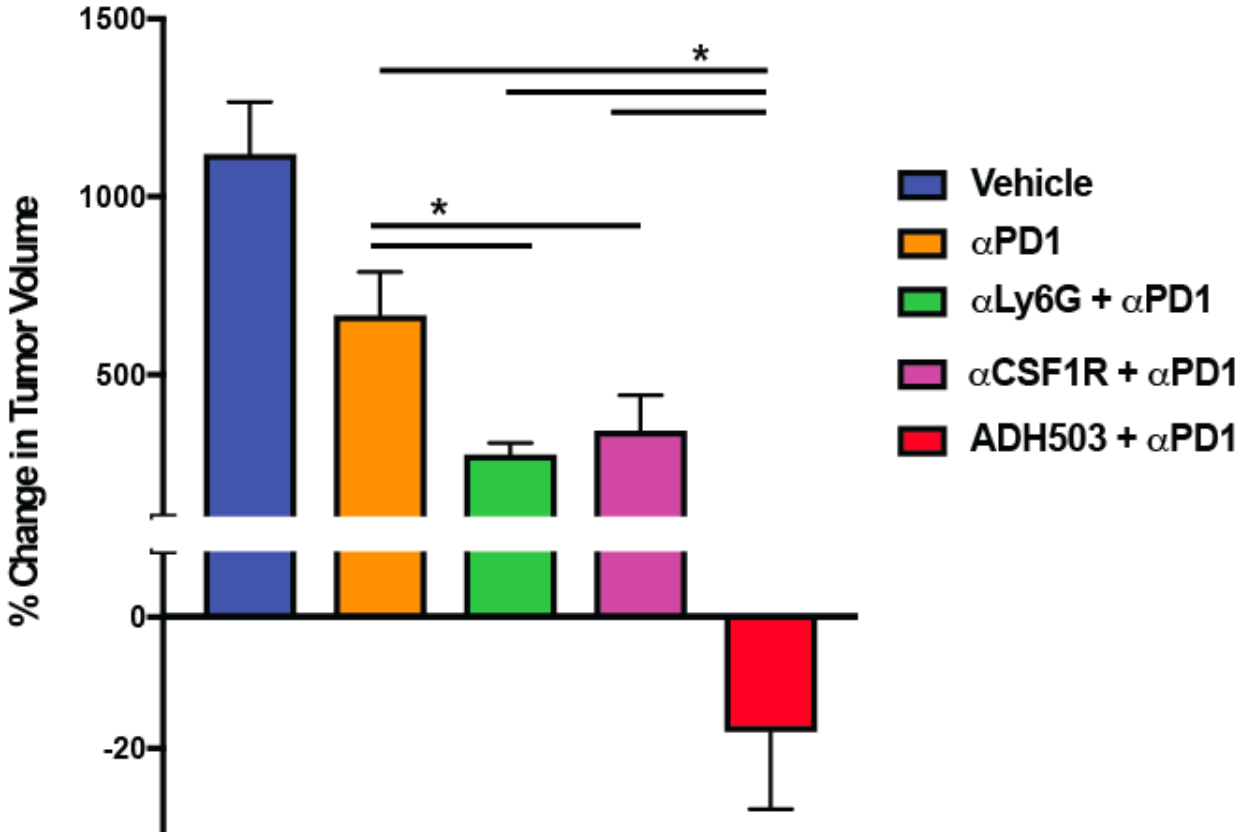


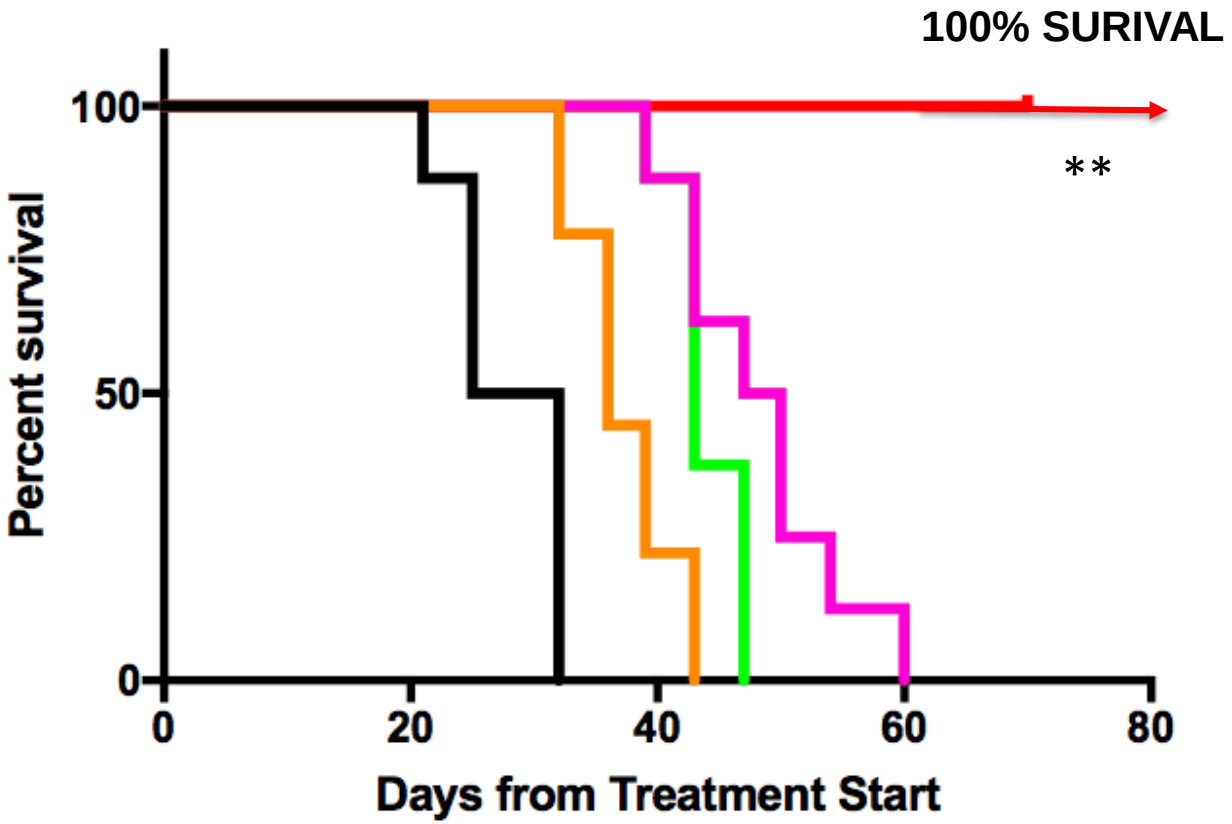
Sub-Q Re-challenge 0/5



Head to Head vs. Other Approaches

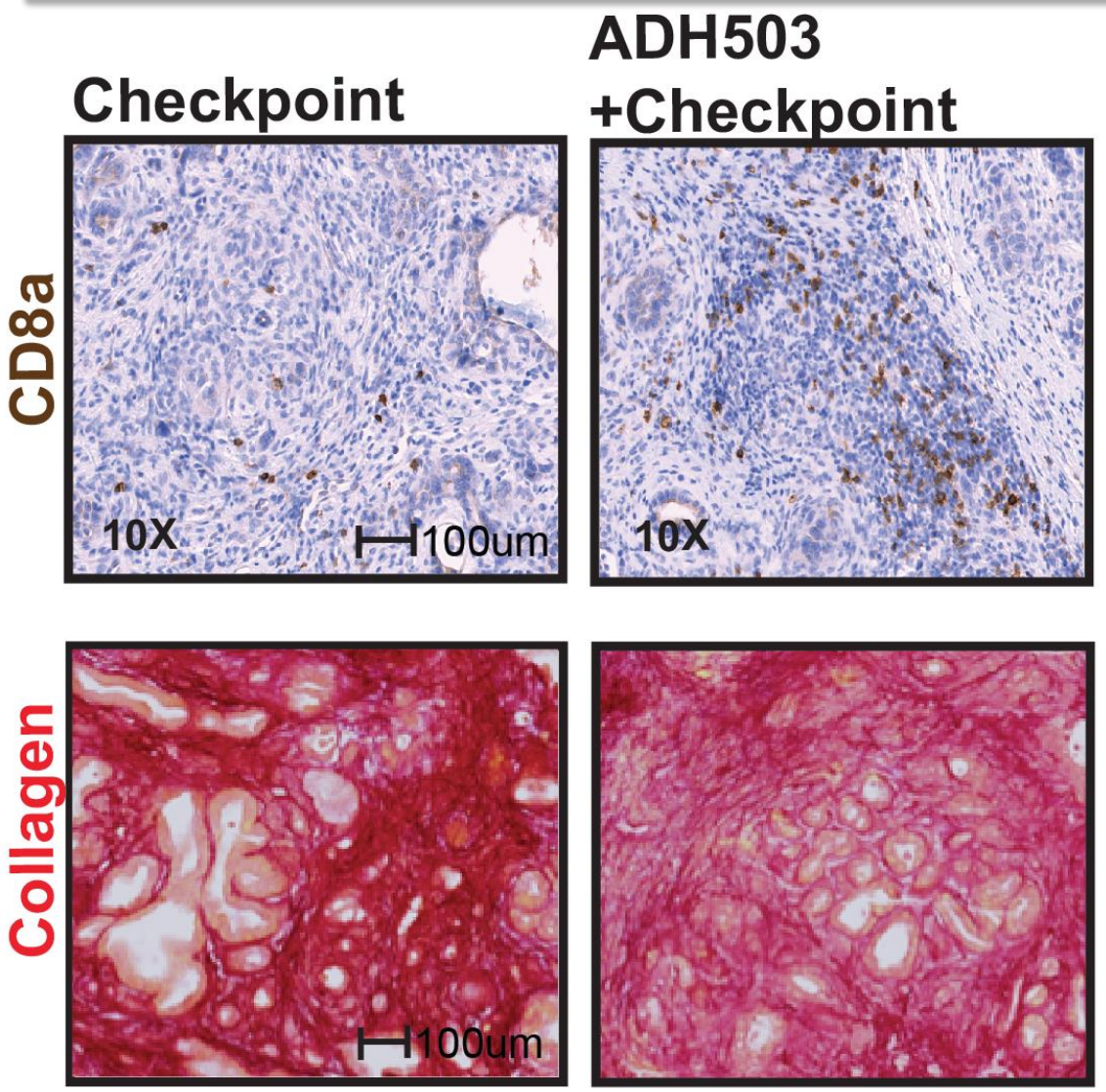
Orthotopic PDAC (KP2)

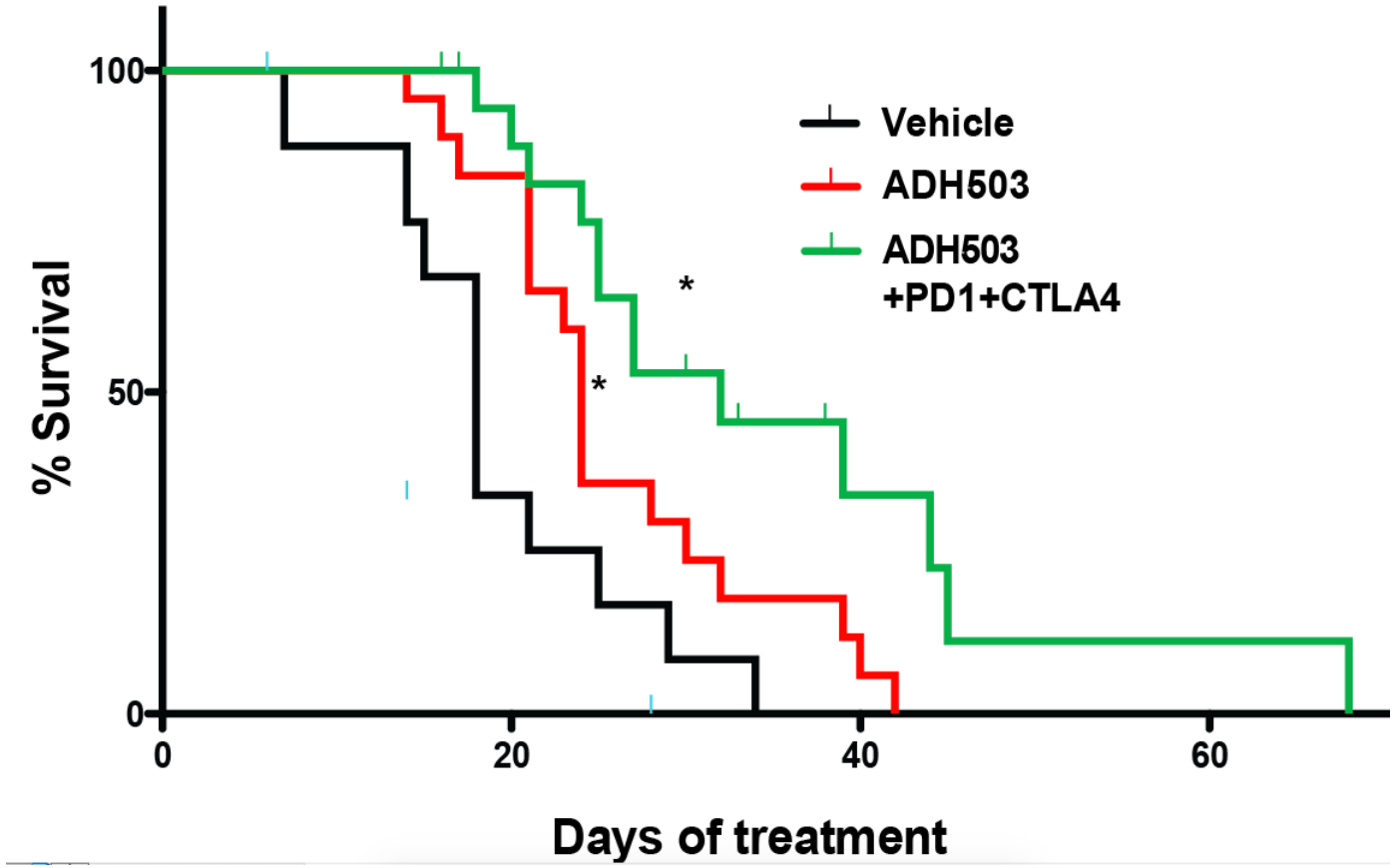




ADH503 improves immunotherapy

KPC GEMM

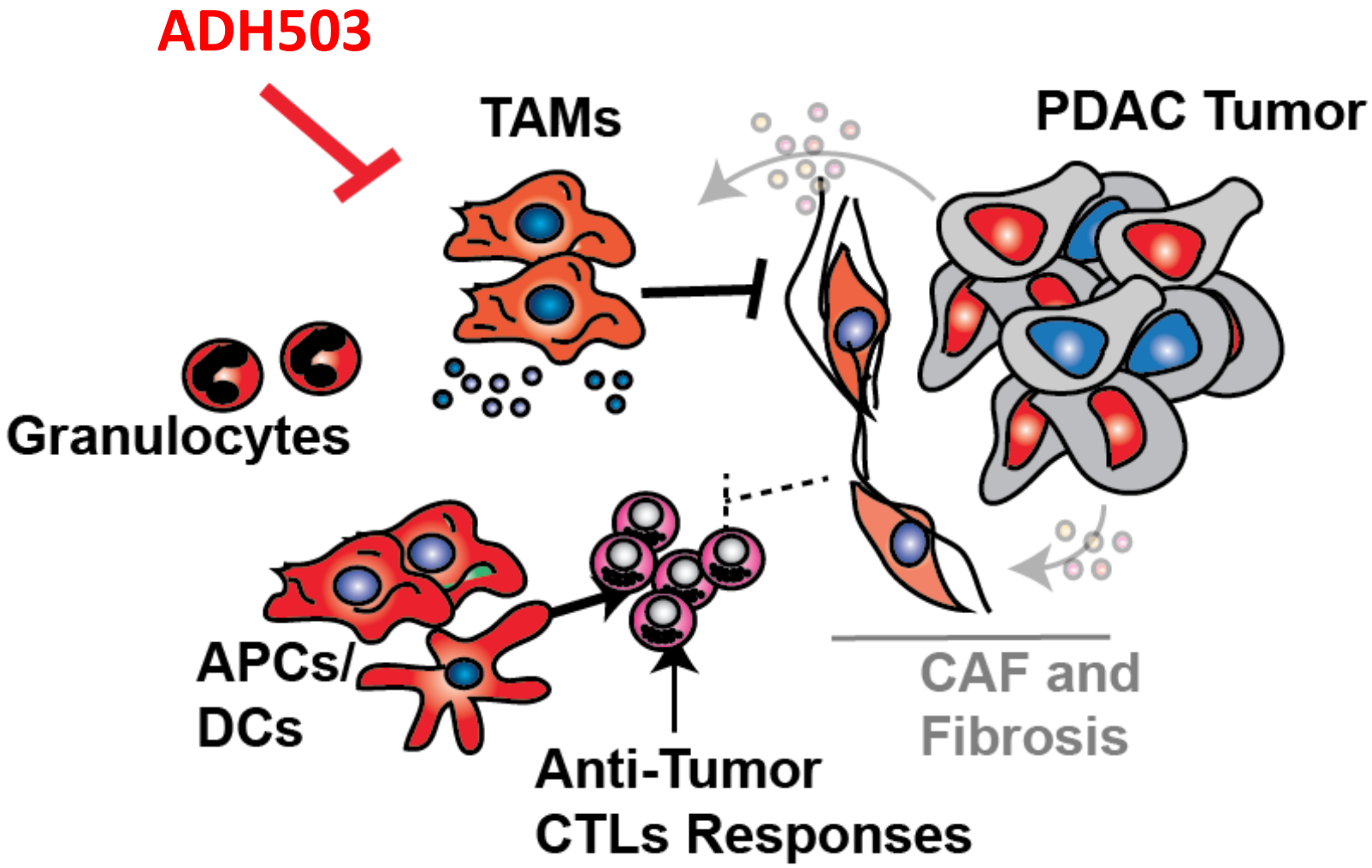




Therapeutic Model

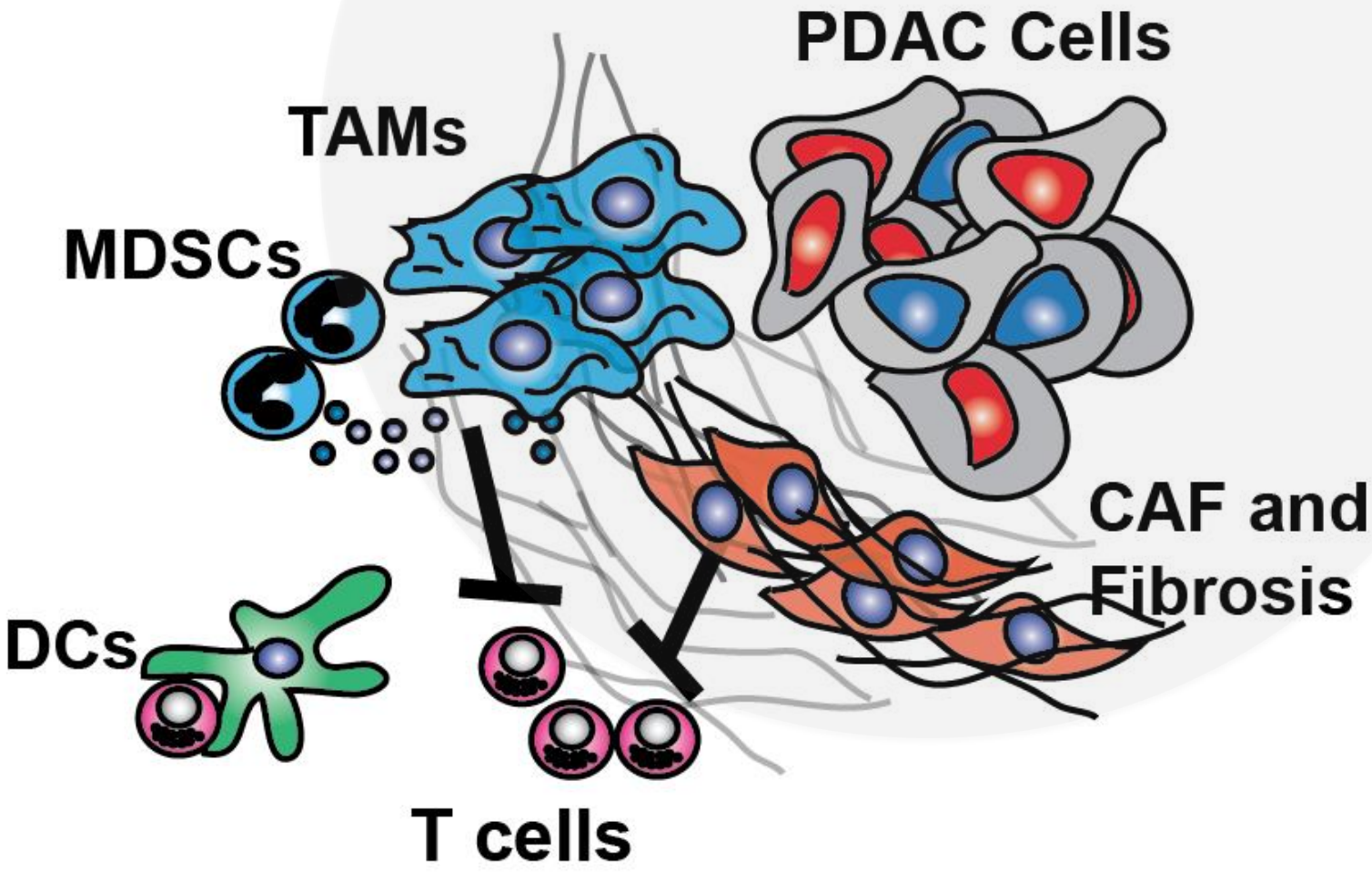
Take homes

- Target Integrins
- Myeloid/DC Interface

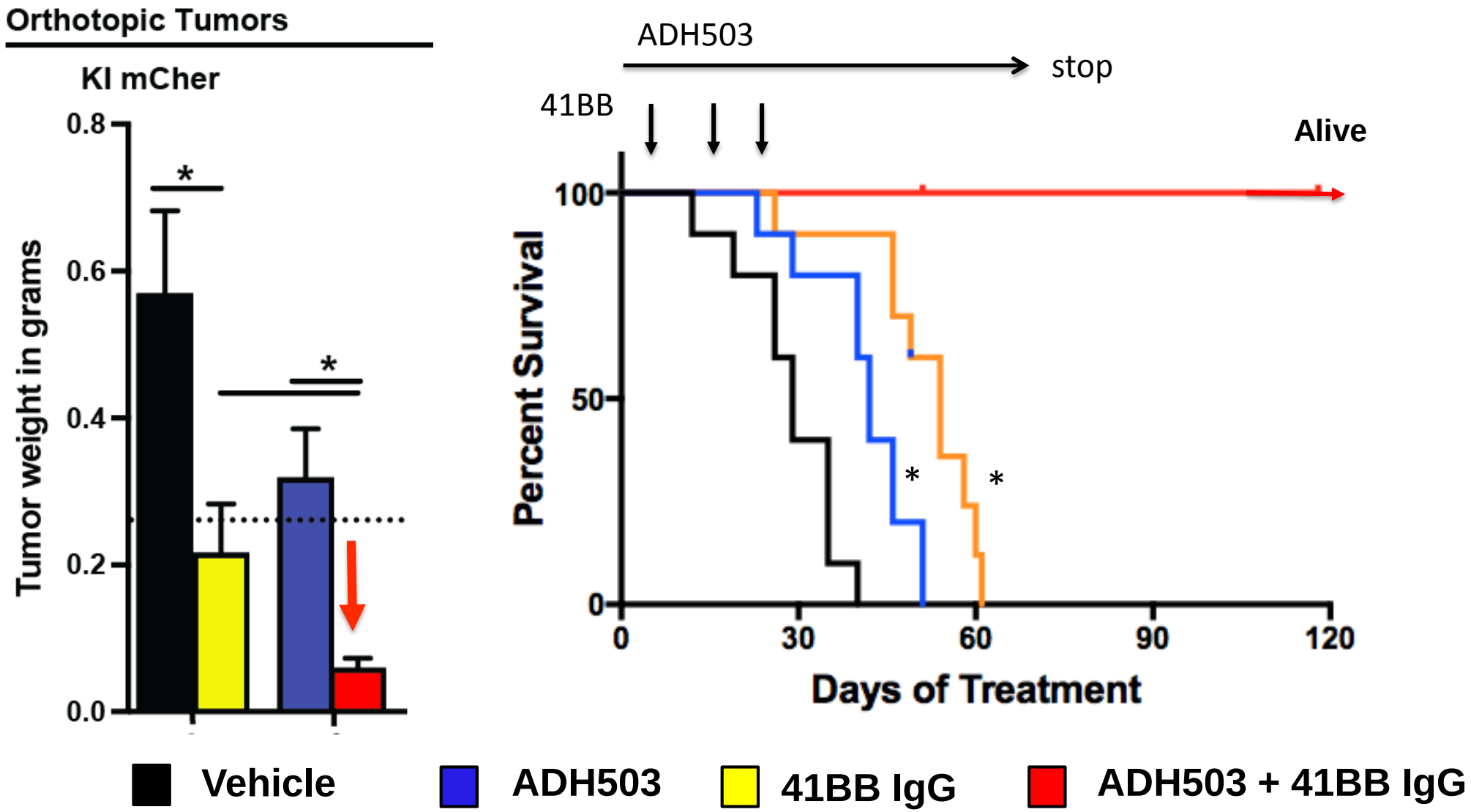


“QUESTIONS?

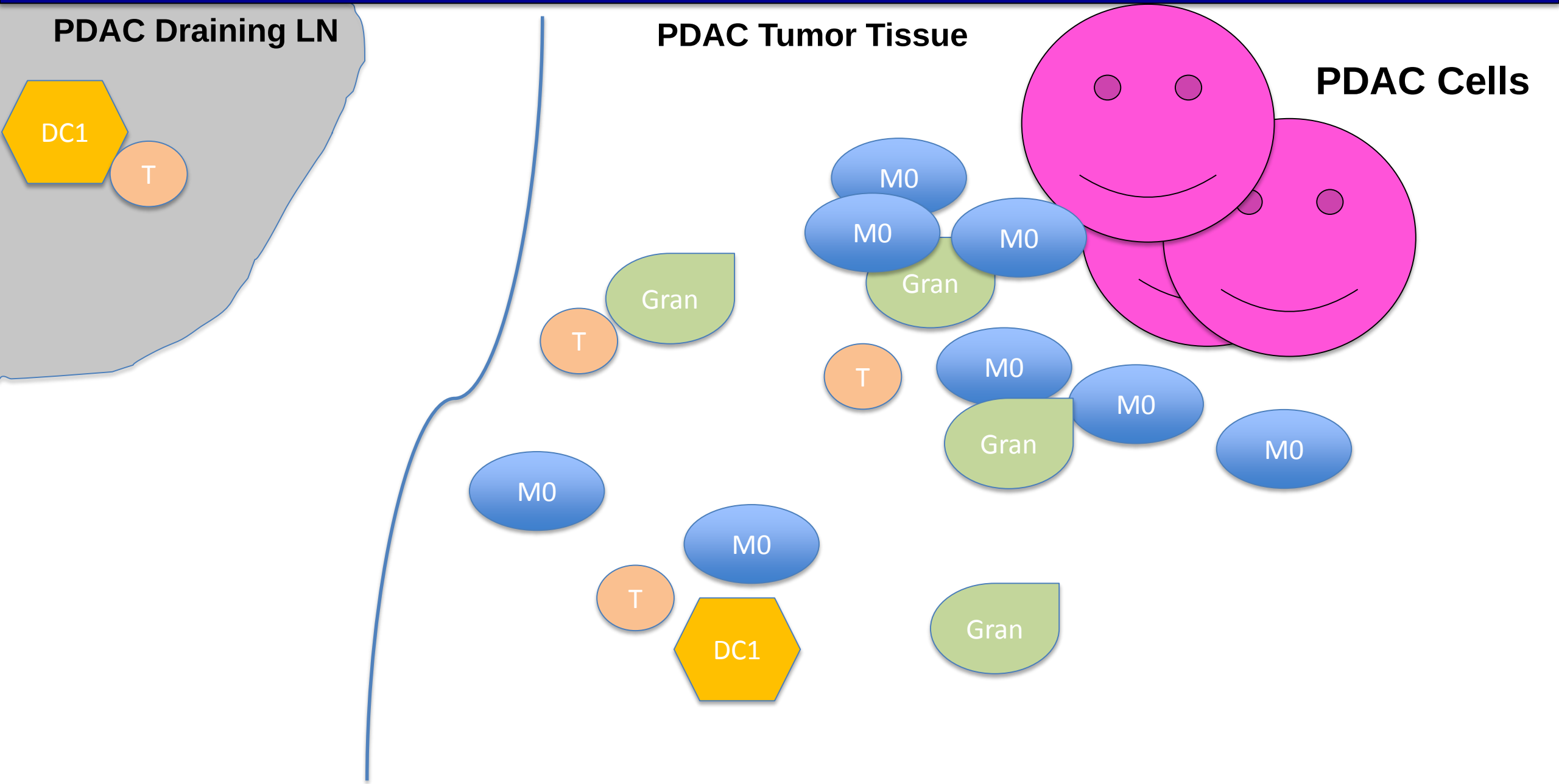
Targeting PDAC Microenvironment



ADH503 improves immunotherapy



UNTREATED


PDAC Draining LN
DC1
T
PDAC Tumor Tissue
PDAC Cells
M0
M0
M0
Gran
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T
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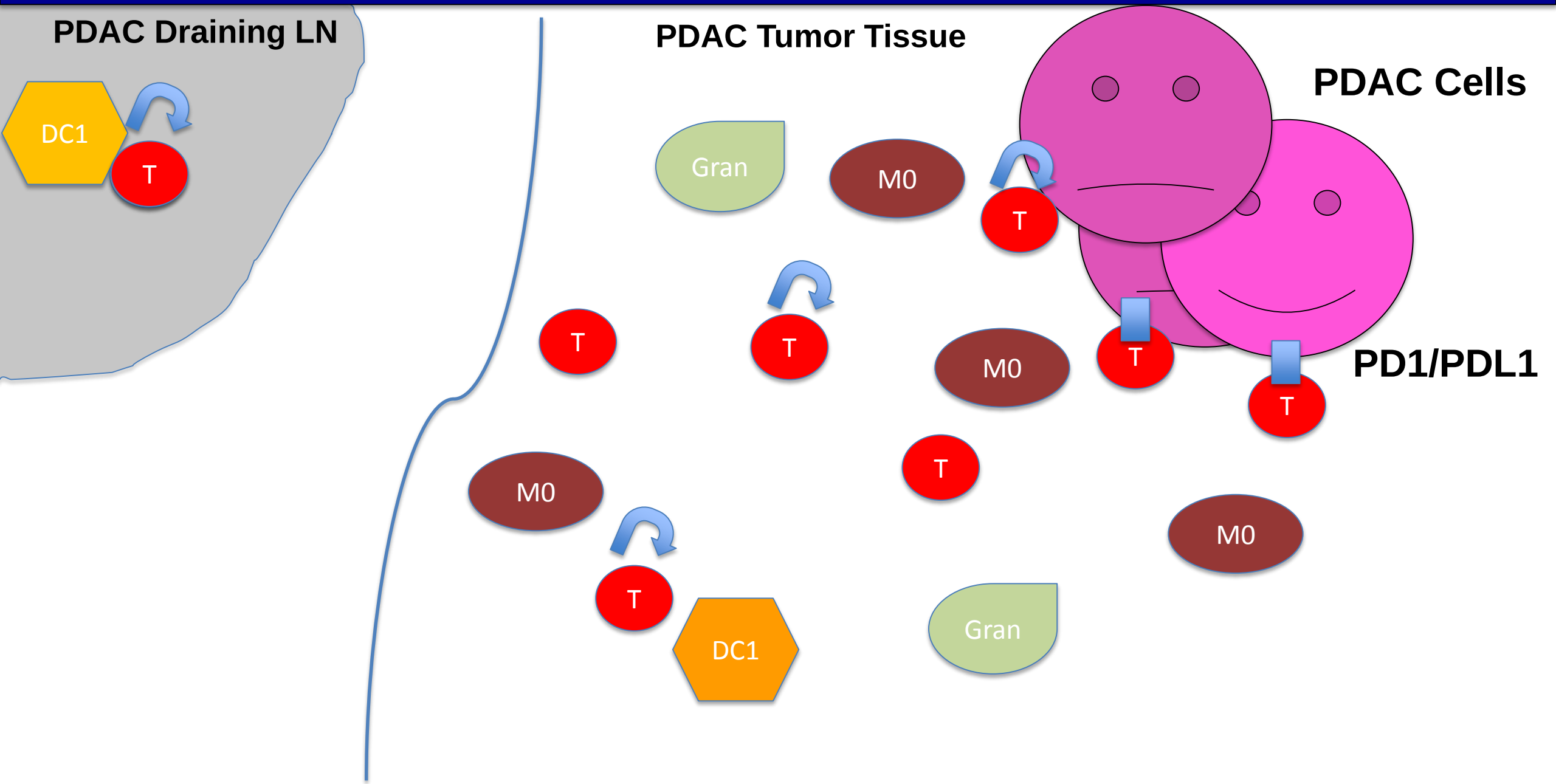
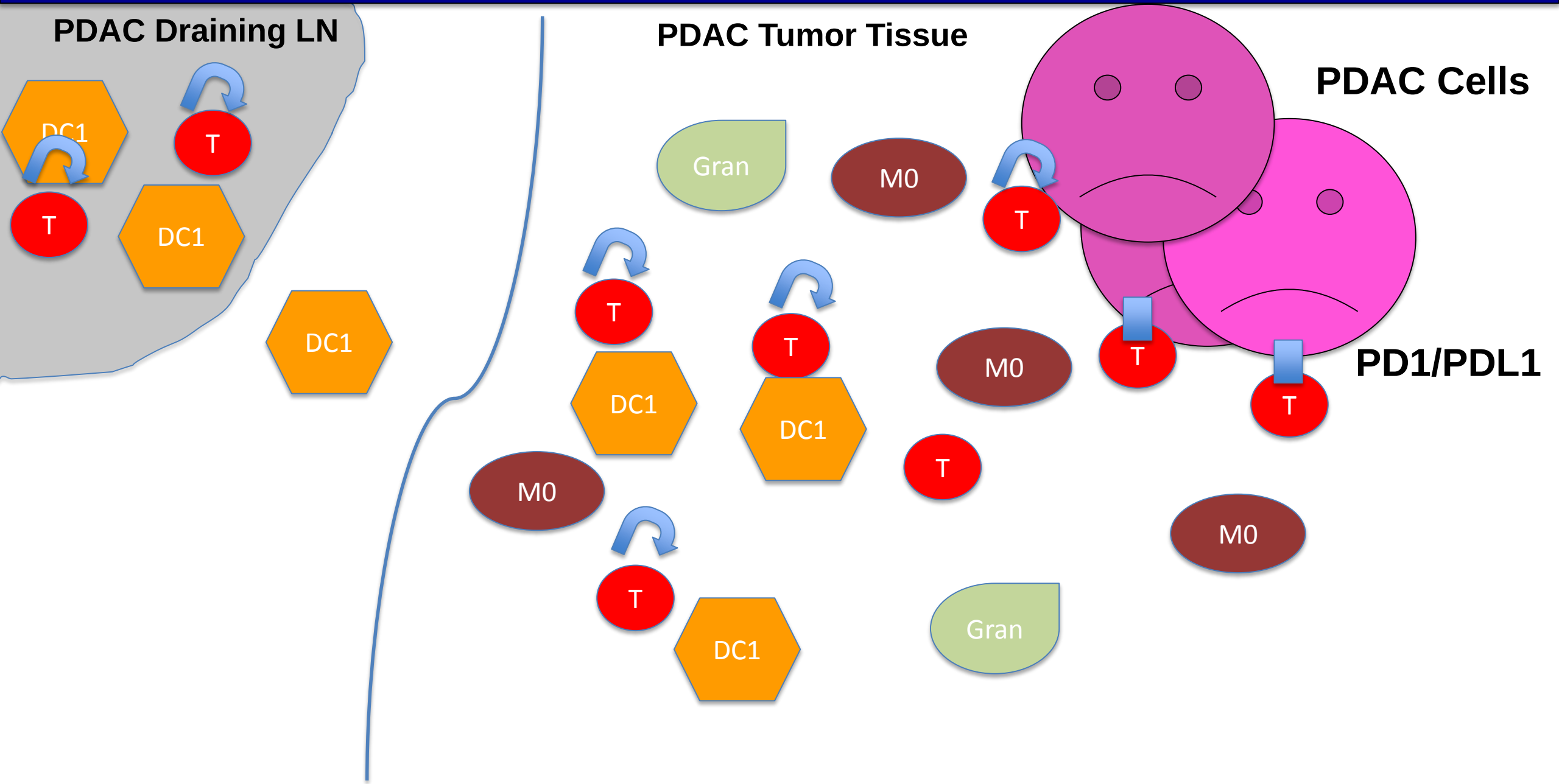
DC1
Gran

DAY 6-8 Of ADH503



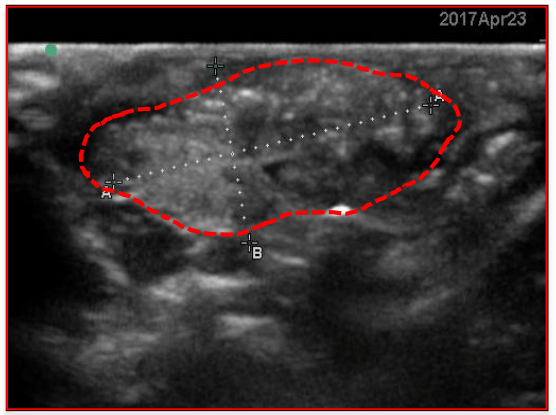
DAY 10-12 Of Treatment



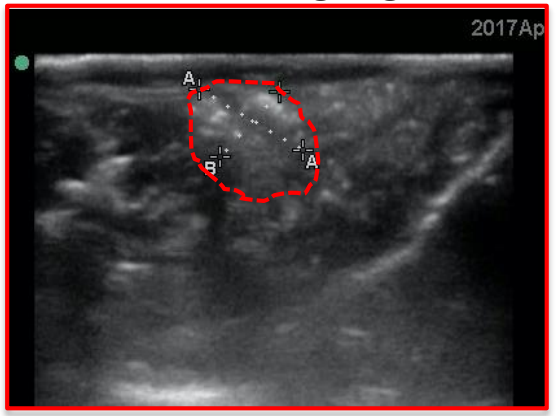
ADH503 Restrains Tumor Progression

Orthotopic PDAC (KP2)

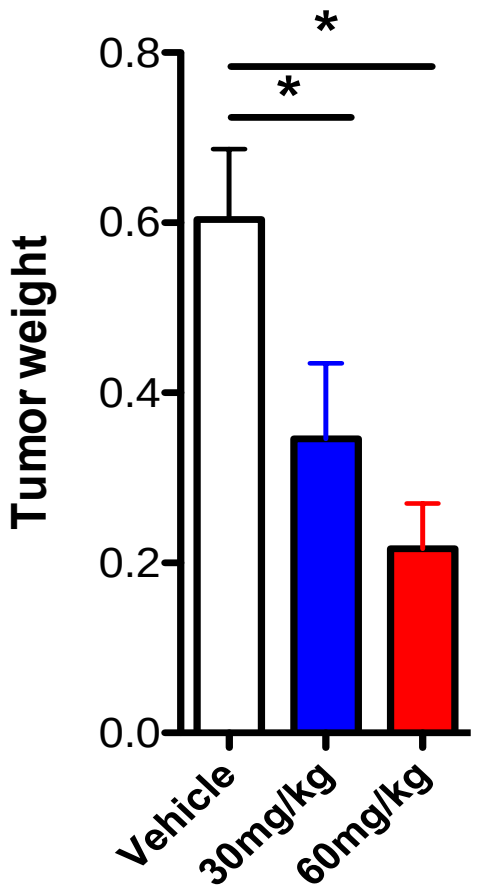
Vehicle

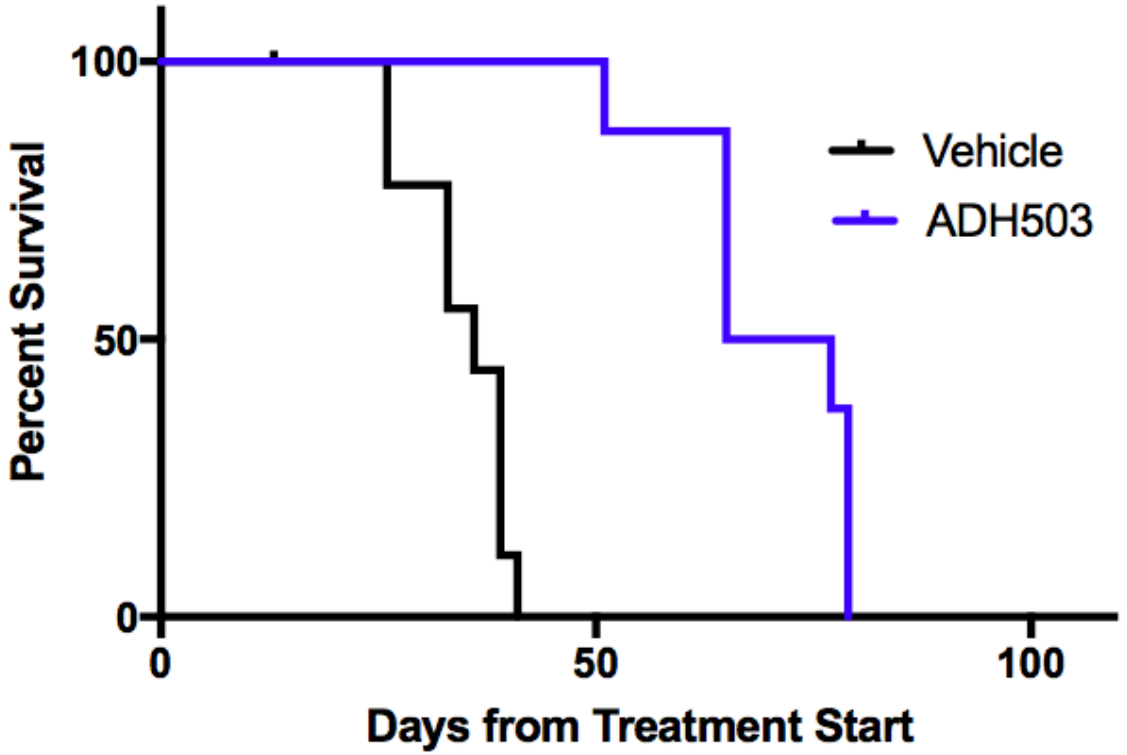


ADH503 60mg/kg



ADH503

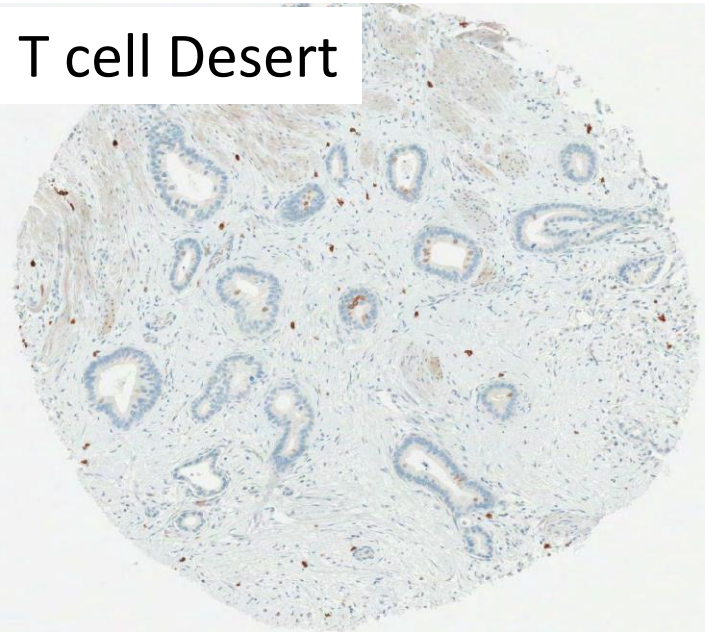




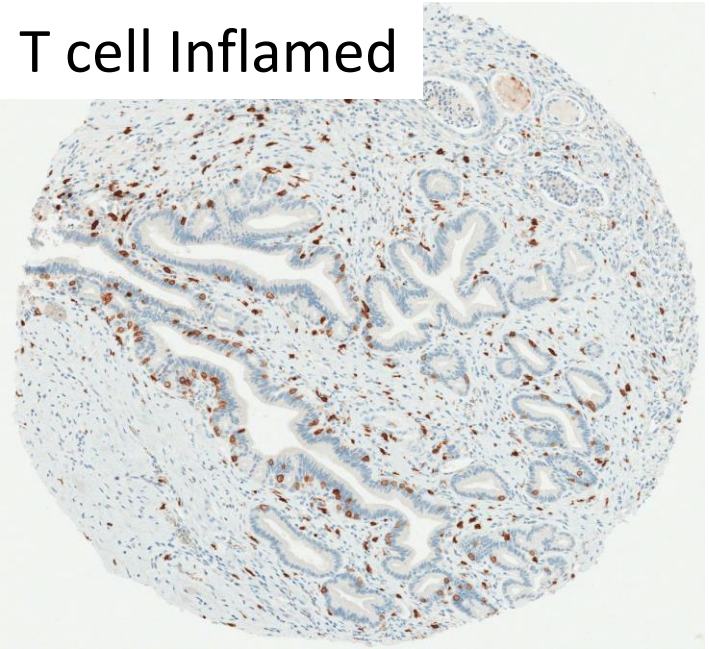
Repeated in 3 independent PDAC models and 5 other cancer models

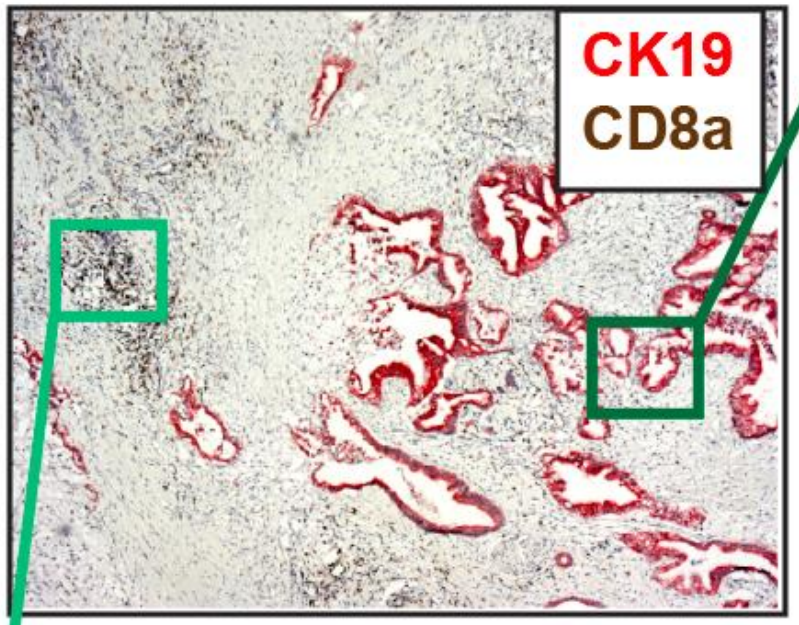
Diverse Immune Responses Impact Patient Outcomes

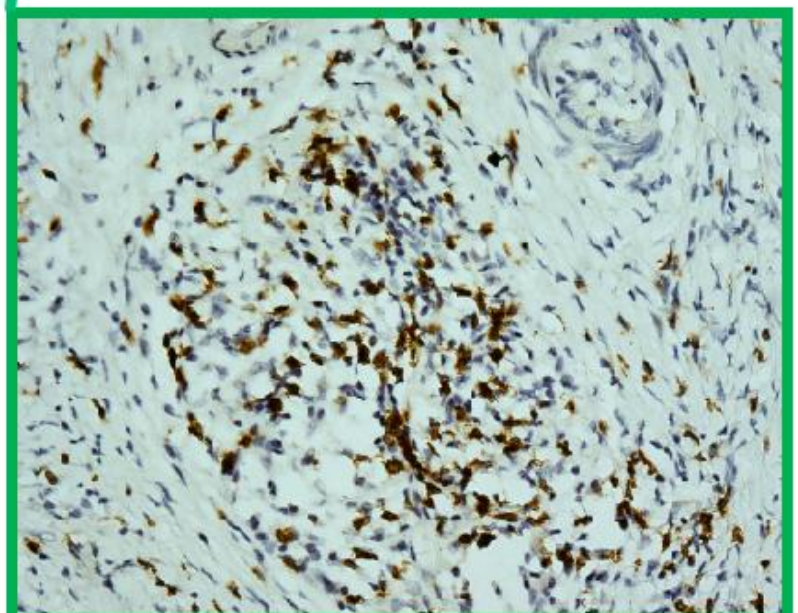
T cell Desert

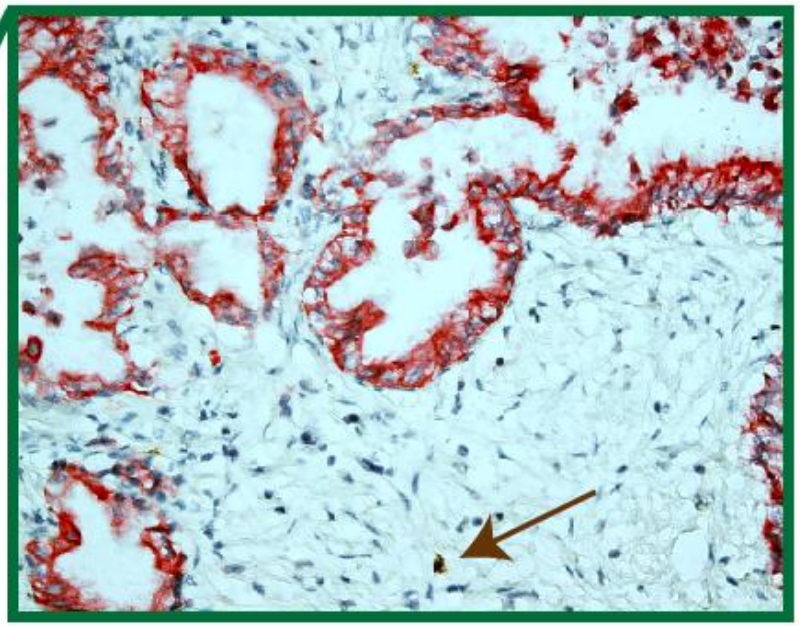


T cell Inflamed

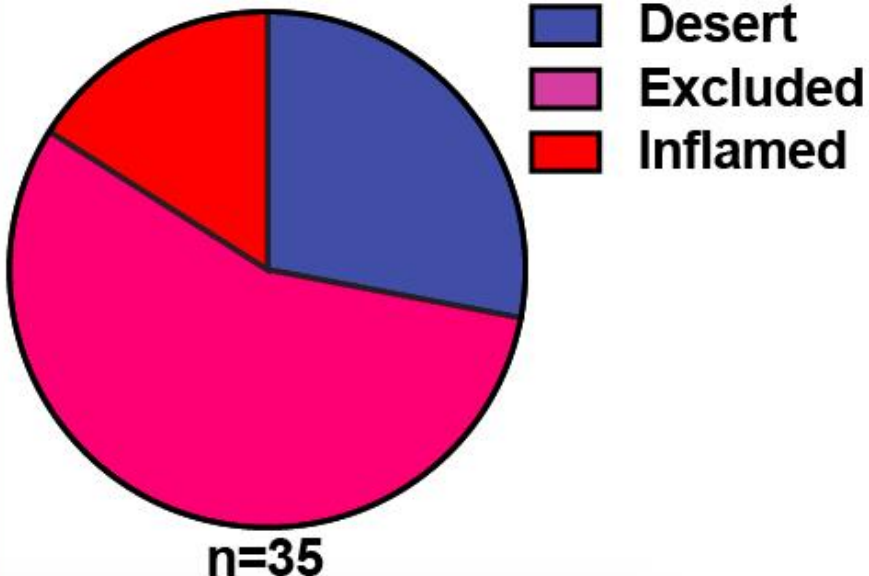




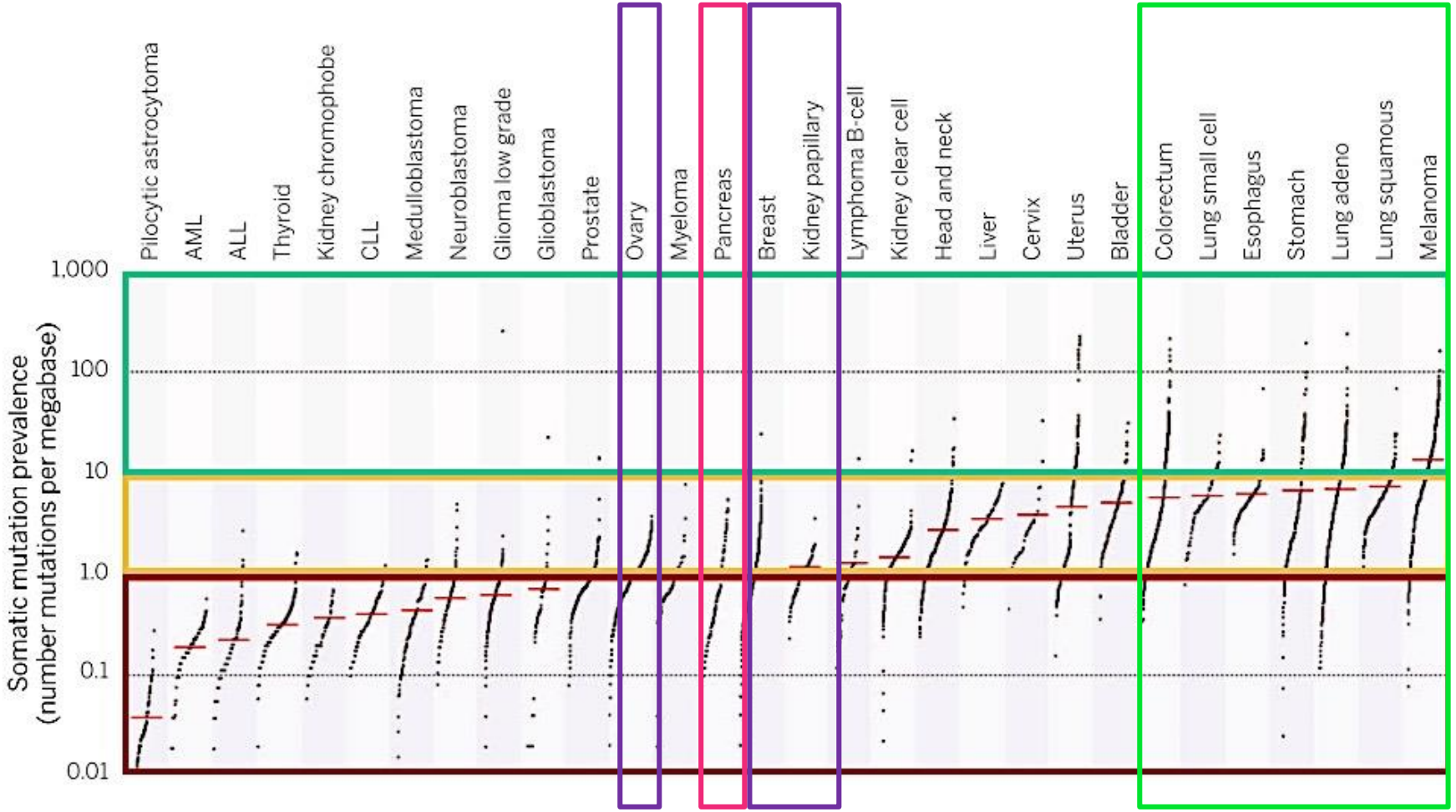




T Cell Phenotype



Pancreatic cancer is poorly responsive to T cell-directed immunotherapy for reasons not completely understood

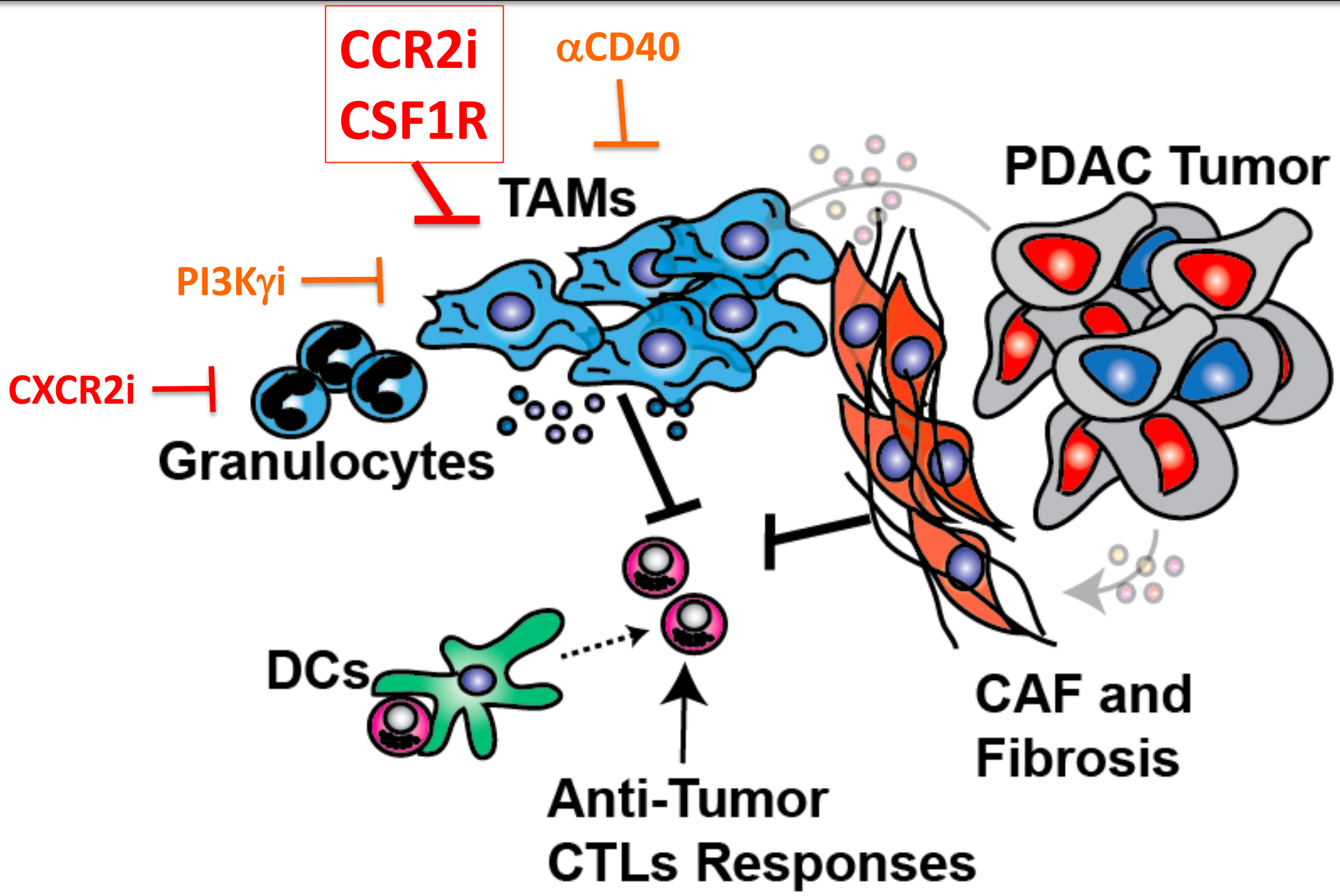


Responsive to T cell immunotherapy

Have some response to T cell immunotherapy

Schumacher, T. N., and Schreiber, R. D. Science **2015**

Targeting PDAC Microenvironment



Challenges to Current Approaches

CSF1R

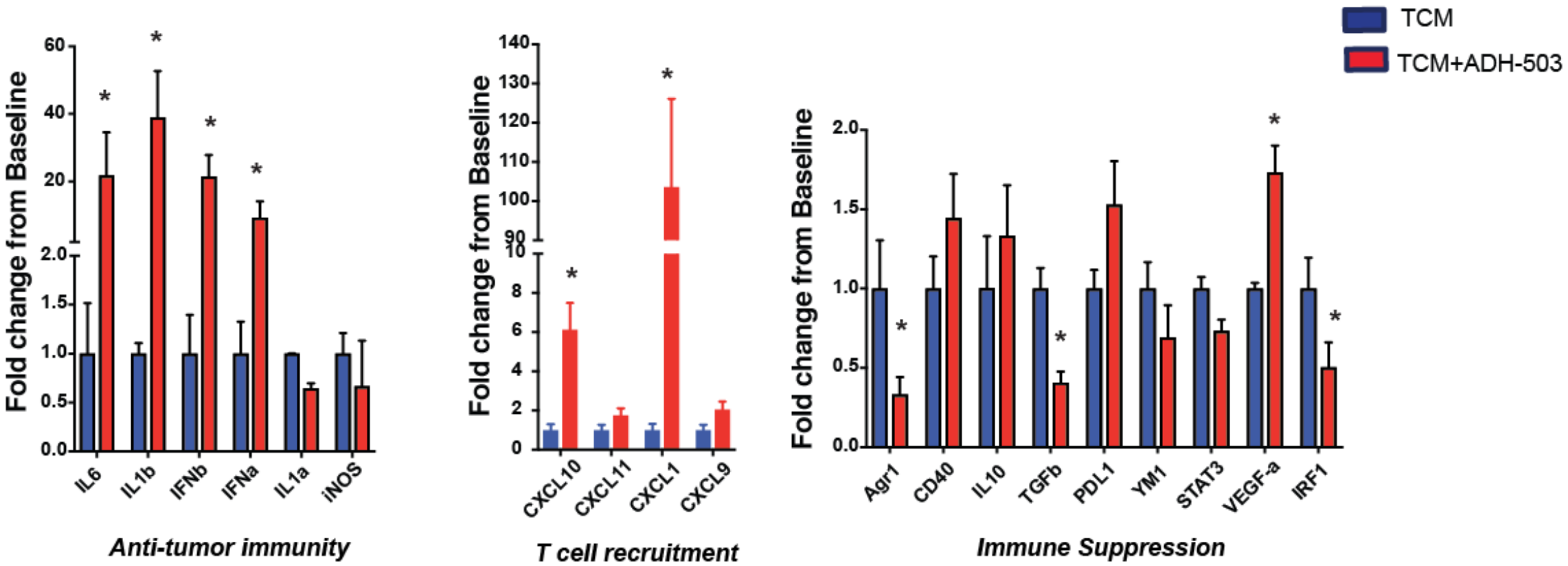
- Compensated for by granulocyte/G-MDCS expansion
- Targets macrophages in normal tissues leading to added toxicity in combination.
- Blocks maturation of macrophages

CCR2

- Compensated for by granulocyte/G-MDCS expansion
- Does not impact resident macrophages

ADH503 Disrupts Multiple Myeloid Cell Populations

C *Macrophage Gene Expression In vitro (KP2.0/B6)*



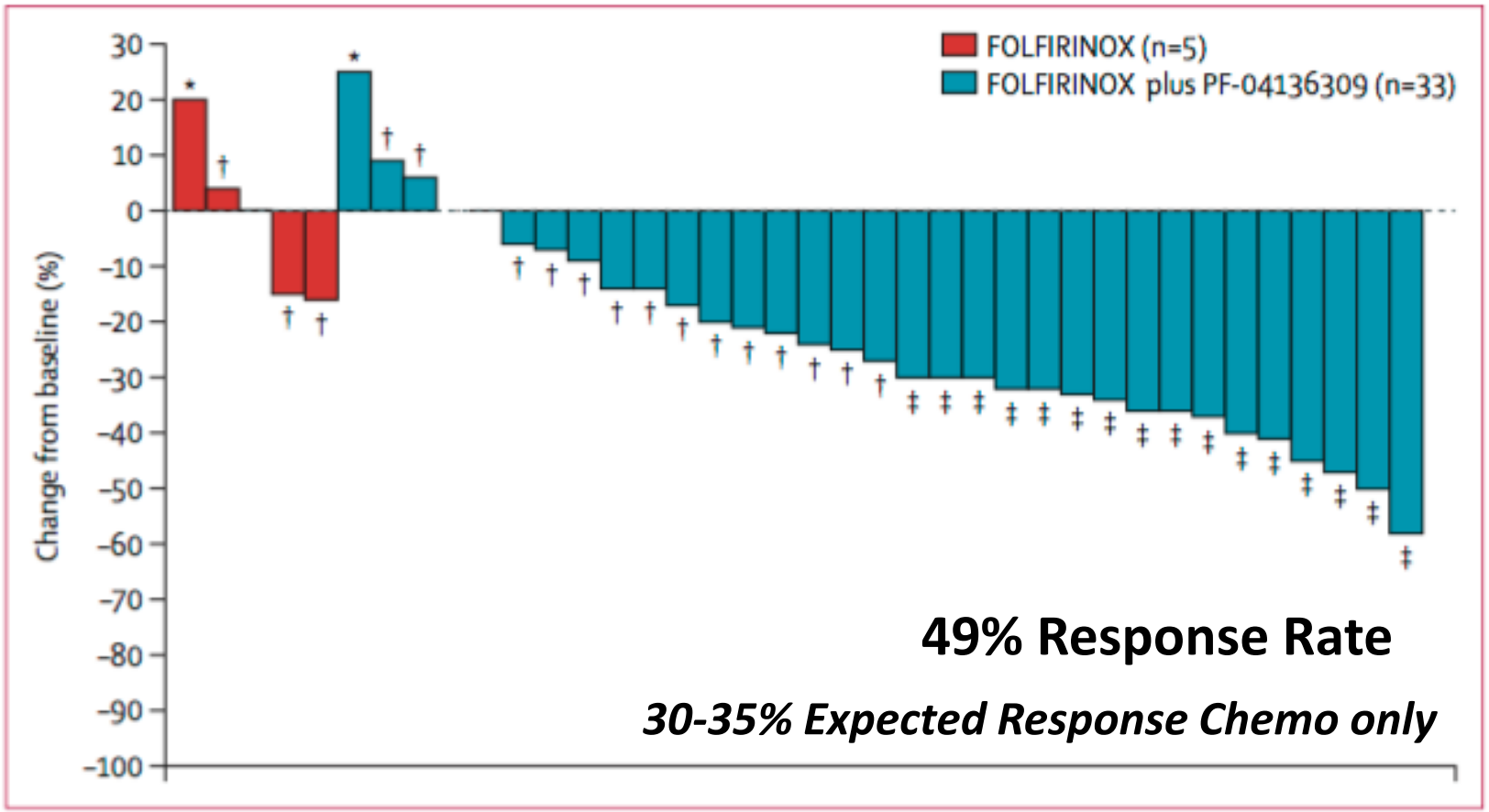
Consistent Across Three PDAC Models

CCR2 Inhibition in Combination with Chemotherapy Has Shown Some Activity in PDAC Patients

Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial

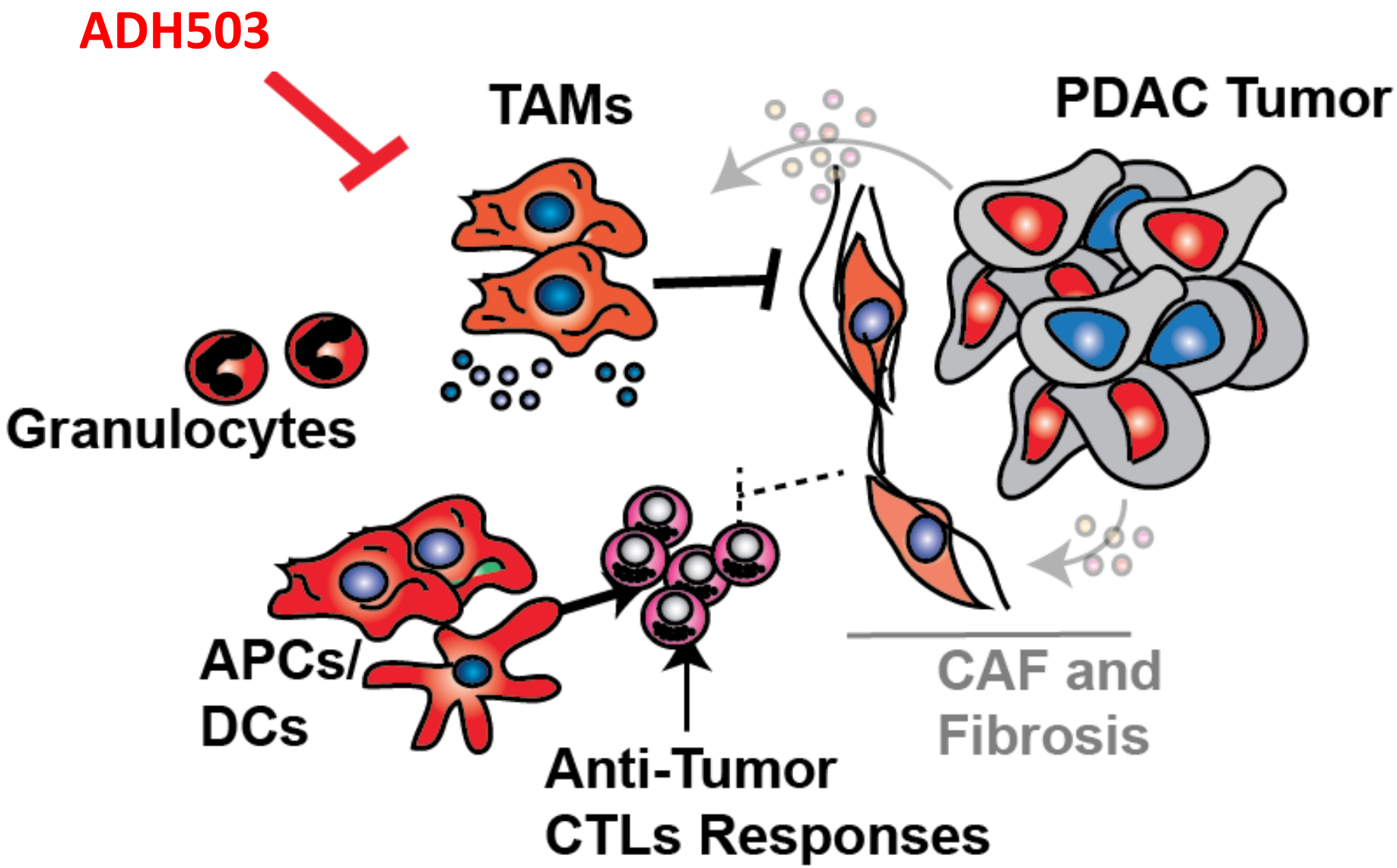
THE LANCET Oncology

Volume 17, Issue 5, May 2016, Pages 651–662

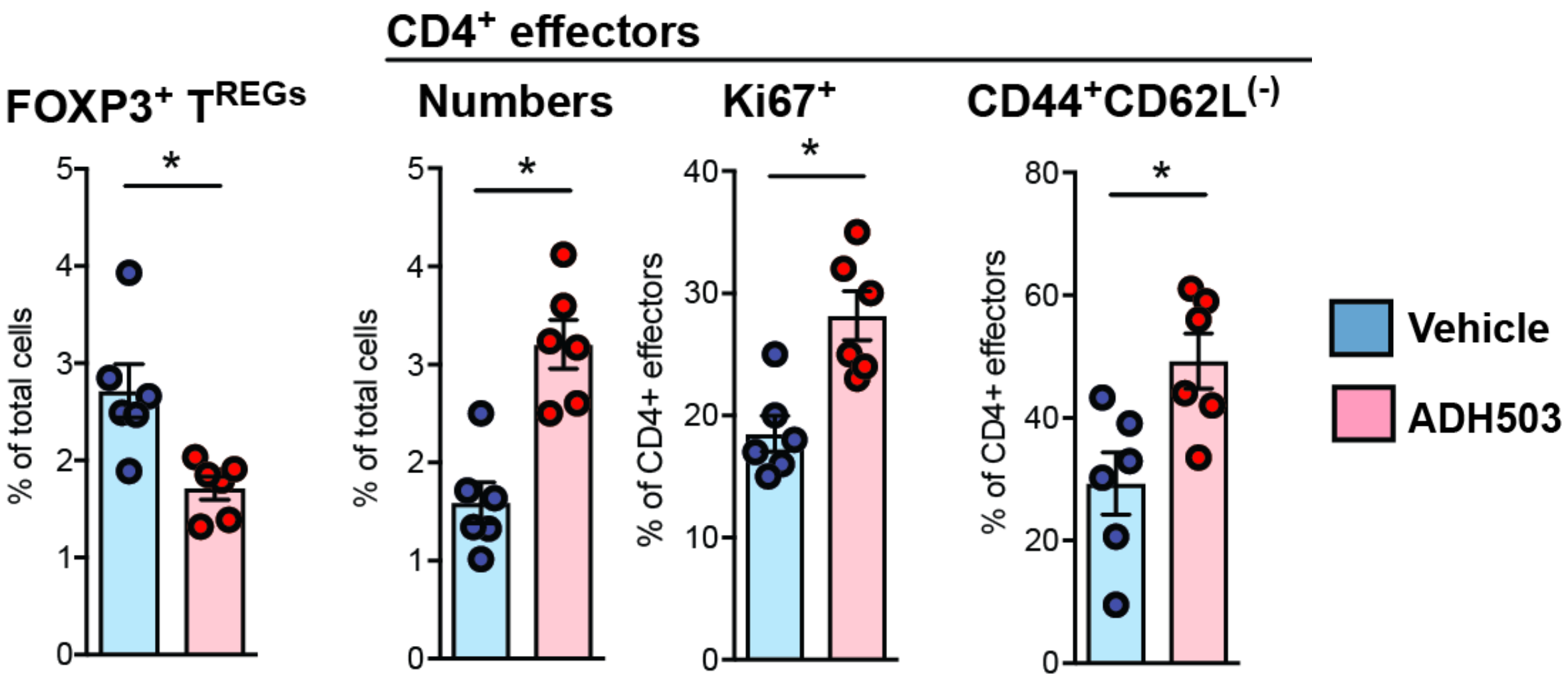


Nywening et al. Lancet Onc 2016

If we were dreaming of agents



CD11-Agonists Invigorate T cell Responses



Consistent Across Three PDAC Models

ADH503 Restrains Tumor Progression

KPC GEMM

14 days