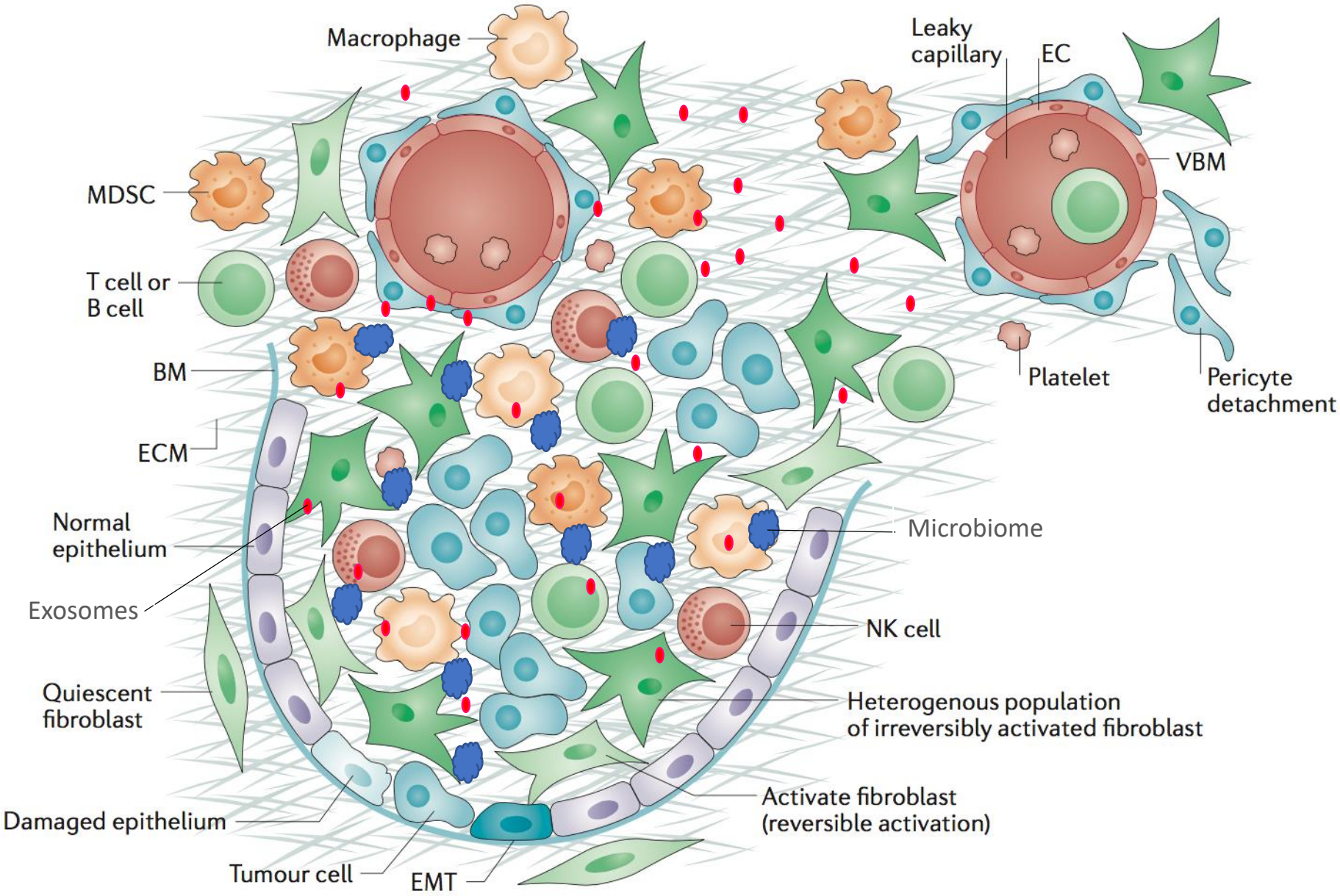
The Functional Contribution of Stromal Fibroblasts and Collagen in the Pathogenesis and Immunotherapy Response in Pancreatic Cancer

Raghu Kalluri, MD, PhD

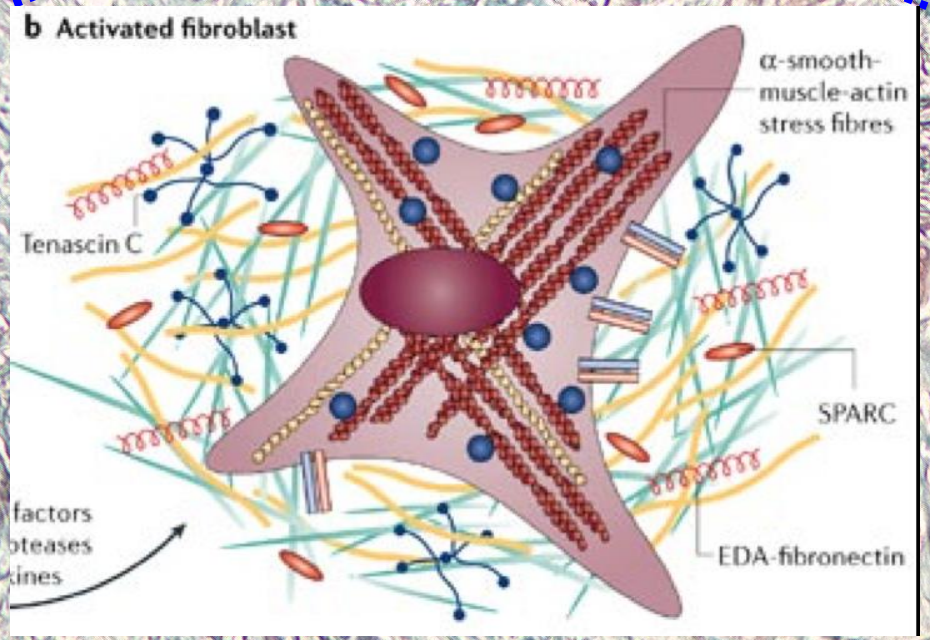
Professor and Chair
Department of Cancer Biology
Frederick F. Becker Distinguished University Chair in Cancer Research
Director, Metastasis Research Center
Director, Office of Training and Mentoring of Scientists
Director, Operations and Management, James P. Allison Institute
University of Texas MD Anderson Cancer Center
Houston

Conflict of Interest Disclosure Relevant to this Lecture: NONE

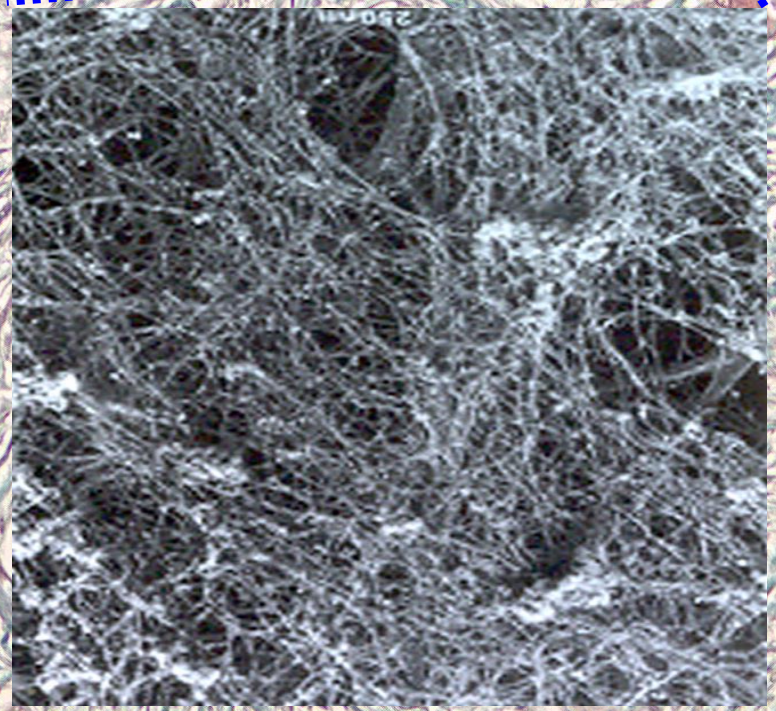
Regenerative Biology and Tumor Microenvironment



Fibroblasts and Collagen are major components of the ‘stroma’

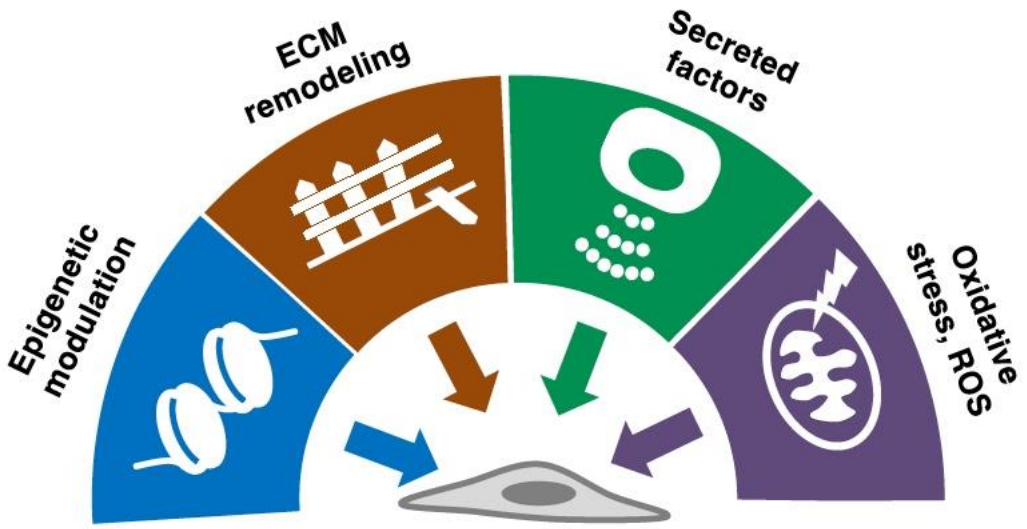


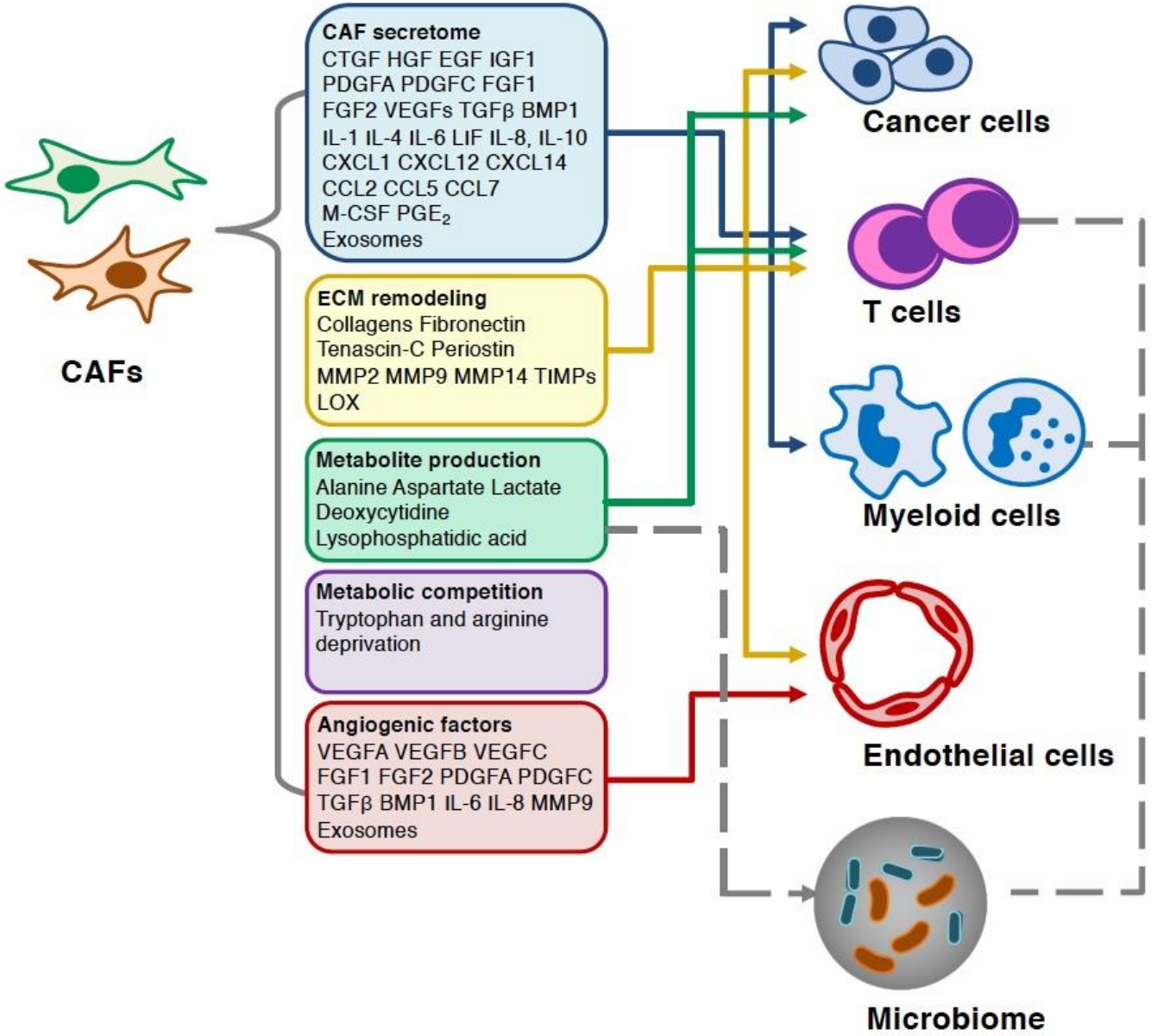
Fibroblasts



Type I collagen

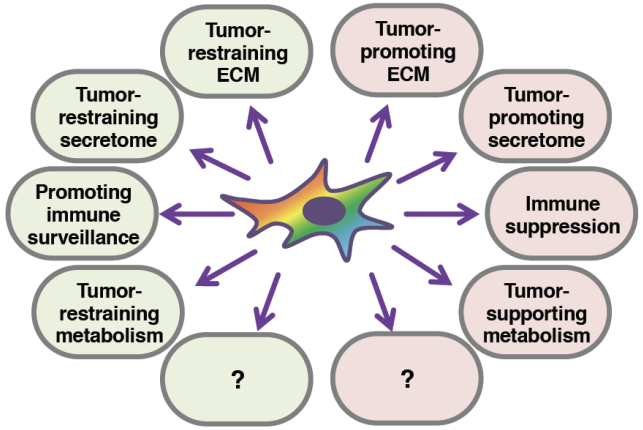
Evolving Biology of Carcinoma Associated Fibroblasts (CAFs)

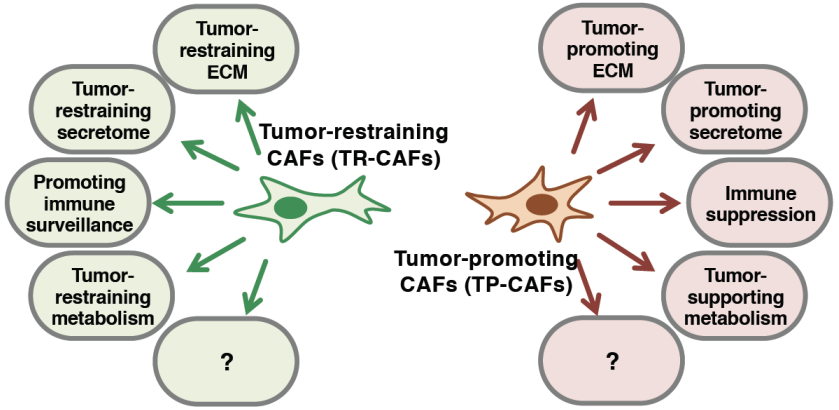


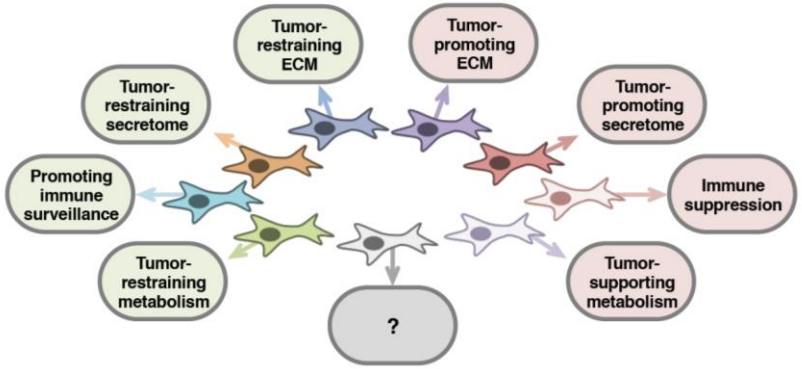


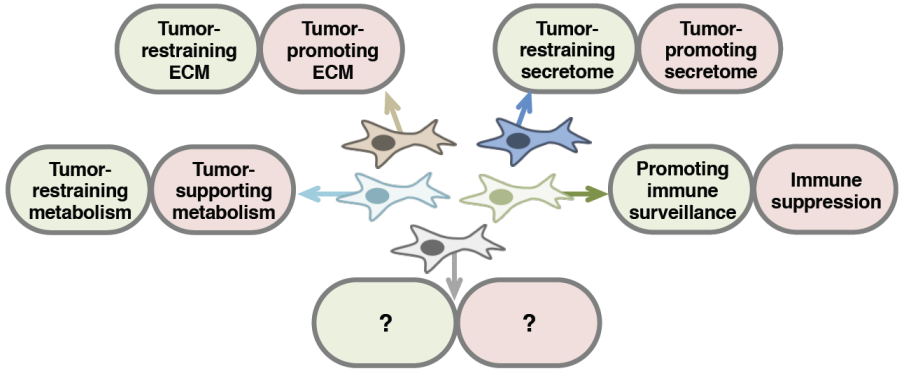
Chen, McAndrews et al Nature Reviews Clinical Oncology 2021

Fibroblasts are a heterogeneous population





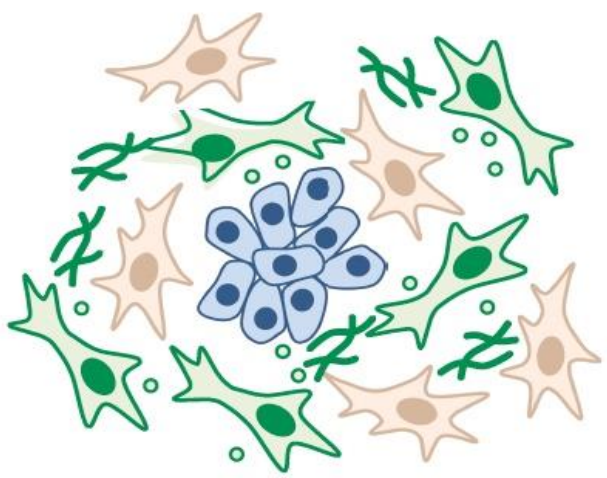




Selectively target for therapeutic benefit

Spare these CAF functions for enhanced therapy response

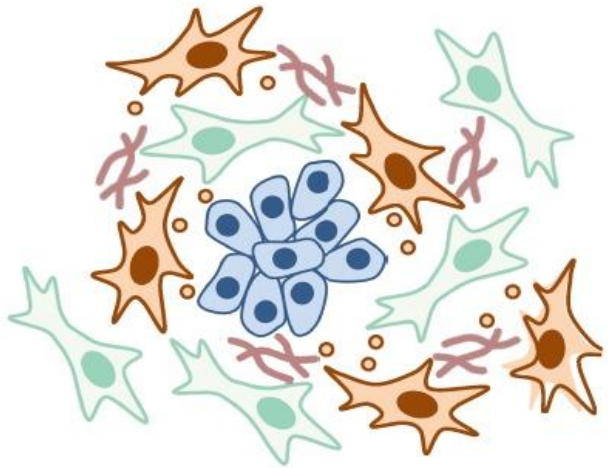
Fibroblasts are a heterogeneous population



Tumor-restraining CAFs (TR-CAFs)

- Deposition of tumor-restraining ECM
- Regulation of immune response
- Tumor-restraining metabolism
- Other tumor-restraining signals
- Hedgehog (SHH-SMO) signaling pathway

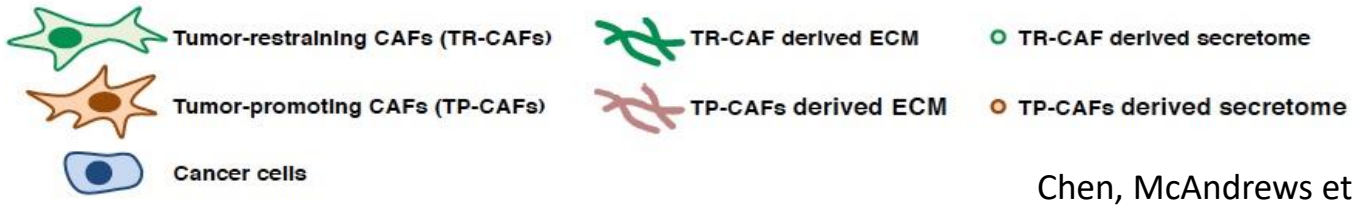
αSMA⁺ CAFs



Tumor-promoting CAFs (TP-CAFs)

- Immune suppressive secretome
- Tumor-promoting factors and exosomes
- Tumor-promoting metabolite secretion
- ECM remodeling and aberrant stroma
- Inflammation and angiogenesis

FAP⁺ CAFs



Chen, McAndrews et al Nature Reviews Clinical Oncology 2021

Cancer Cell
Article

Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with Reduced Survival

Berna C. Özdemir,[1,2] Tsvetelina Pentcheva-Hoang,[3] Julienne L. Carstens,[1] Xiaofeng Zheng,[1] Chia-Chin Wu,[4] Tyler R. Simpson,[3] Hanane Laklai,[5] Hikaru Sugimoto,[1,2] Christoph Kahlert,[1,2] Sergey V. Novitskiy,[6] Ana De Jesus-Acosta,[7] Padmanee Sharma,[3] Pedram Heidari,[8] Umar Mahmood,[8] Lynda Chin,[4] Harold L. Moses,[6] Valerie M. Weaver,[5] Anirban Maitra,[9] James P. Allison,[3] Valerie S. LeBleu,[1,2] and Raghu Kalluri[1,2,*]

CANCER DISCOVERY

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COVID-19 WEBINARS 10TH ANNIVERSARY

RESEARCH ARTICLE | MARCH 29 2022

Identification of Functional Heterogeneity of Carcinoma-Associated Fibroblasts with Distinct IL-6 Mediated Therapy Resistance in Pancreatic Cancer

Kathleen M. McAndrews ; Yang Chen ; J Kebbeh. Darpolor ; Xiaofeng Zheng; Sujuan Yang; Julienne L. Carstens ; Bingrui Li; Huamin Wang; Toru Miyake; Pedro Correa de Sampaio; Michelle L. Kirtley; Mariangela Natale ; Chia-Chin Wu ; Hikaru Sugimoto; Valerie S. LeBleu; Raghu Kalluri

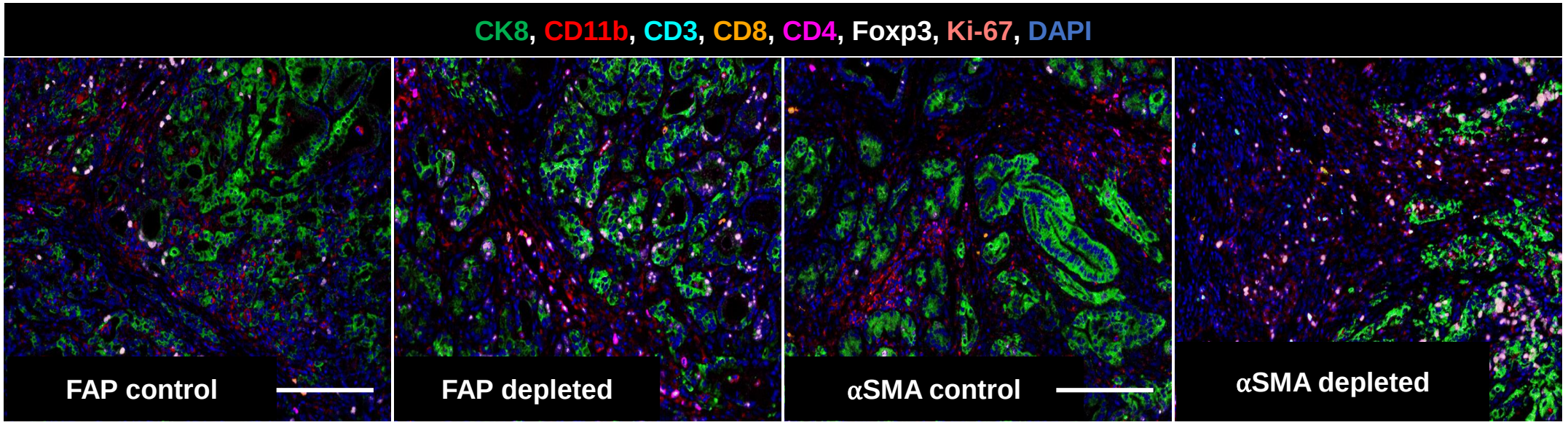
+ Author & Article Information

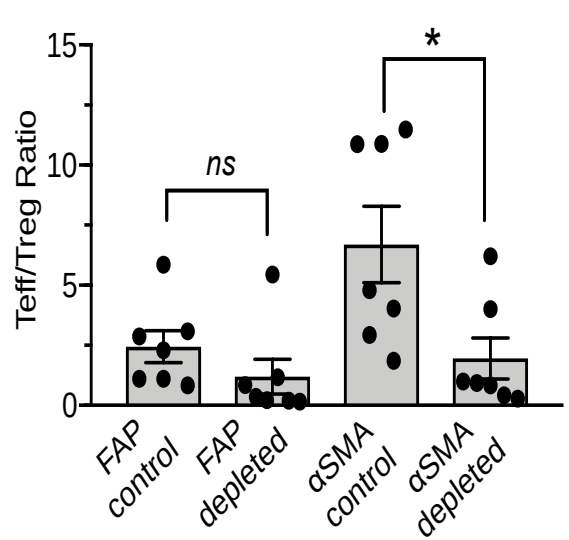
Cancer Discov candisc.1484.2020.

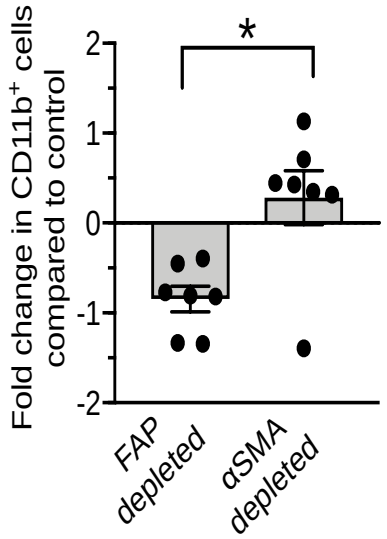
https://doi.org/10.1158/2159-8290.CD-20-1484 **Article history**

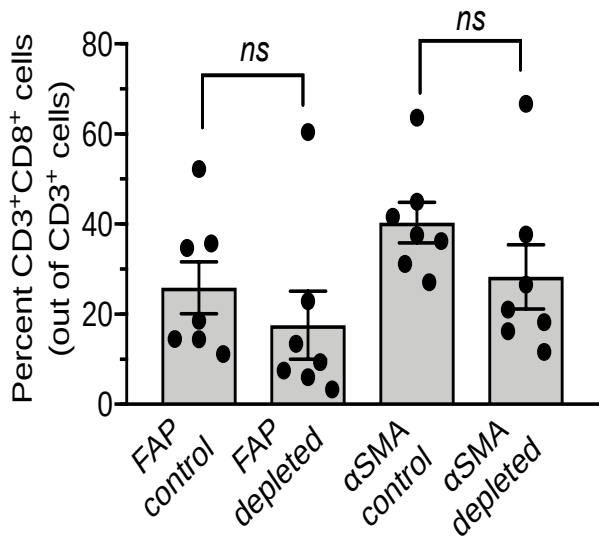
Kate McAndrews

αSMA⁺ CAFs impact Tregs and FAP⁺ CAFs impact CD11b⁺ cells in PDAC

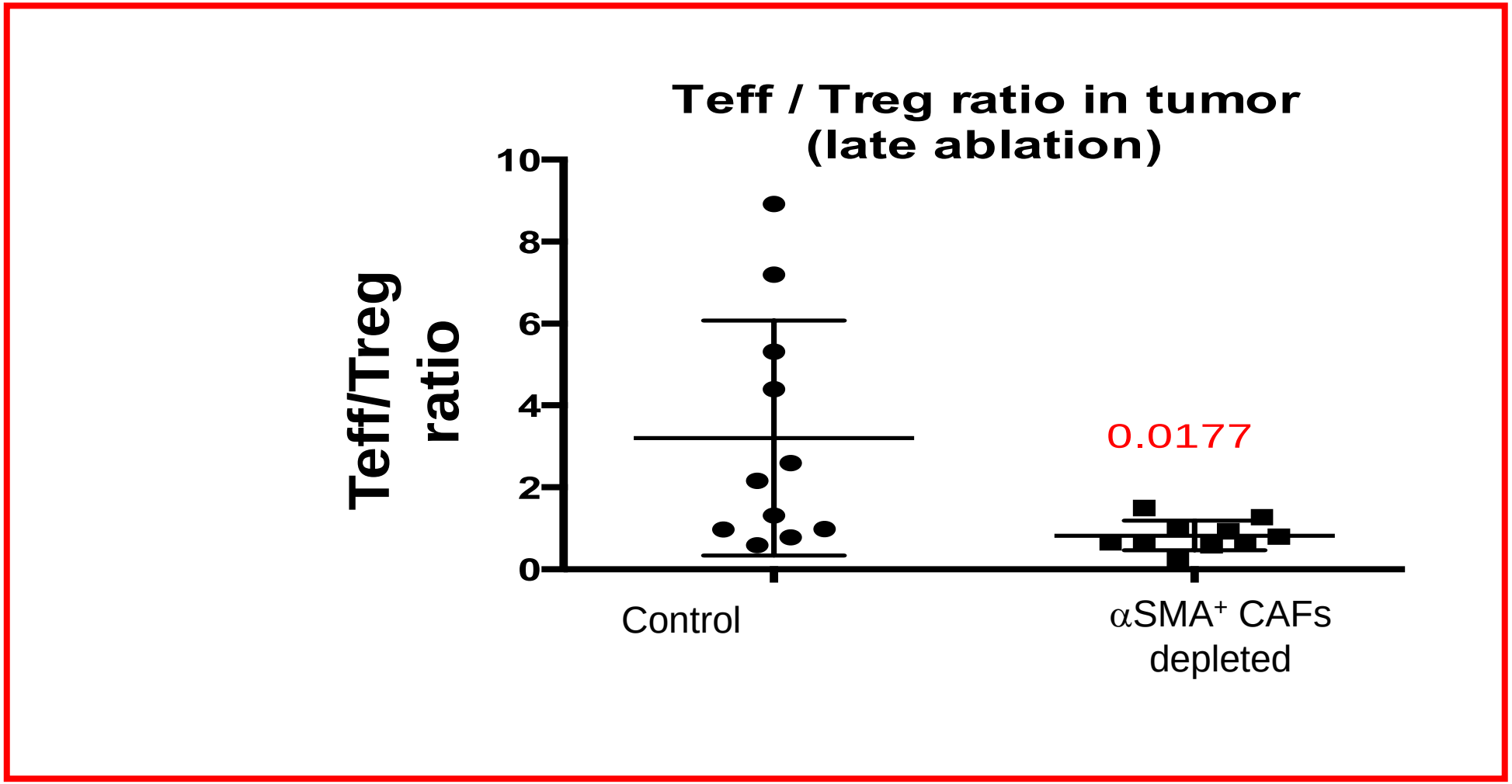






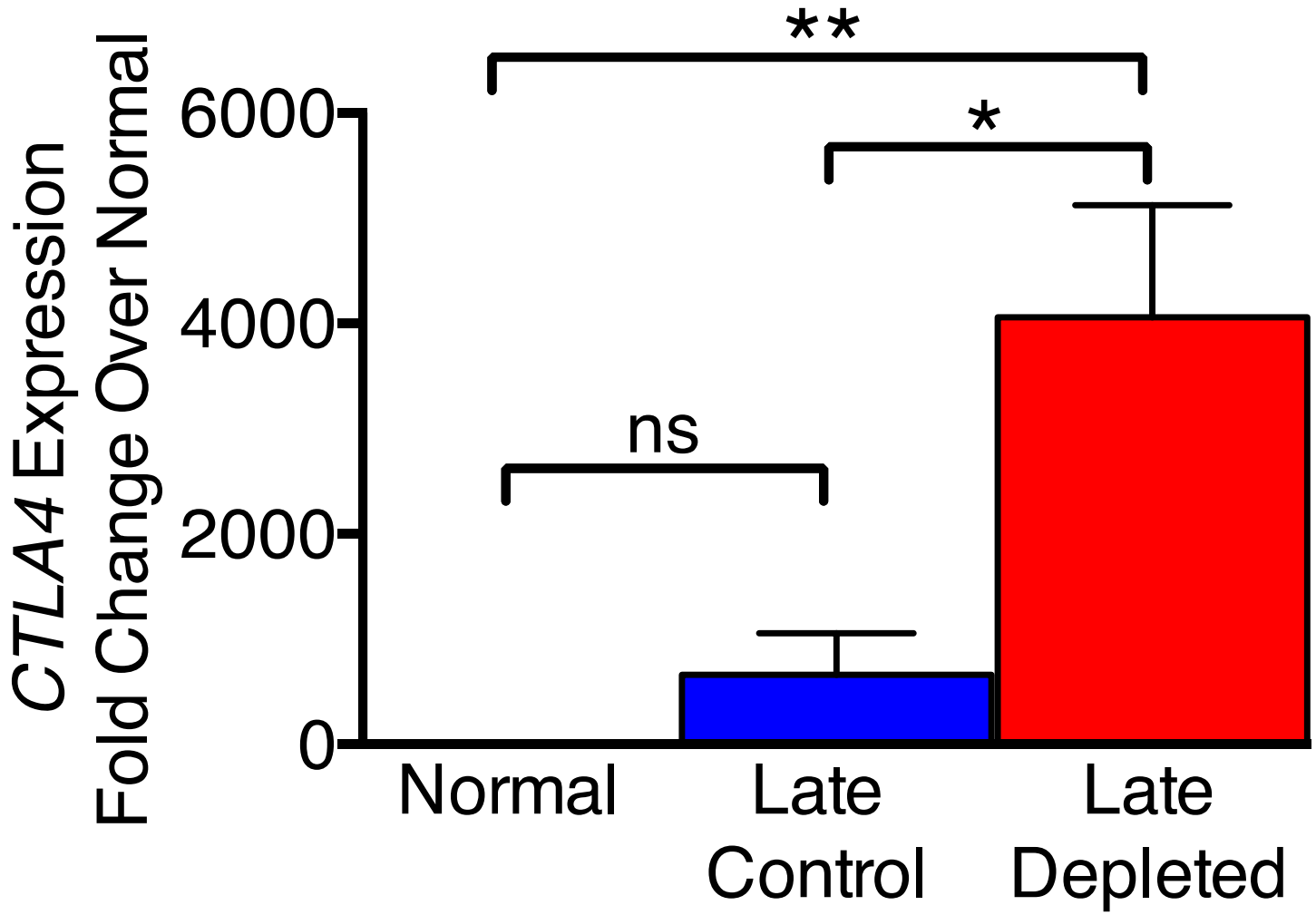


αSMA$^+$ CAF depletion results in a decrease in Teff/Treg ratio



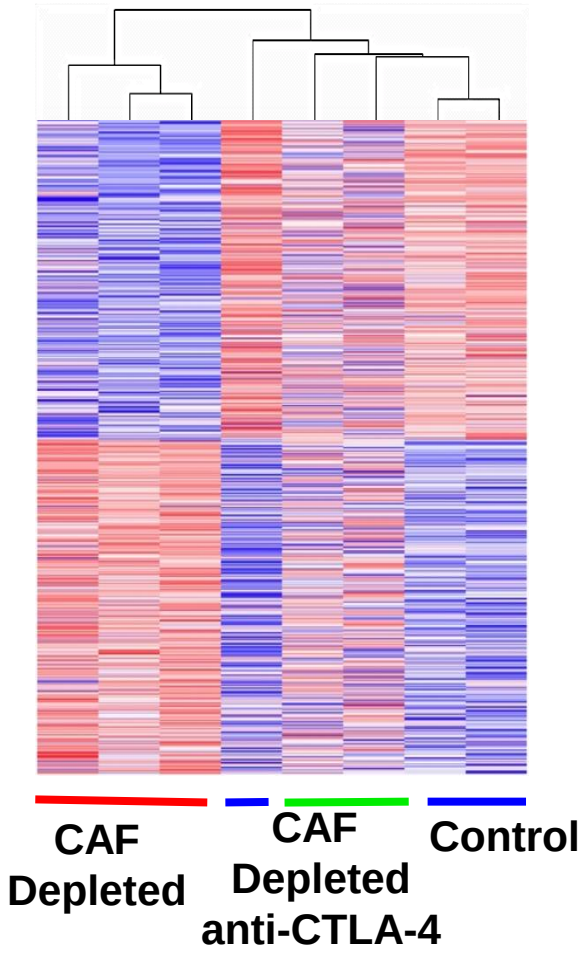
In collaboration with Jim Allison (MDACC)

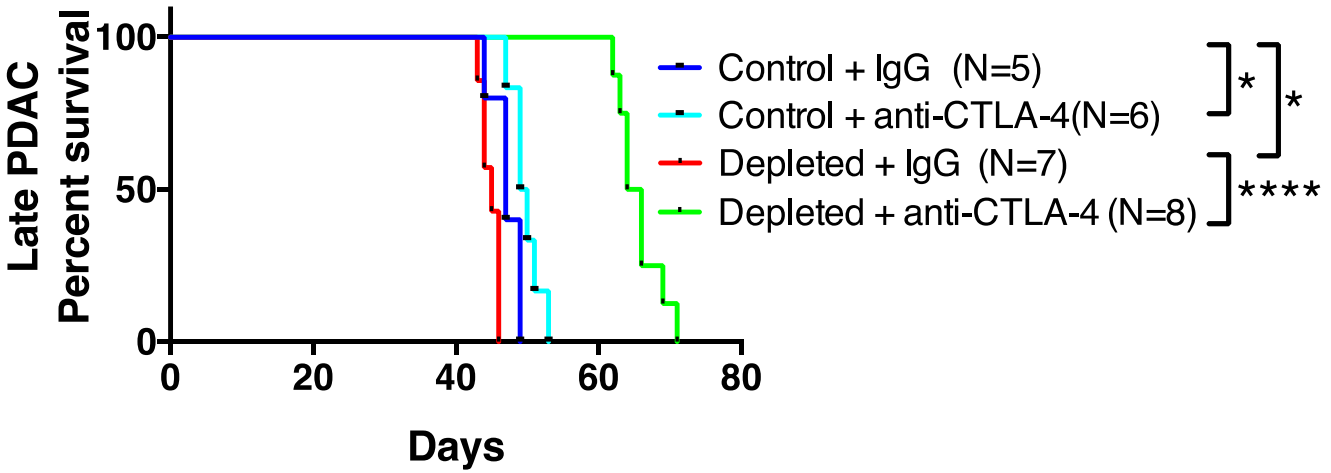
Depletion of αSMA⁺ CAFs leads to increased expression of CTLA-4

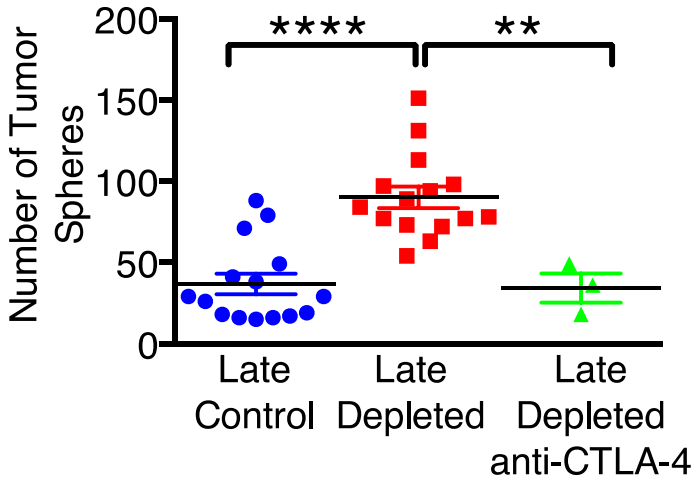


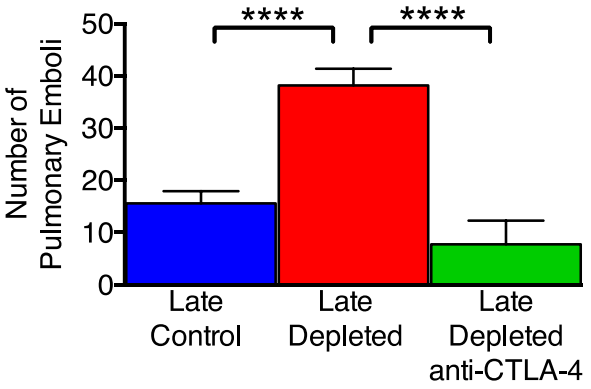
In collaboration with Jim Allison

Anti-CTLA4 immunotherapy in the context of αSMA⁺ CAFs depletion improves overall survival









Inhibition of Hedgehog Signaling (shh inhibitor) depletes αSMA+ CAFs and leads to poor survival

Inhibition of Hedgehog Signaling Enhances Delivery of Chemotherapy in a Mouse Model of Pancreatic Cancer

Kenneth P. Olive,[1] Michael A. Jacobetz,[1]* Christian J. Davidson,[2]* Aarthi Gopinathan,[1,2]* Dominick McIntyre,[1] Davina Honess,[1] Basetti Madhu,[1] Mae A. Goldgraben,[1] Meredith E. Caldwell,[1] David Allard,[1] Kristopher K. Frese,[1] Gina DeNicola,[1,2] Christine Feig,[1] Chelsea Combs,[2] Stephen P. Winter,[1] Heather Ireland-Zecchini,[1] Stefanie Reichelt,[1] William J. Howat,[1] Alex Chang,[3] Mousumi Dhara,[3] Lifu Wang,[2,4] Felix Rückert,[5] Robert Grützmann,[5] Christian Pilarsky,[5] Kamel Izeradjene,[6] Sunil R. Hingorani,[6] Pearl Huang,[7] Susan E. Davies,[8] William Plunkett,[9] Merrill Egorin,[10] Ralph H. Hruban,[3] Nigel Whitebread,[11] Karen McGovern,[11] Julian Adams,[11] Christine Iacobuzio-Donahue,[3] John Griffiths,[1] David A. Tuveson[1]†

PNAS

Stromal response to Hedgehog signaling restrains pancreatic cancer progression

John J. Lee[a,b,1], Rushika M. Perera[c,1], Huaijun Wang[d,2], Dai-Chen Wu[a,2], X. Shawn Liu[a,2], Shiwei Han[e], Julien Fitamant[c], Phillip D. Jones[a], Krishna S. Ghanta[c], Sally Kawano[a], Julia M. Nagle[c], Vikram Deshpande[c], Yves Boucher[e], Tomoyo Kato[f], James K. Chen[f], Jürgen K. Willmann[d], Nabeel Bardeesy[c,3], and Philip A. Beachy[a,g,h,3]

[a]Institute for Stem Cell Biology and Regenerative Medicine, [b]Division of Oncology, Department of Medicine, [g]Department of Biochemistry, [f]Department o Chemical and Systems Biology, and [d]Molecular Imaging Program, Department of Radiology, Stanford University School of Medicine, Stanford, CA 94305; [c]Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114; [e]Edwin L. Steele Laboratory, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114; and [h]Howard Hughes Medical Institute, Stanford, CA 94305

Cancer Cell
Article

Stromal Elements Act to Restrain, Rather Than Support, Pancreatic Ductal Adenocarcinoma

Andrew D. Rhim,[1,2,8] Paul E. Oberstein,[3,8] Dafydd H. Thomas,[4,5,8] Emily T. Mirek,[2] Carmine F. Palermo,[4,5] Stephen A. Sastra,[4,5] Erin N. Dekleva,[2] Tyler Saunders,[6] Claudia P. Becerra,[5] Ian W. Tattersall,[5] C. Benedikt Westphalen,[4] Jan Kitajewski,[5] Maite G. Fernandez-Barrena,[7] Martin E. Fernandez-Zapico,[7] Christine Iacobuzio-Donahue,[6] Kenneth P. Olive,[4,5,*] and Ben Z. Stanger[2,*]

CellPress

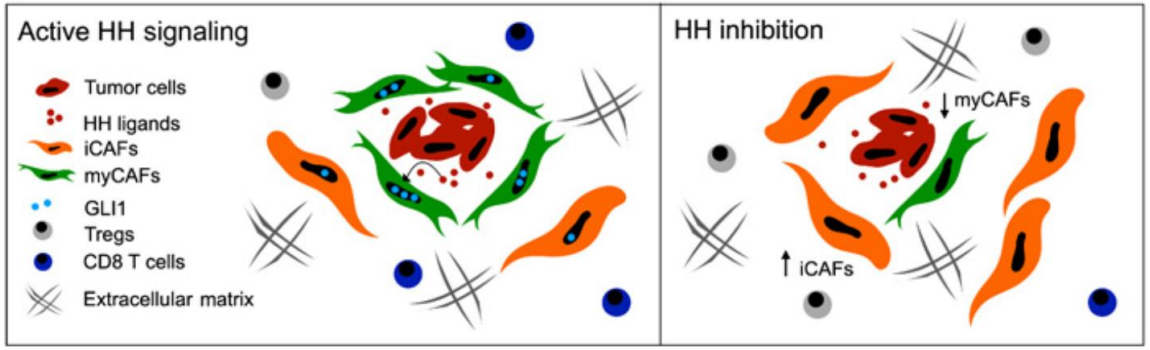
ARTICLE
Clinical Study

Phase 2 study of vismodegib, a hedgehog inhibitor, combined with gemcitabine and nab-paclitaxel in patients with untreated metastatic pancreatic adenocarcinoma

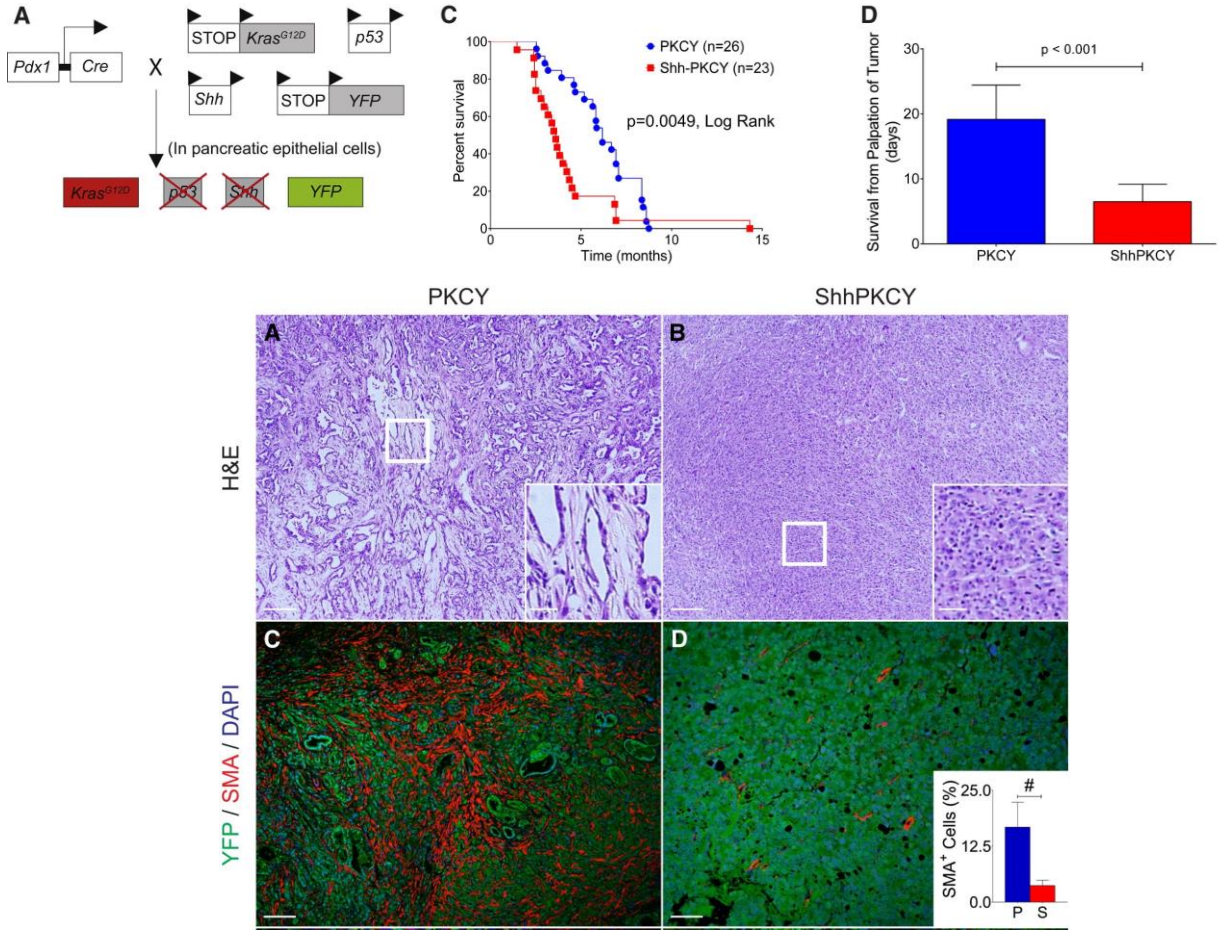
Ana De Jesus-Acosta[1], Elizabeth A. Sugar[2], Peter J. O'Dwyer[3], Ramesh K. Ramanathan[4], Daniel D. Von Hoff[4], Zeshaan Rasheed[1], Lei Zheng[1], Asma Begum[5], Robert Anders[6], Anirban Maitra[7], Florencia McAllister[8], N. V. Rajeshkumar[5], Shinichi Yabuuchi[9], Roeland F. de Wilde[6], Bhavina Batukbhai[1], Ismet Sahin[10] and Daniel A. Laheru[1]

CONCLUSIONS: Adding vismodegib to chemotherapy did not improve efficacy as compared with historical rates observed with chemotherapy alone in patients with newly diagnosed metastatic pancreatic cancer. This study does not support the further evaluation of Hh inhibitors in this patient population.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01088815.

Inhibition of Hedgehog Signaling (shh inhibitor) depletes αSMA$^+$ CAFs

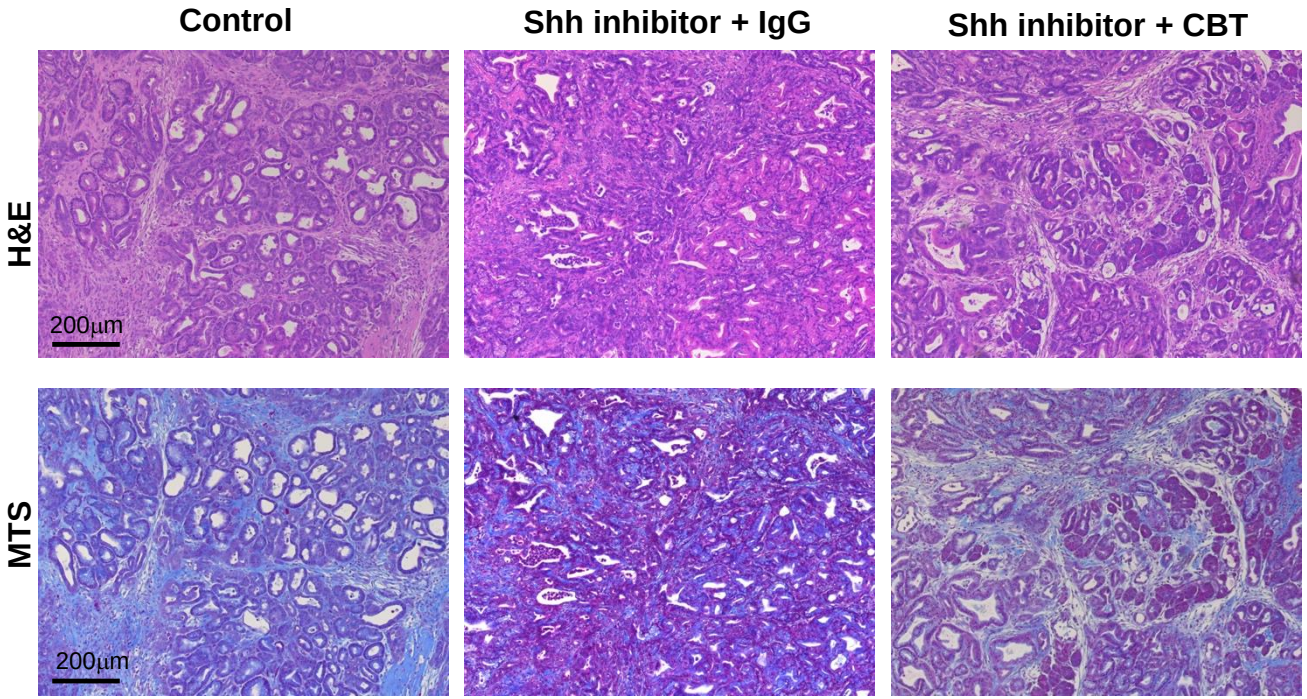


Steele, N.G., et al. *Clinical Cancer Research* 2021. 27(7):2023-2037.



Rhim, A.D., et al. *Cancer Cell* 2014. 25(6):735-747

Inhibition of Hedgehog Signaling (shh inhibitor) in combination with checkpoint blockade immunotherapy leads to suppression of PDAC



Inhibition of Hedgehog Signaling (shh inhibitor) in combination with checkpoint blockade immunotherapy in PDAC

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site | PRS Login

Home > Search Results > Study Record Detail

Save this study

Study to Evaluate the Safety and Efficacy of Treatment With NLM-001 and Standard Chemotherapy Plus Zalifrelimab in Patients With Advanced Pancreatic Cancer (NUMANTIA)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

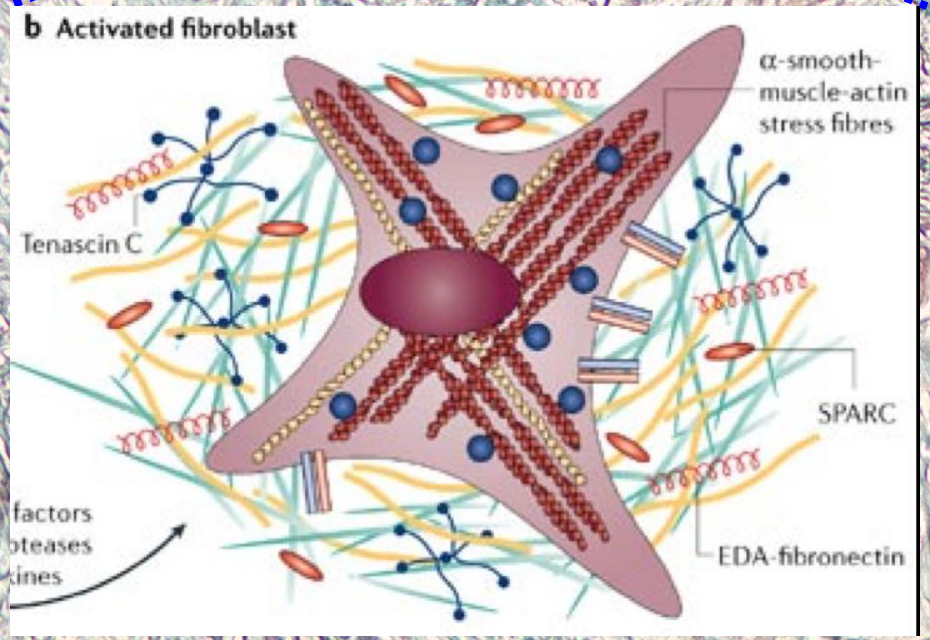
ClinicalTrials.gov Identifier: NCT04827953

Recruitment Status : Recruiting
First Posted : April 1, 2021
Last Update Posted : February 28, 2022

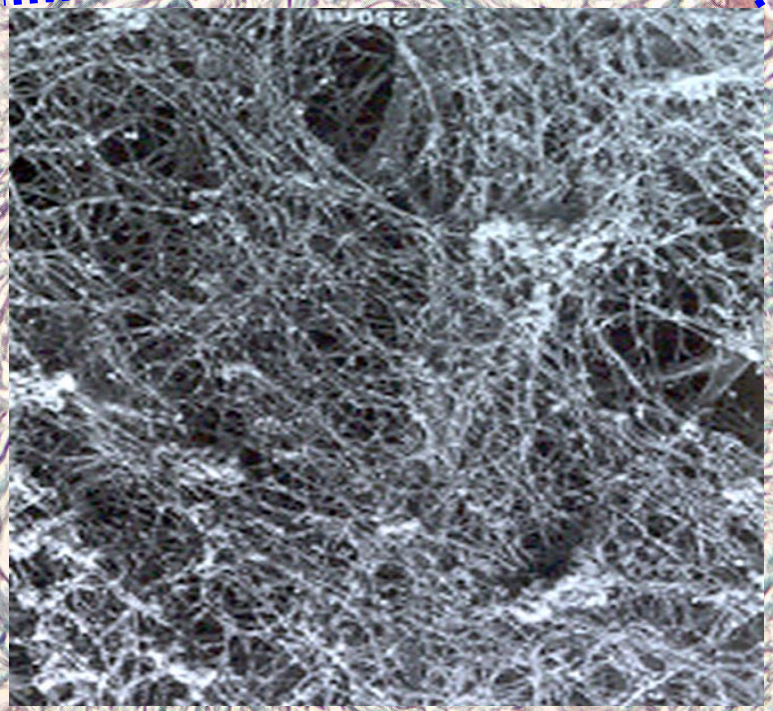
See Contacts and Locations

Manuel Hidalgo, M.D., Ph.D-Cornell

Fibroblasts and Collagen are major components of the ‘stroma’



Fibroblasts



Type I collagen

Type I Collagen (Col1)

- Collagens (27) are present outside the cell and form large network structures and examples include collagen I, collagen II, collagen III and collagen IV

- Collagen I is the MOST abundant protein of our body

- Collagen I is present in bones, cartilage, skin, etc

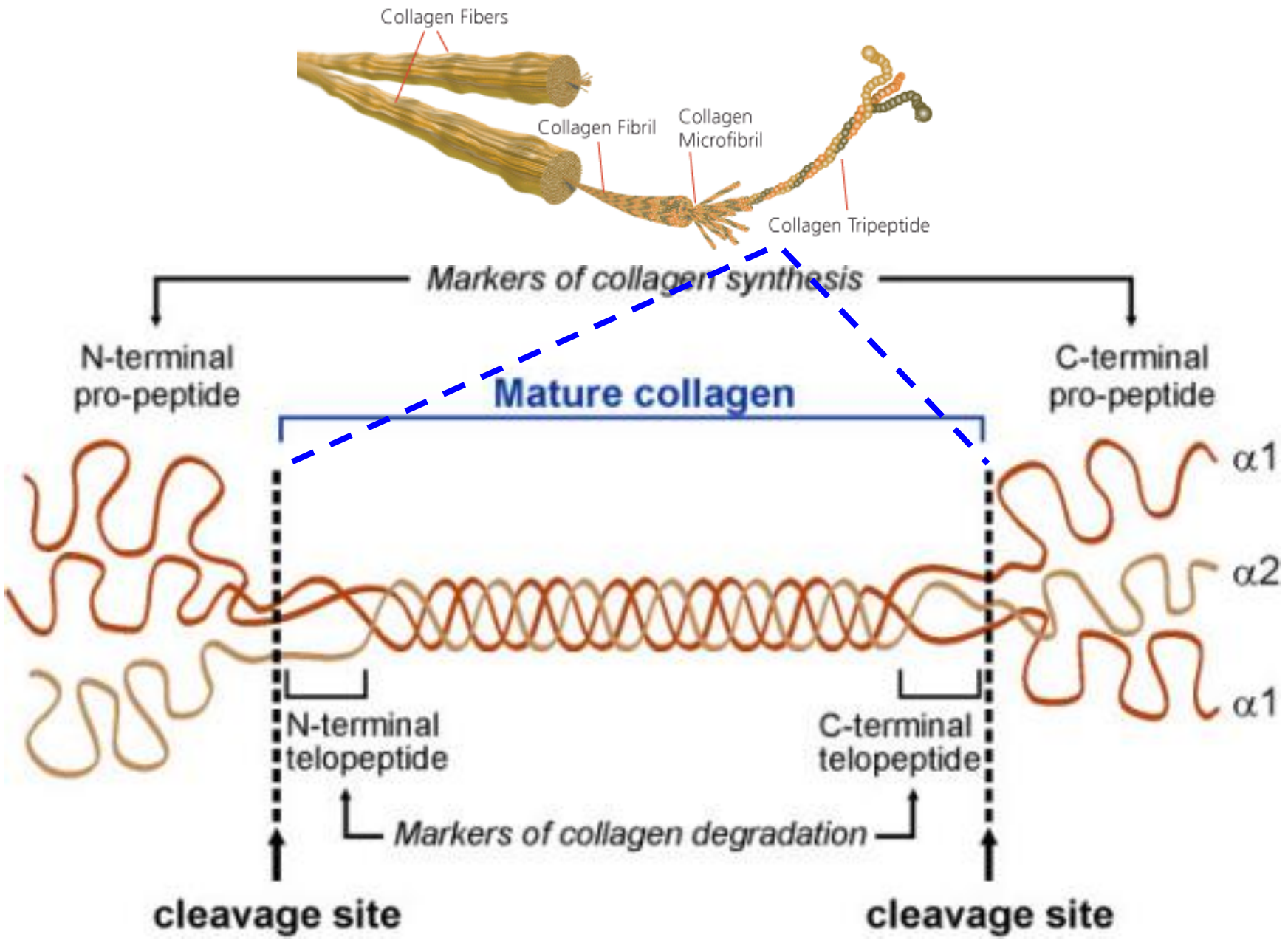
- Form complex fibers in the body via post-translational modification and assembly

- Produced predominantly by fibroblasts

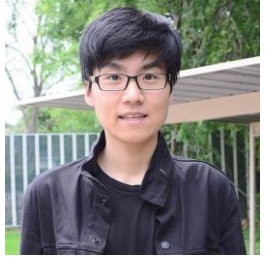
- Thousands of papers have implicated a role for type I collagen in cancer progression and metastasis

- Molecular and functional studies to determine the role of type I collagen in became the focus of a project in the laboratory

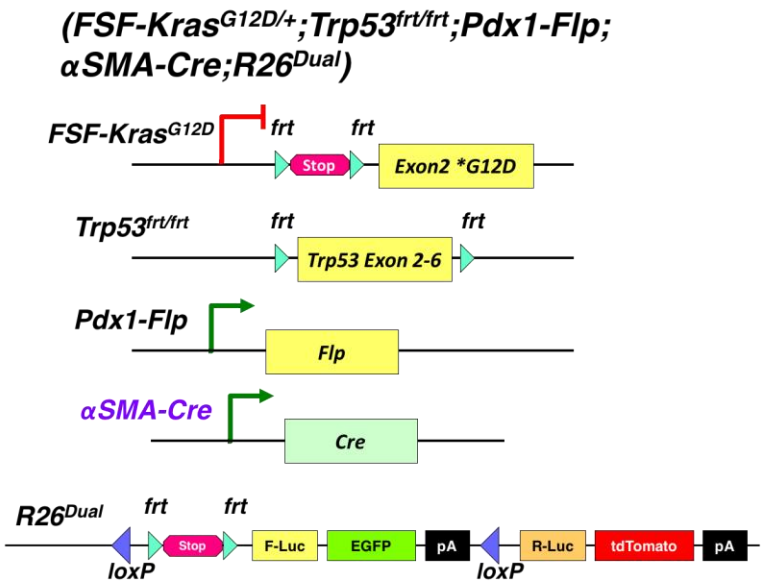
Structure of Type I Collagen

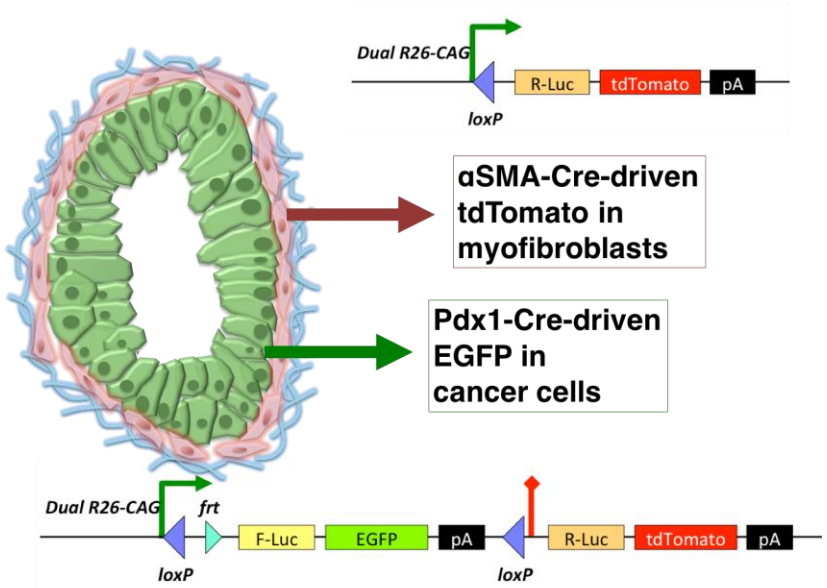


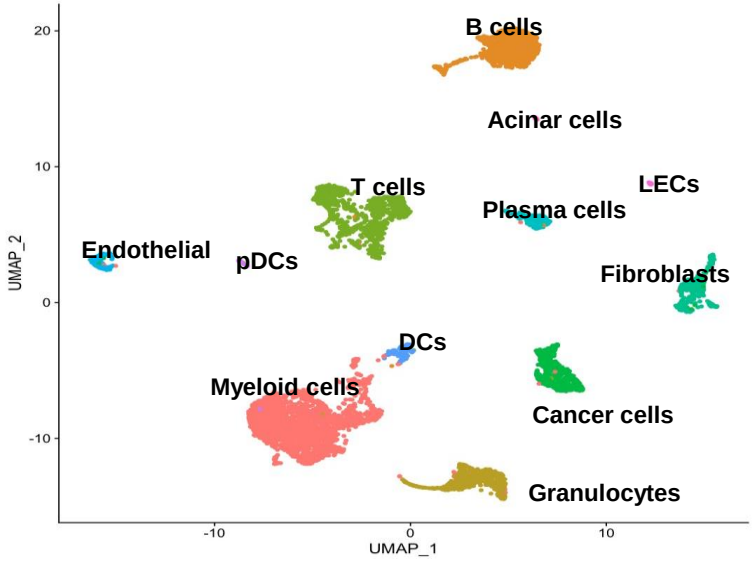
Dual recombinase reporter system for genetic deletion/s in stromal cells

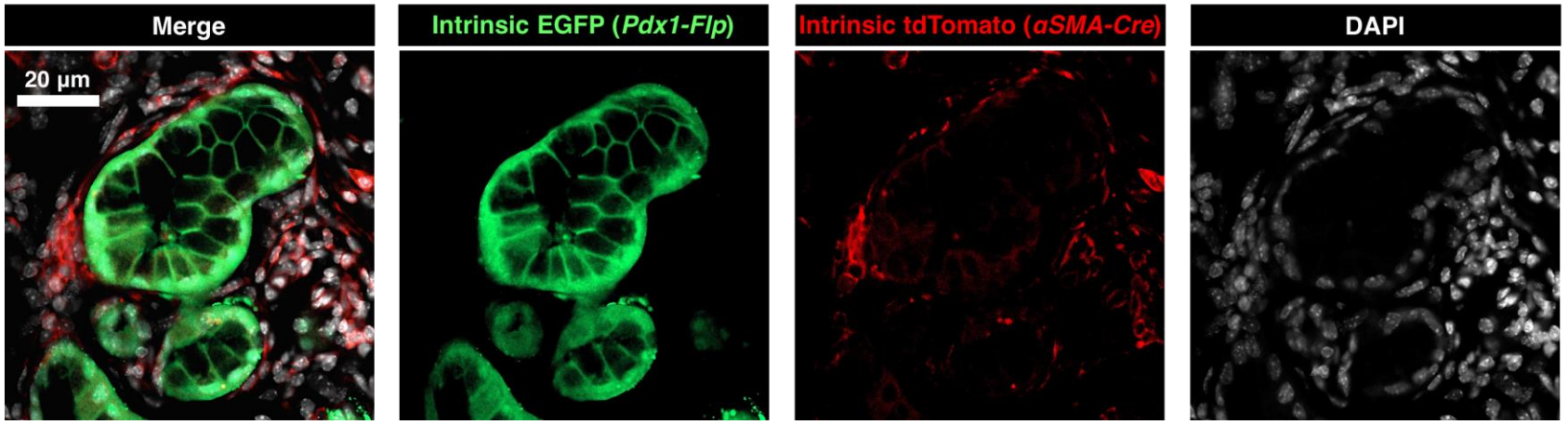


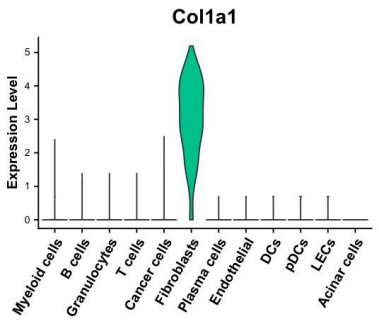
Yang Chen

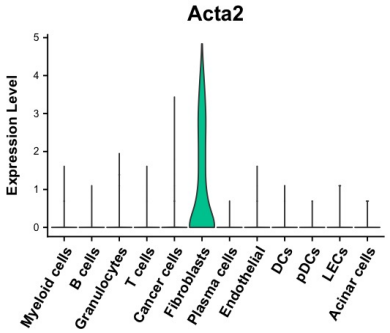




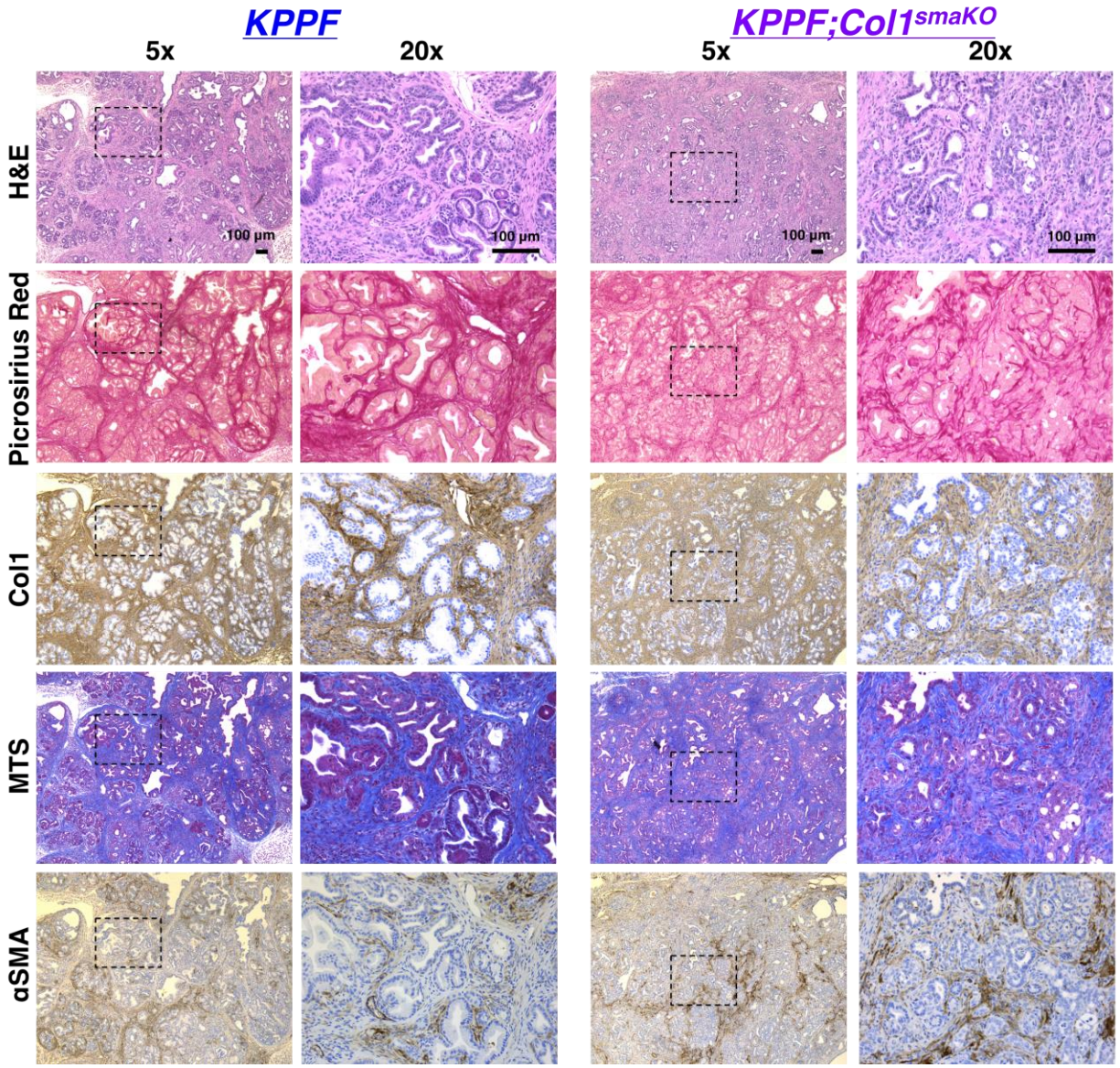


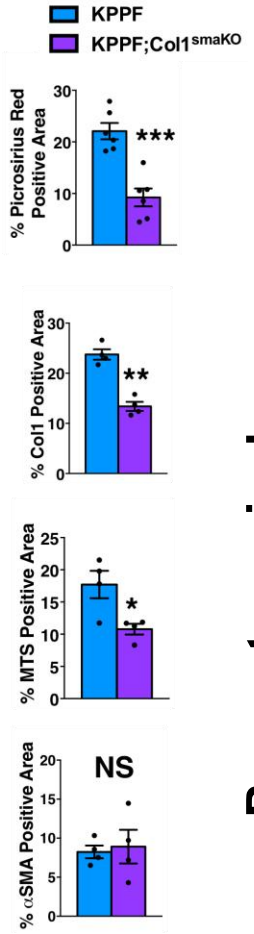


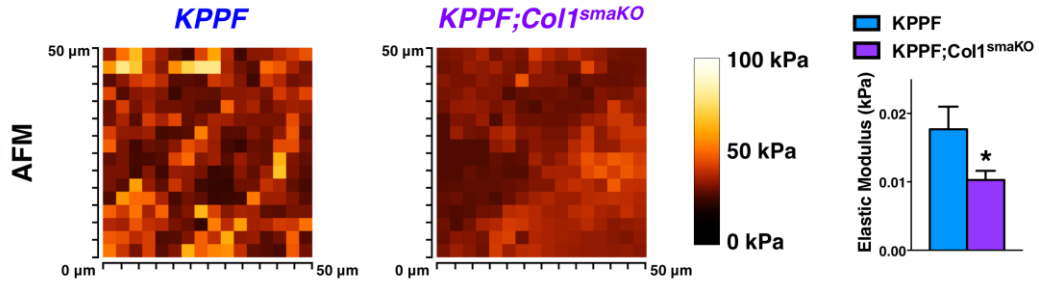


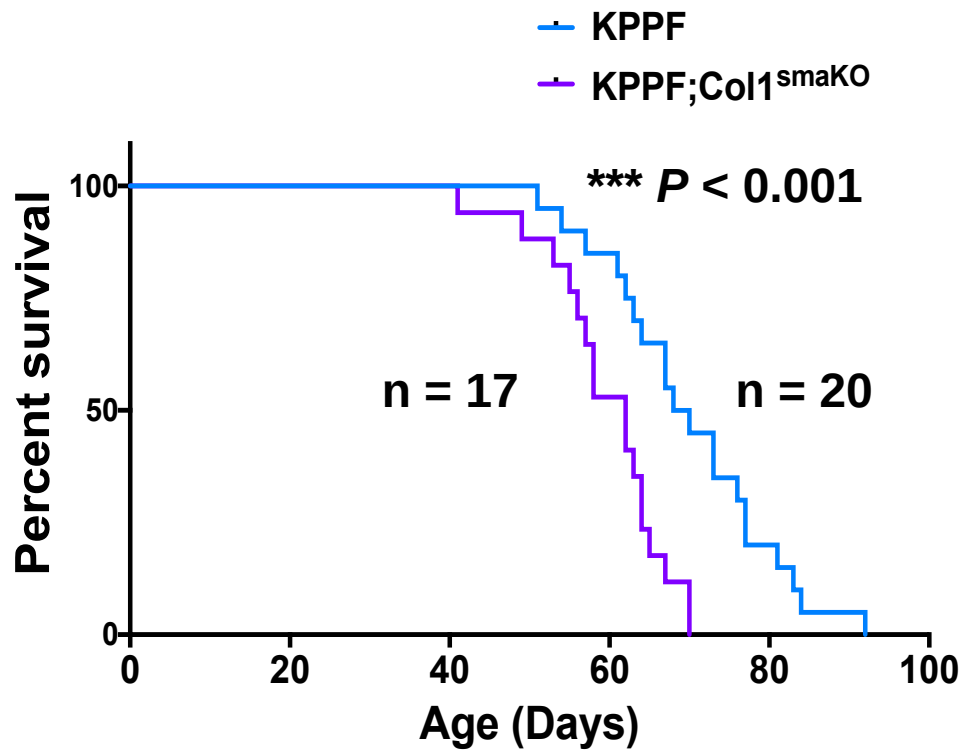


Deletion of Col1 in myofibroblasts leads to decrease in overall tumor type I collagen accelerates PDAC with decreased overall survival

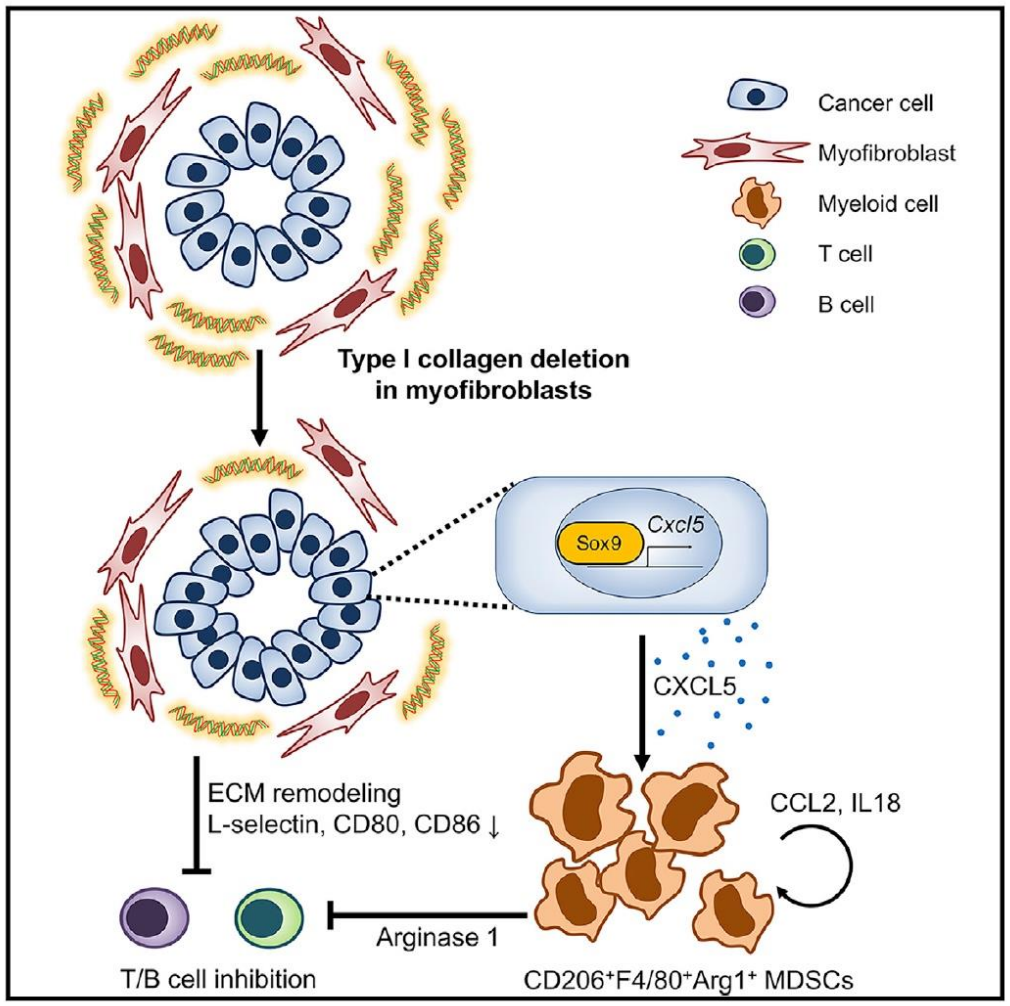


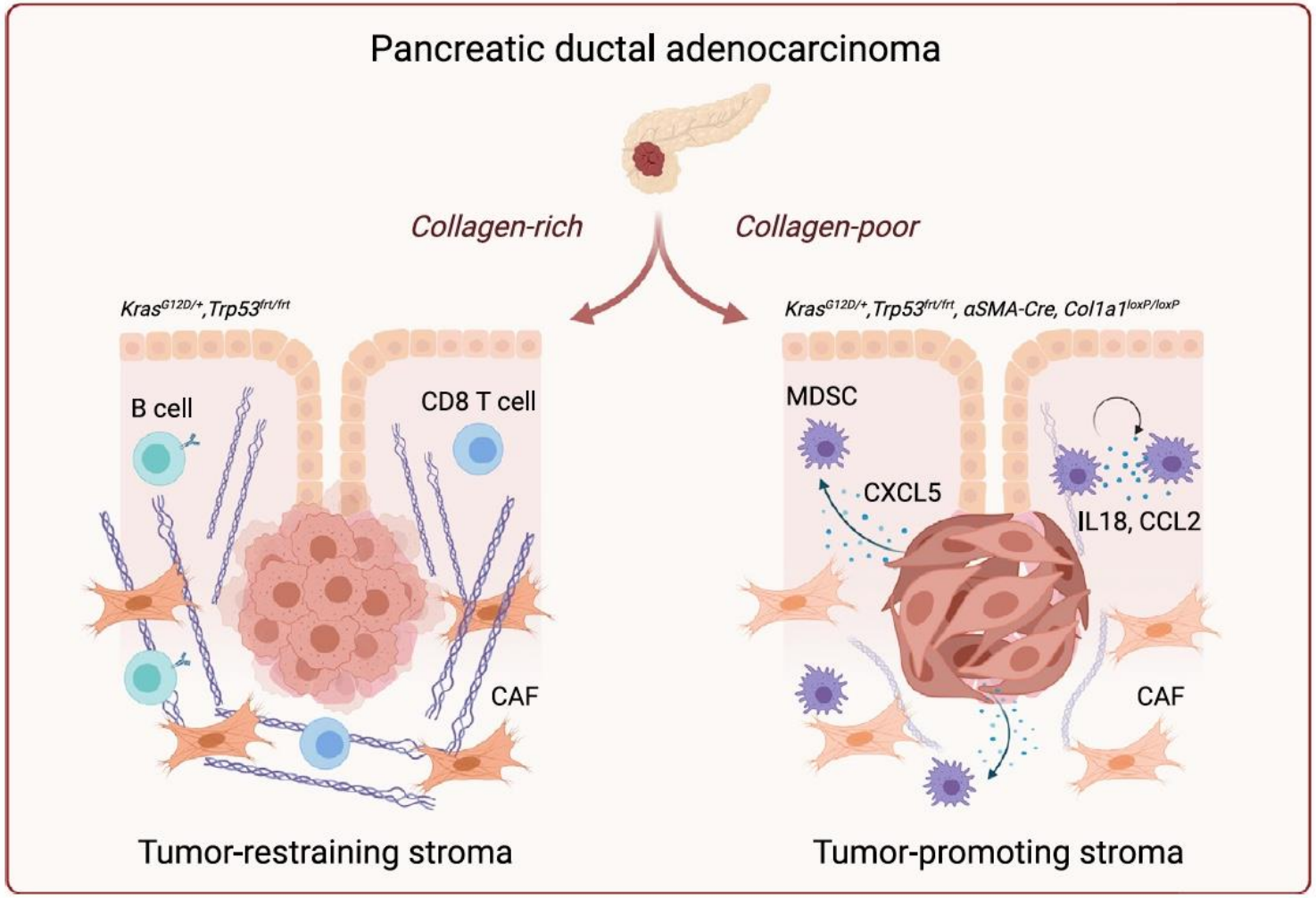






Col1 deletion from αSMA⁺ CAFs impacts immune cells

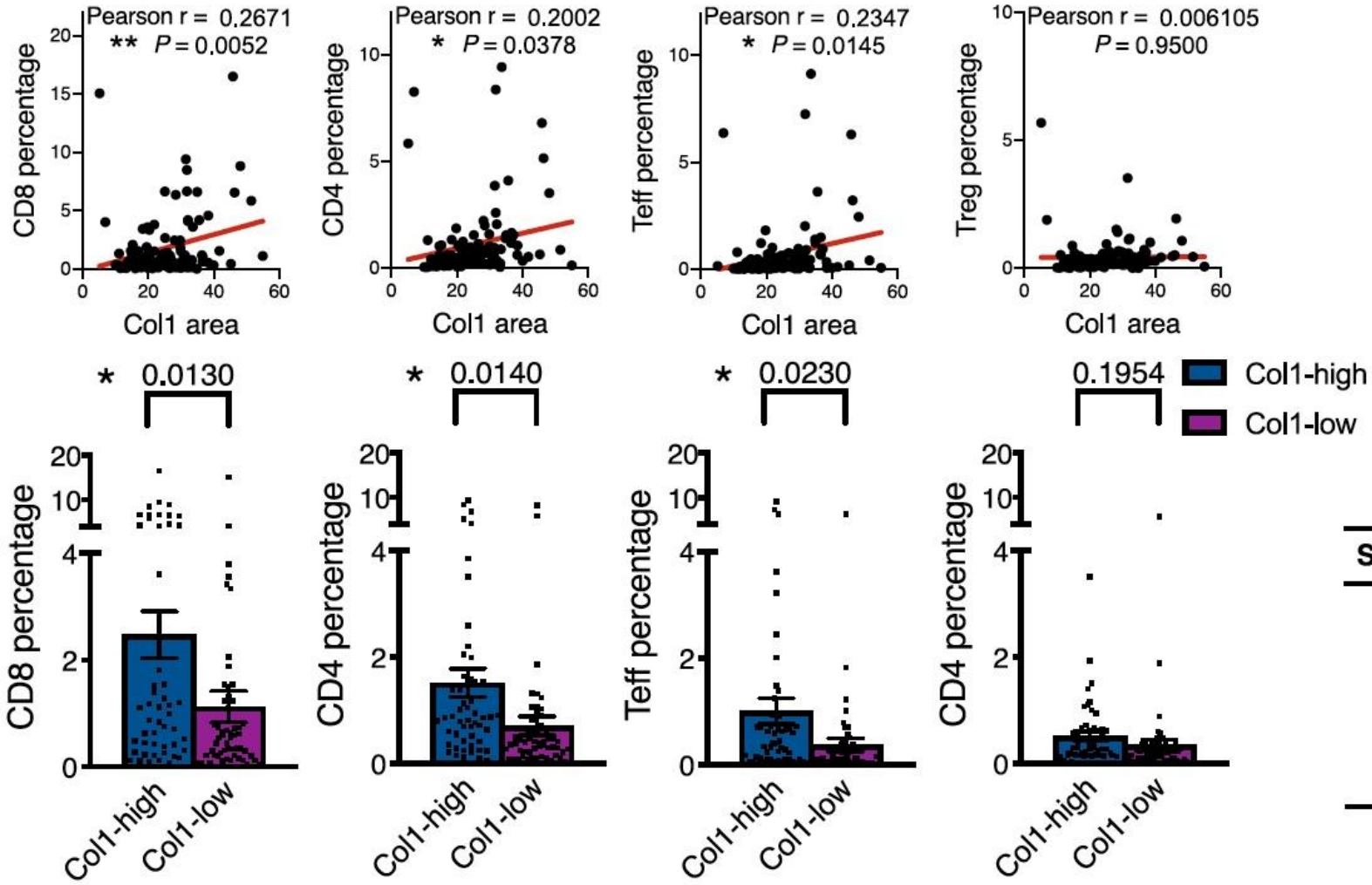




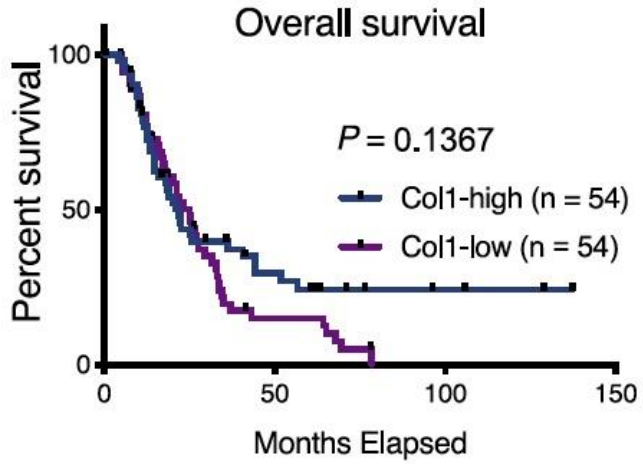
Chen et al 2021

Madsen et al Cancer Cell 2021

T cells correlate with the level of Col1 in human PDAC



C



Survival proportion	Col1-high	Col1-low
1-year survival	76.8%	78.8%
3-year survival	39.7%	19.8%
5-year survival	24.3%	15.1%
7-year survival	24.3%	0%

Cancer Cell

CellPress

Article

Type I collagen deletion in αSMA^{+} myofibroblasts augments immune suppression and accelerates progression of pancreatic cancer

Yang Chen,[1] Jiha Kim,[1] Sujuan Yang,[1] Huamin Wang,[2] Chang-Jiun Wu,[3] Hikaru Sugimoto,[1] Valerie S. LeBleu,[1] and Raghu Kalluri[1,4,*]

[1]Department of Cancer Biology, University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA

[2]Department of Anatomical Pathology, University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA

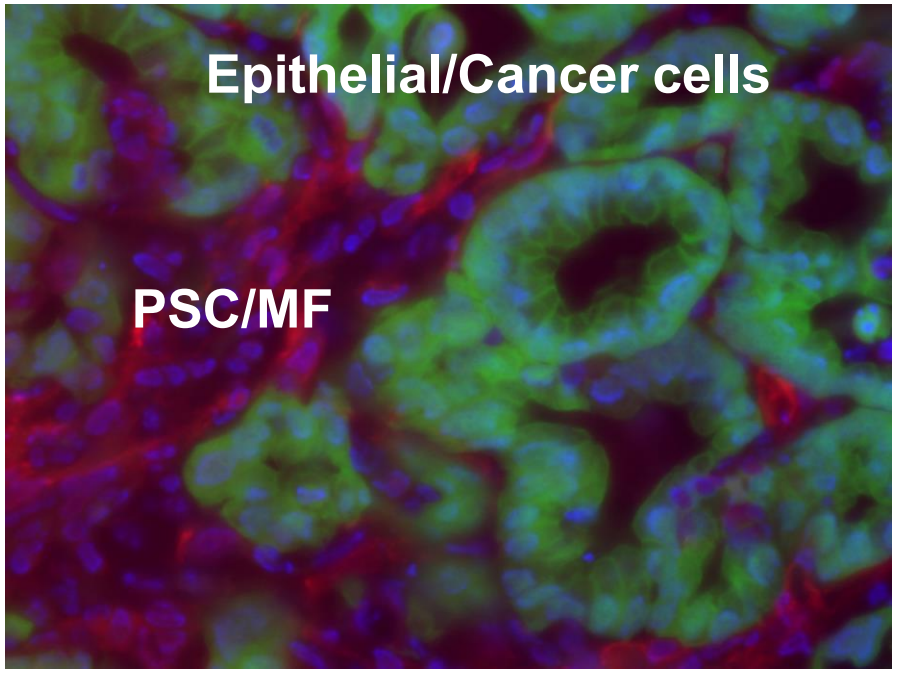
[3]Department of Genomic Medicine, University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA

[4]Lead contact

*Correspondence: rkalluri@mdanderson.org

https://doi.org/10.1016/j.ccell.2021.02.007

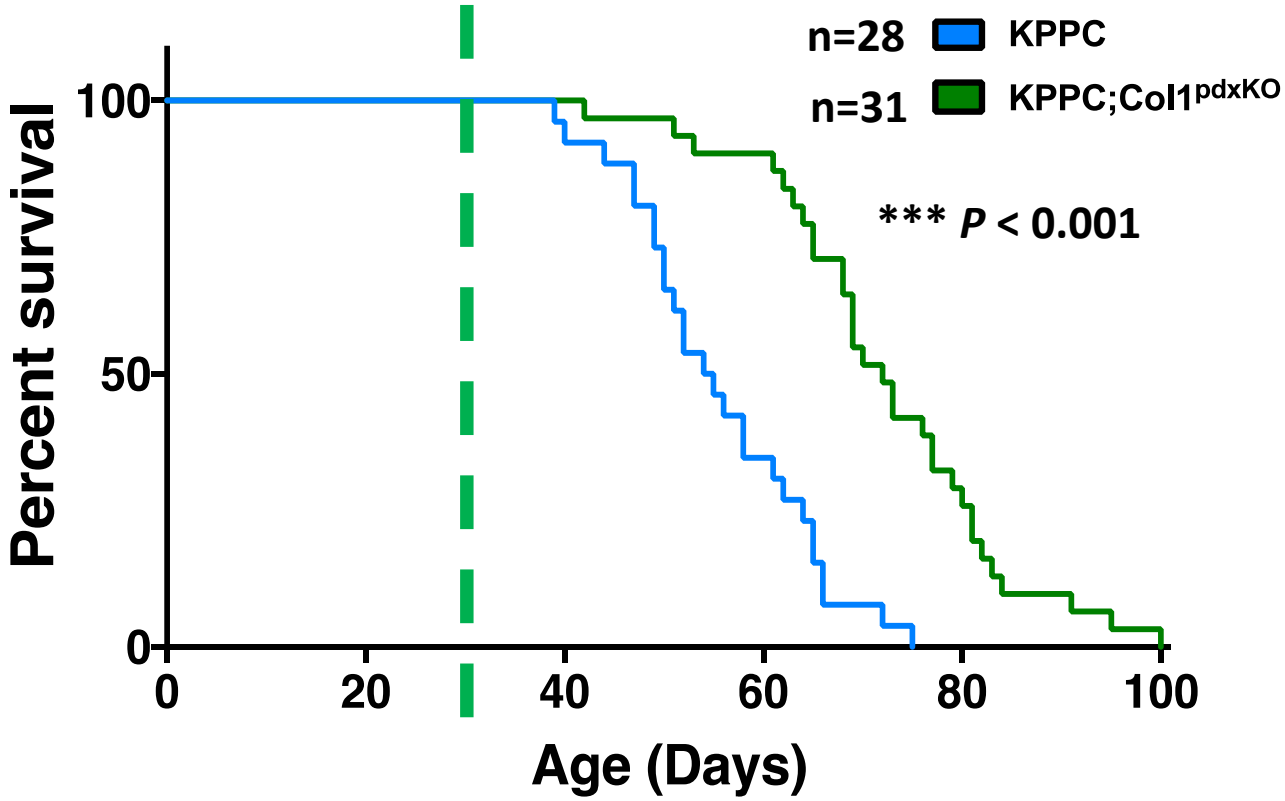
Type I collagen production by αSMA^{+} myofibroblasts, but not S100A4/FSP1^{+}, restrains PDAC initiation and progression

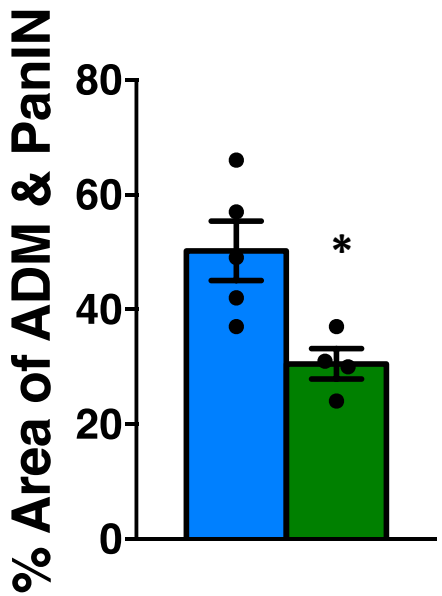


What about the function of type I collagen produced by cancer cells in PDAC?

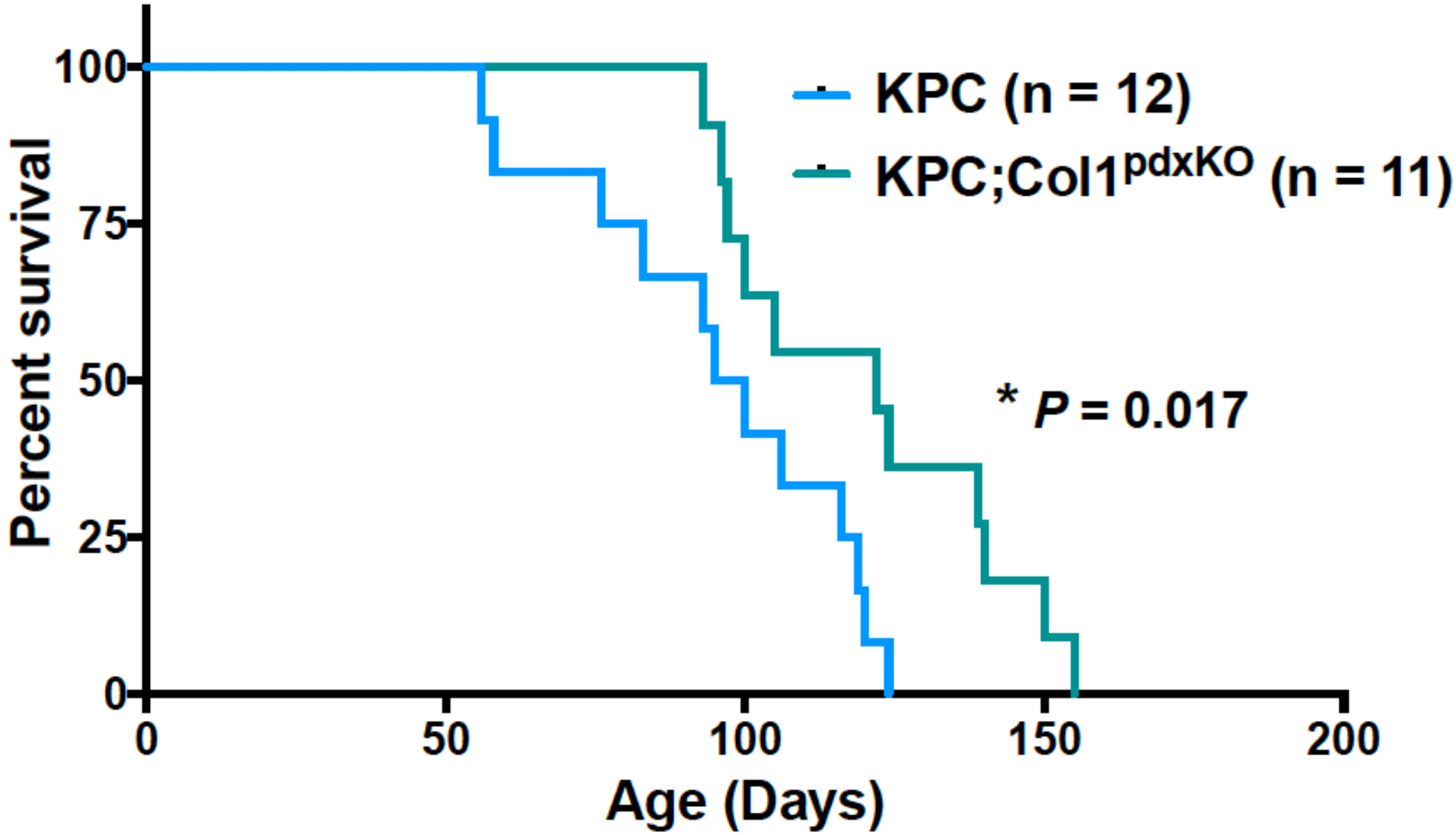
.Naba A et al *Mol Cell Proteomics* 2012;11: M111.014647
.Naba A et al *Elife* 2014;3:e01308 ; Tian et al PNAS 2019

Deletion of type I collagen deletion in cancer cells of KPPC mice leads to increase in overall survival



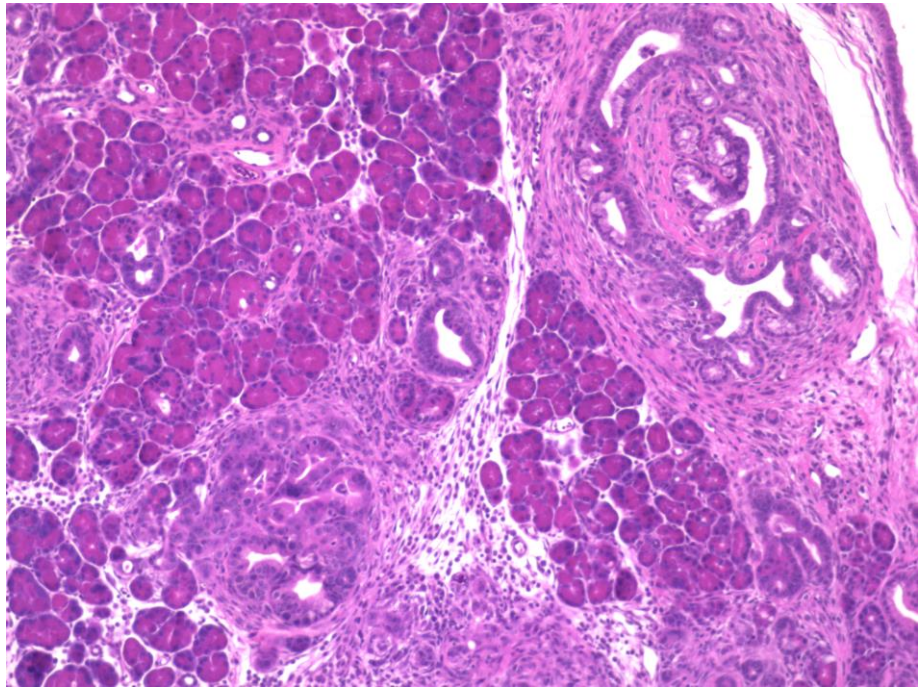


Deletion of type I collagen in cancer cells of KPC mice leads to increase in overall survival

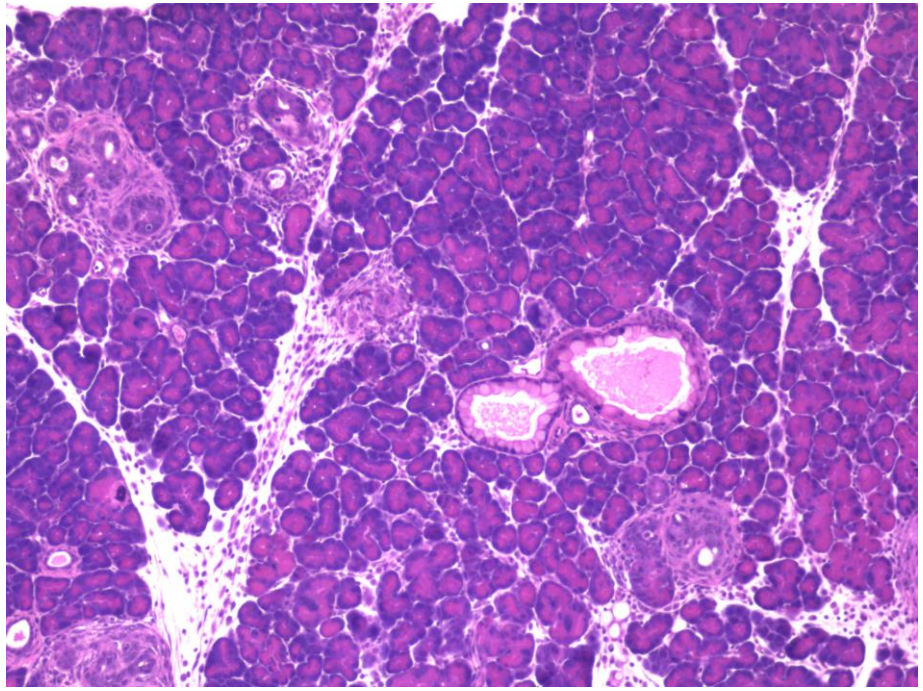


Deletion of type I collagen in cancer cells of KPPC mice improves tissue histology

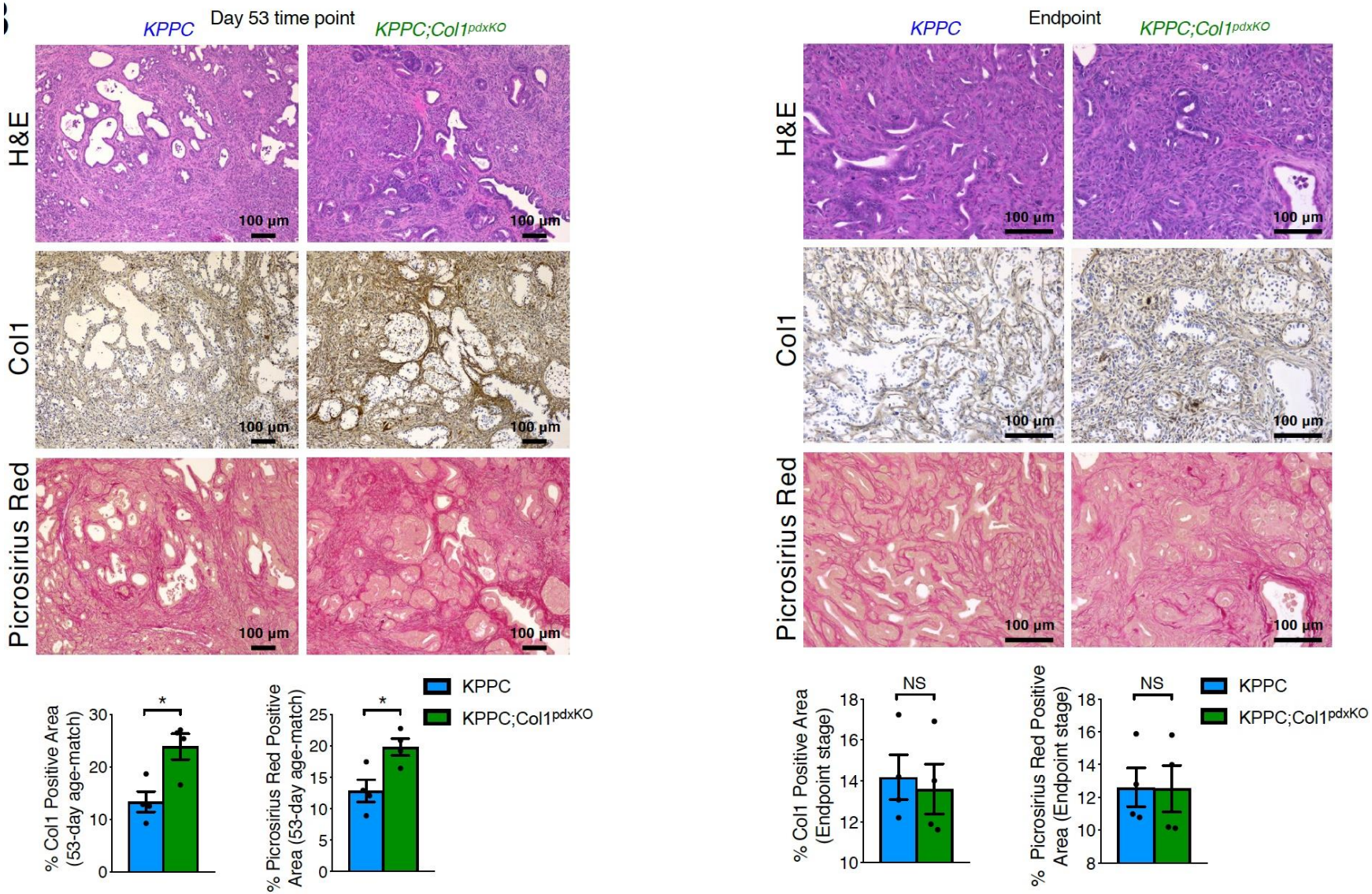
KPPC



KPPC;Col1^{pdxKO}

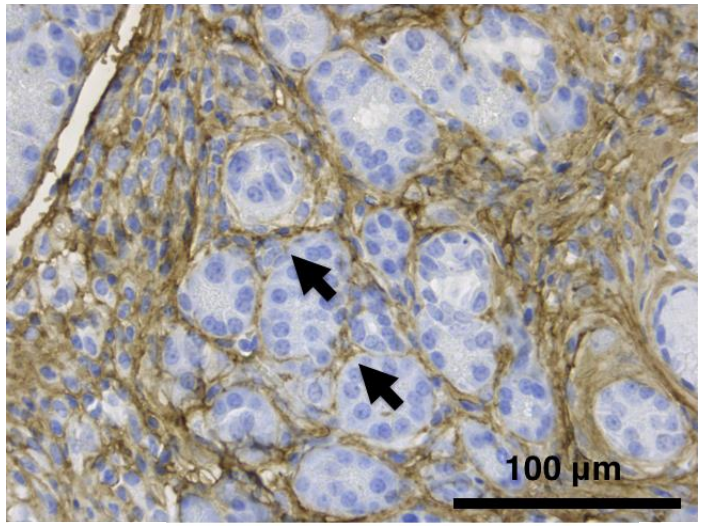


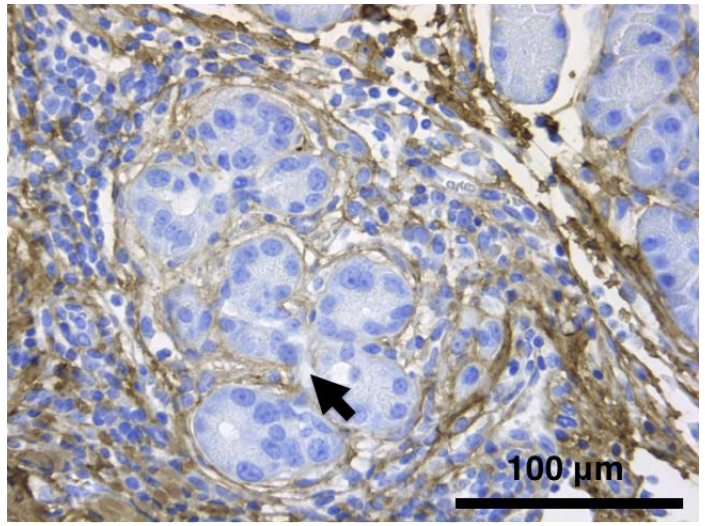
Deletion of Col1 in cancer cells does not impact the total content of tumor Col1 due to dominant stromal contribution

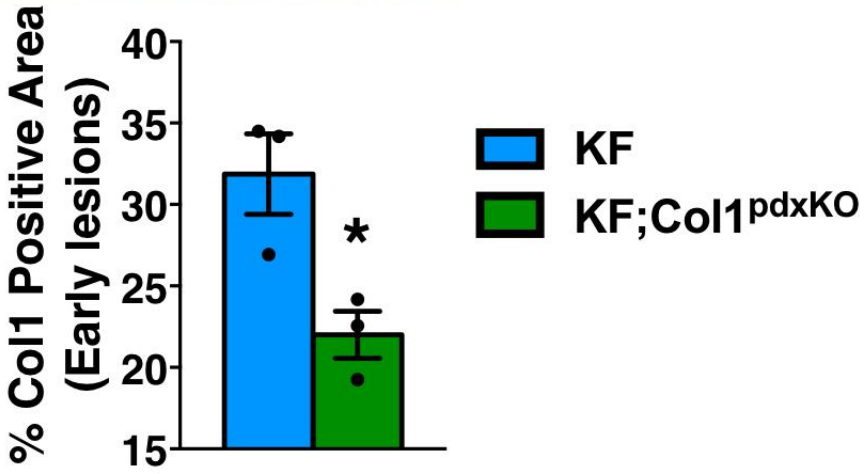


Col1 deletion in cancer cells reveal decreased type I collagen around ADM/PanIN lesions

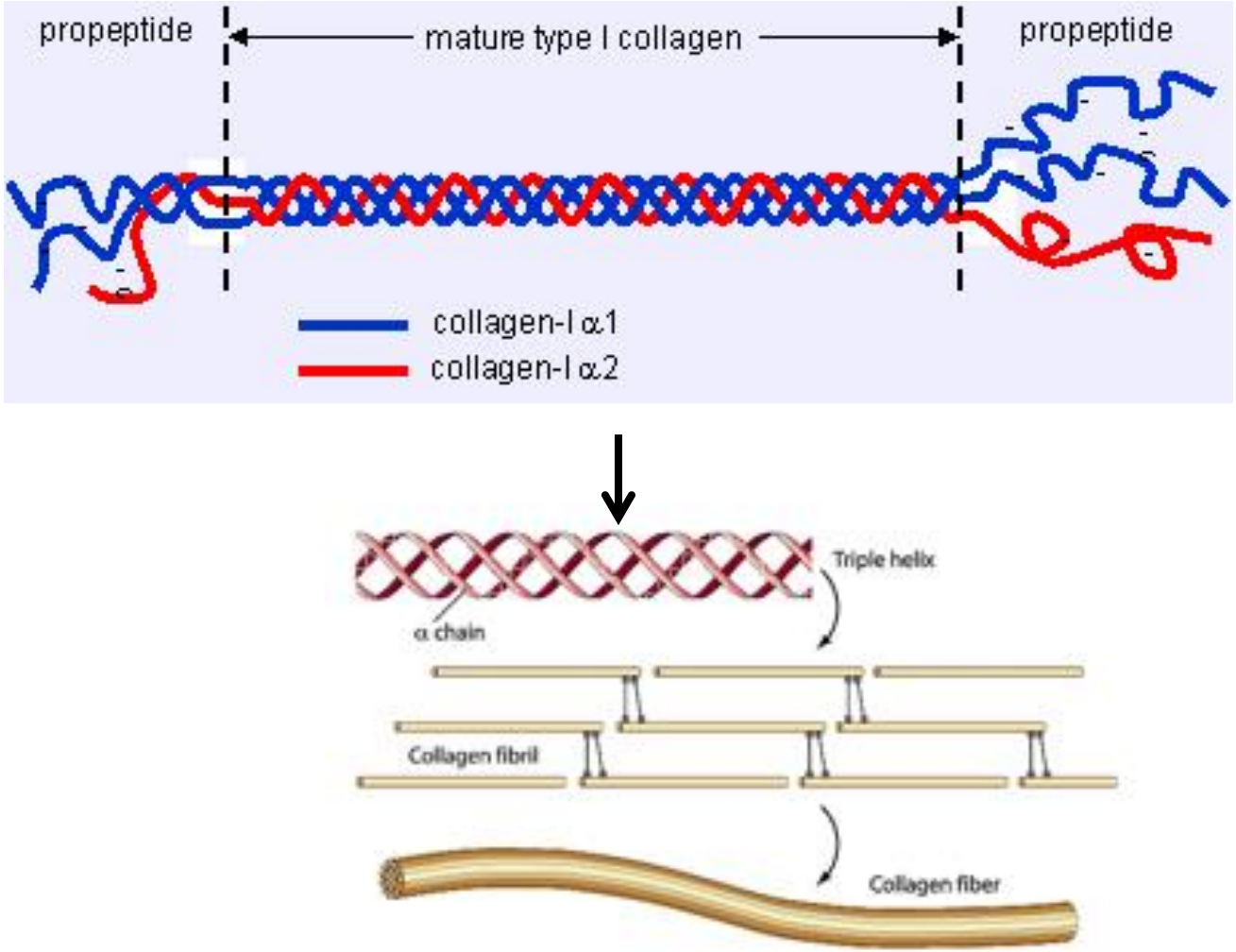
KF ***KF;Col1^{pdxKO}***





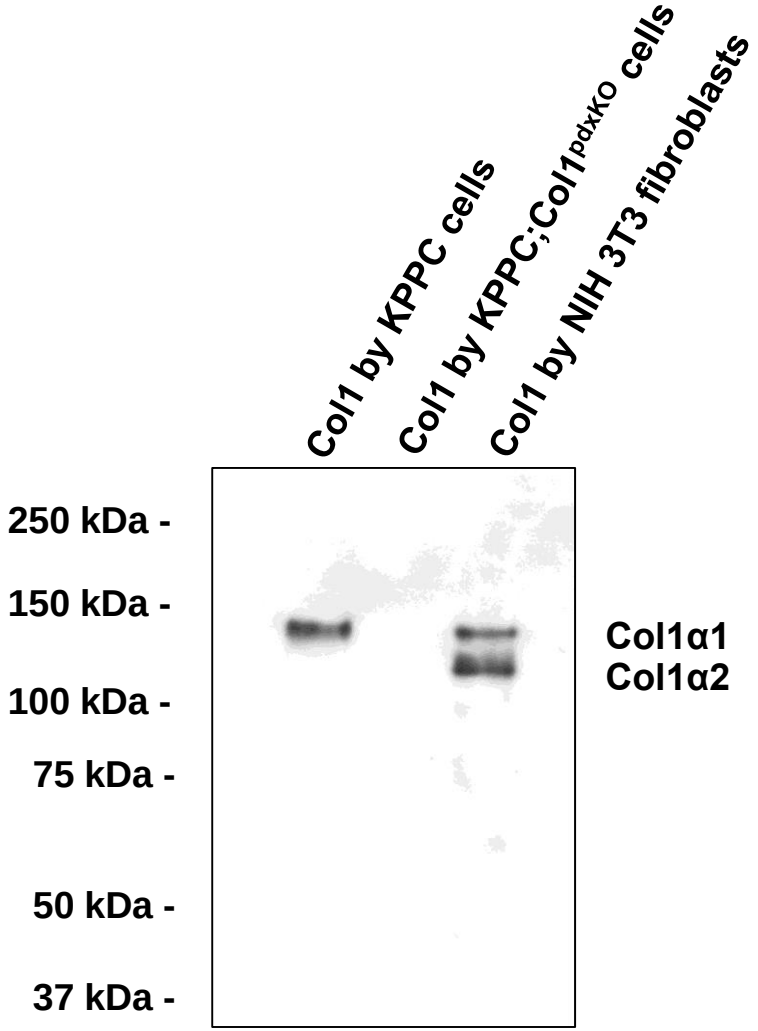


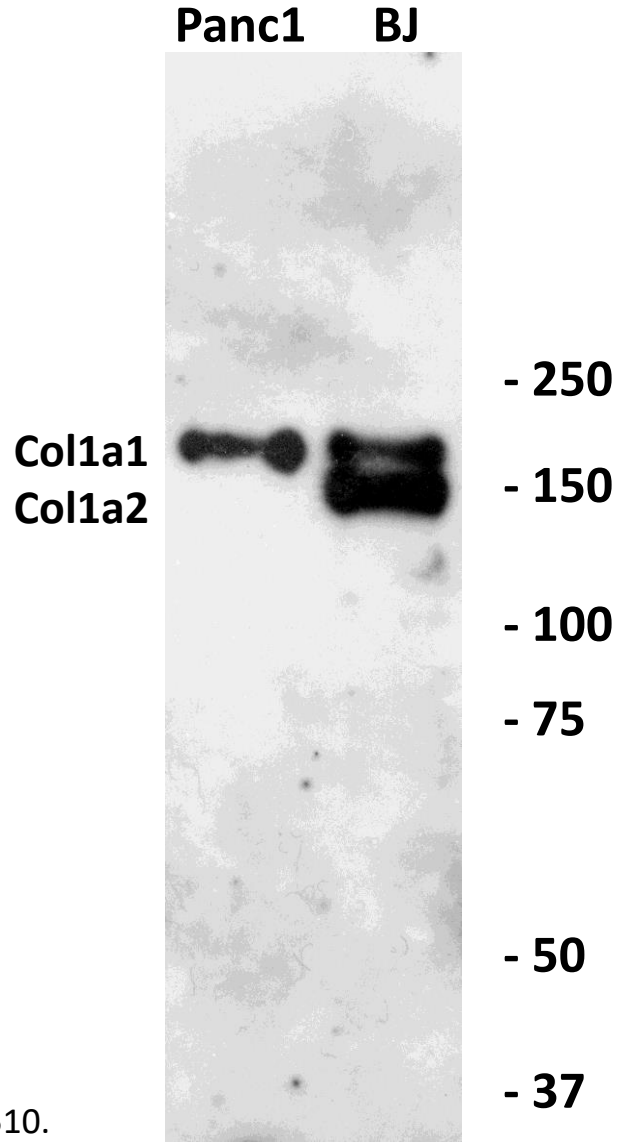
Why is there a difference in the function of type I collagen in PDAC depending on the source?

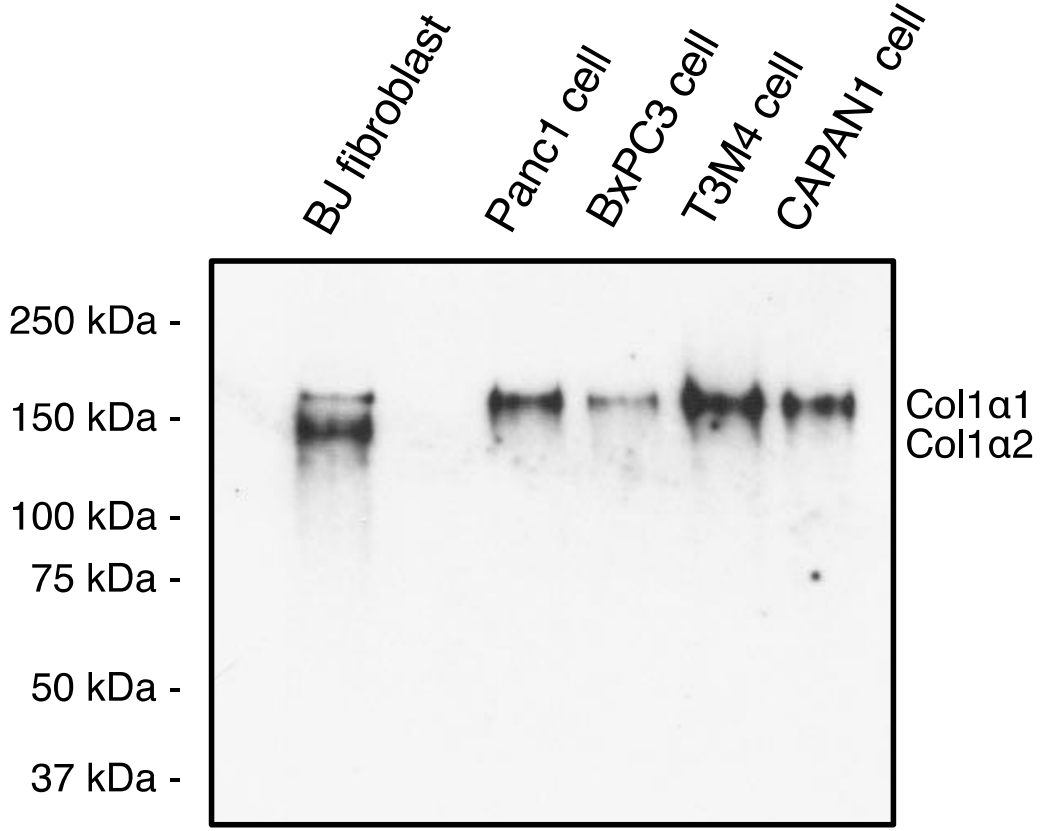


Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_COL1A2.html

Cancer cells produce α1 polypeptide of type I collagen while fibroblasts generate both α1 and α2 polypeptides

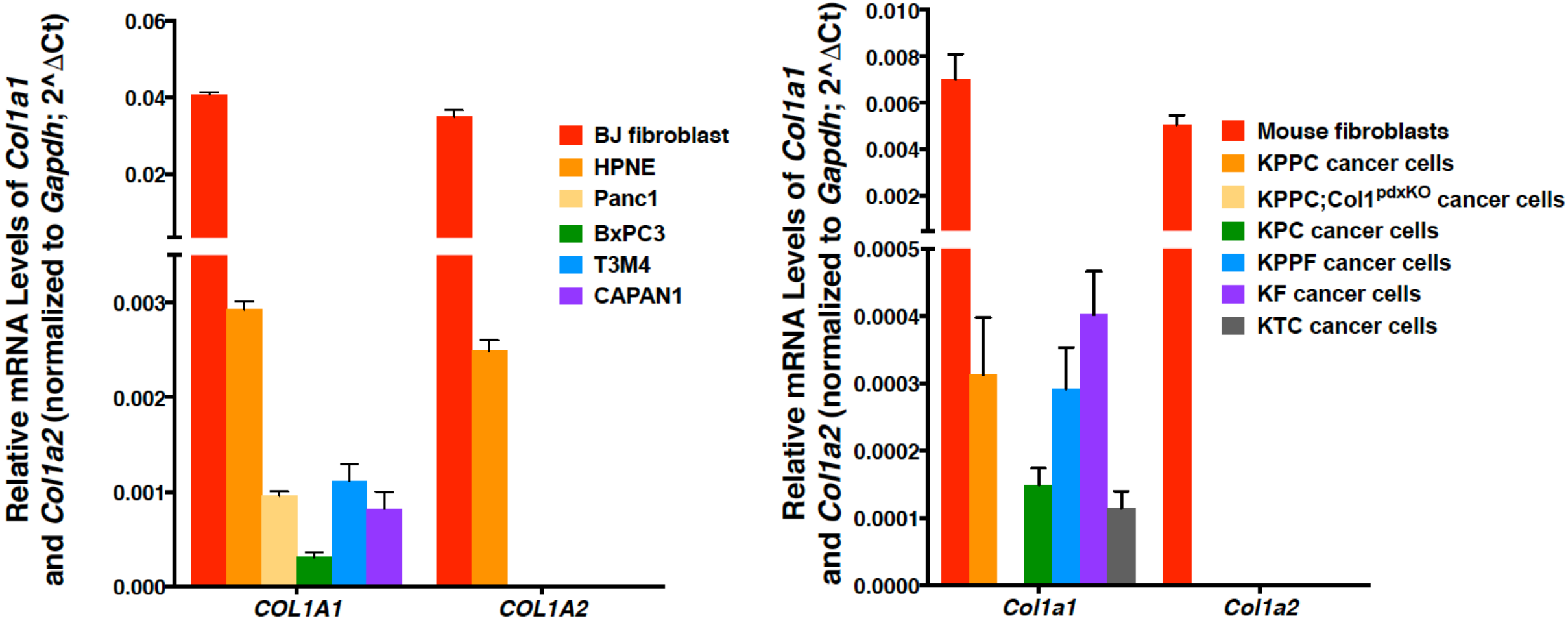




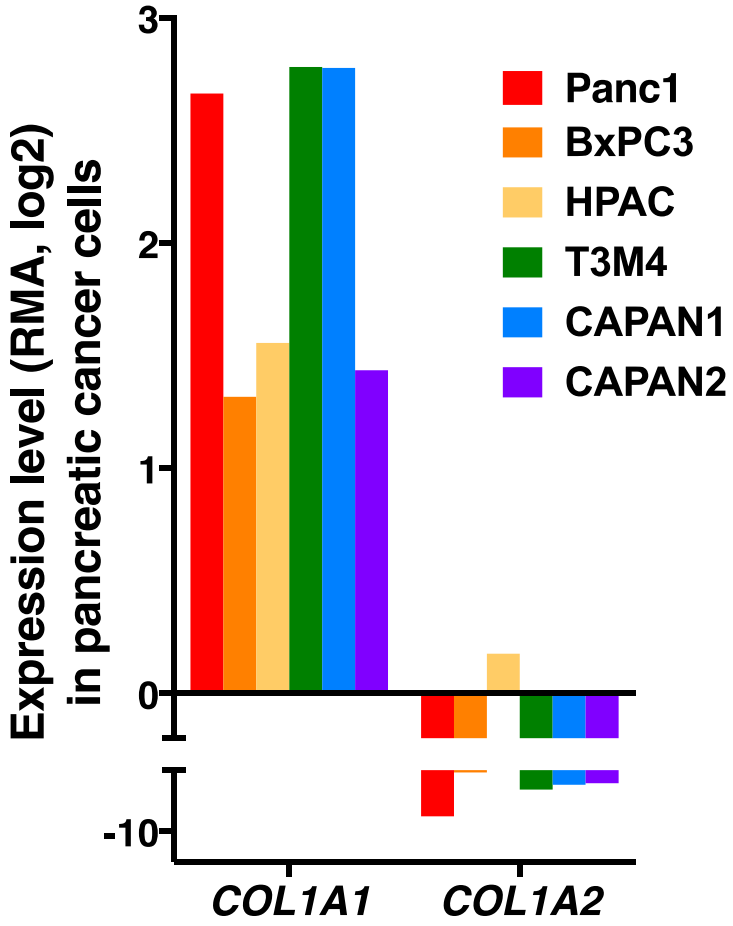


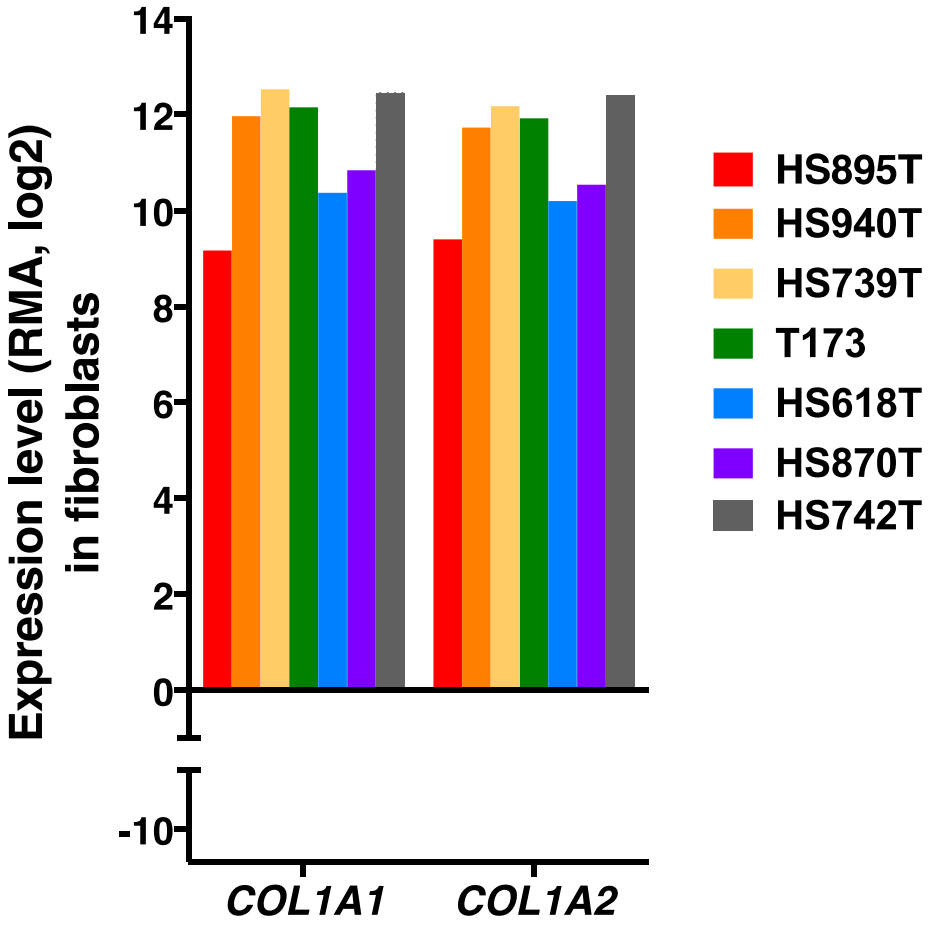
DeClerck, Y.A et al (1987) Cancer research *47*, 6505-6510.

Pancreatic cancer cells do not express α2 chain of type I collagen



Pancreatic cancer cells do not express α2 chain of type I collagen



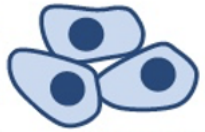


Moro et al (1977) Arch Biochem Biophys Jul;182(1):33-41
Pupard et al (1988) Am J. Pathol Nov;133(2):316-26.

Broad Institute Database

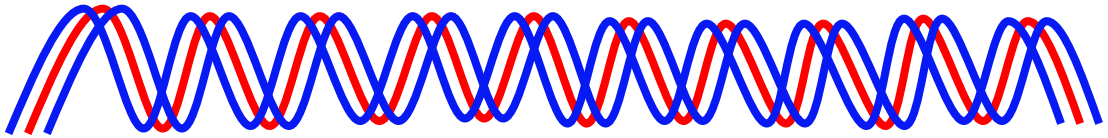
Cancer cells produce α1 polypeptide chain of type I collagen while fibroblasts generate both α1 and α2 polypeptide chains

Fibroblasts/CAFs



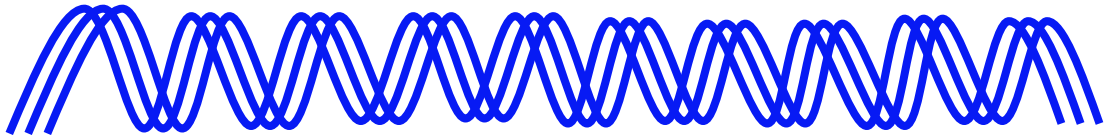
Cancer Cells

α1/α2/α1 HETEROTRIMER



~97% of the Stromal Collagen I in PDAC

α1/α1/α1 Homotrimer



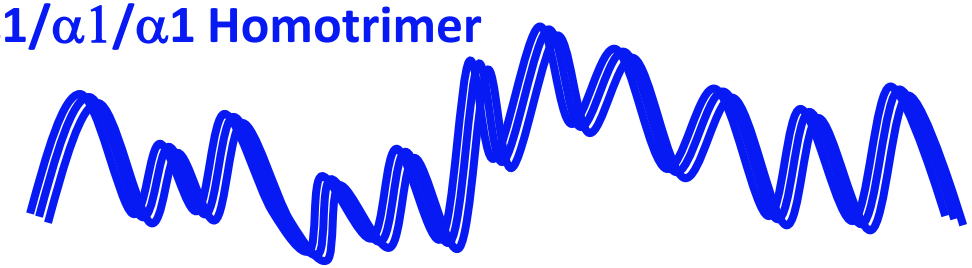
~3% of the Stromal Collagen I in PDAC

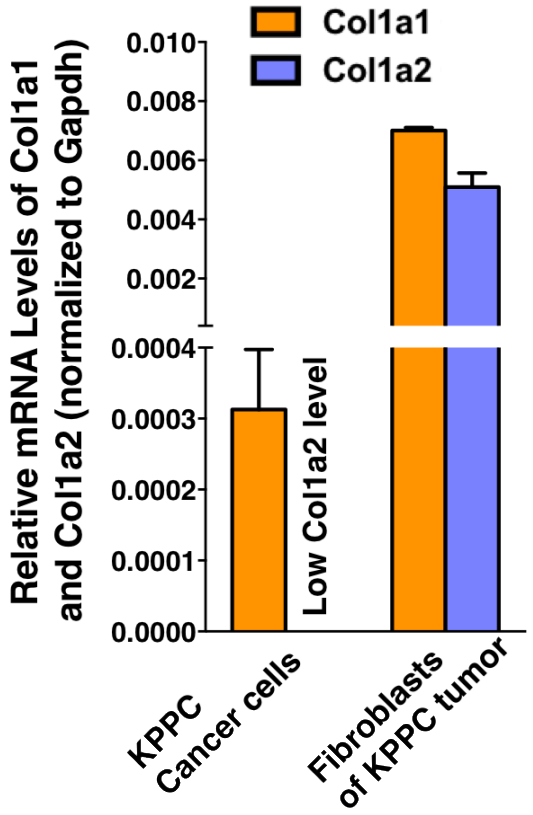
Humans and mice do not have Col1 homotrimers in any tissue

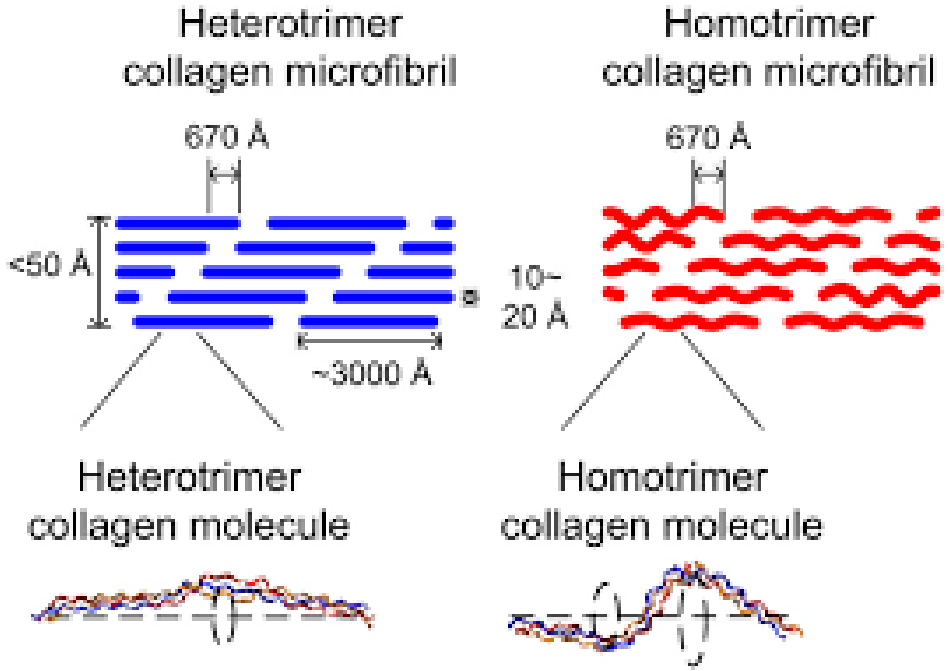
All of the type I collagen in our body are heterotrimeric

Cancer cells produced type I collagen homotrimers have an altered structure

α1/α1/α1 Homotrimer



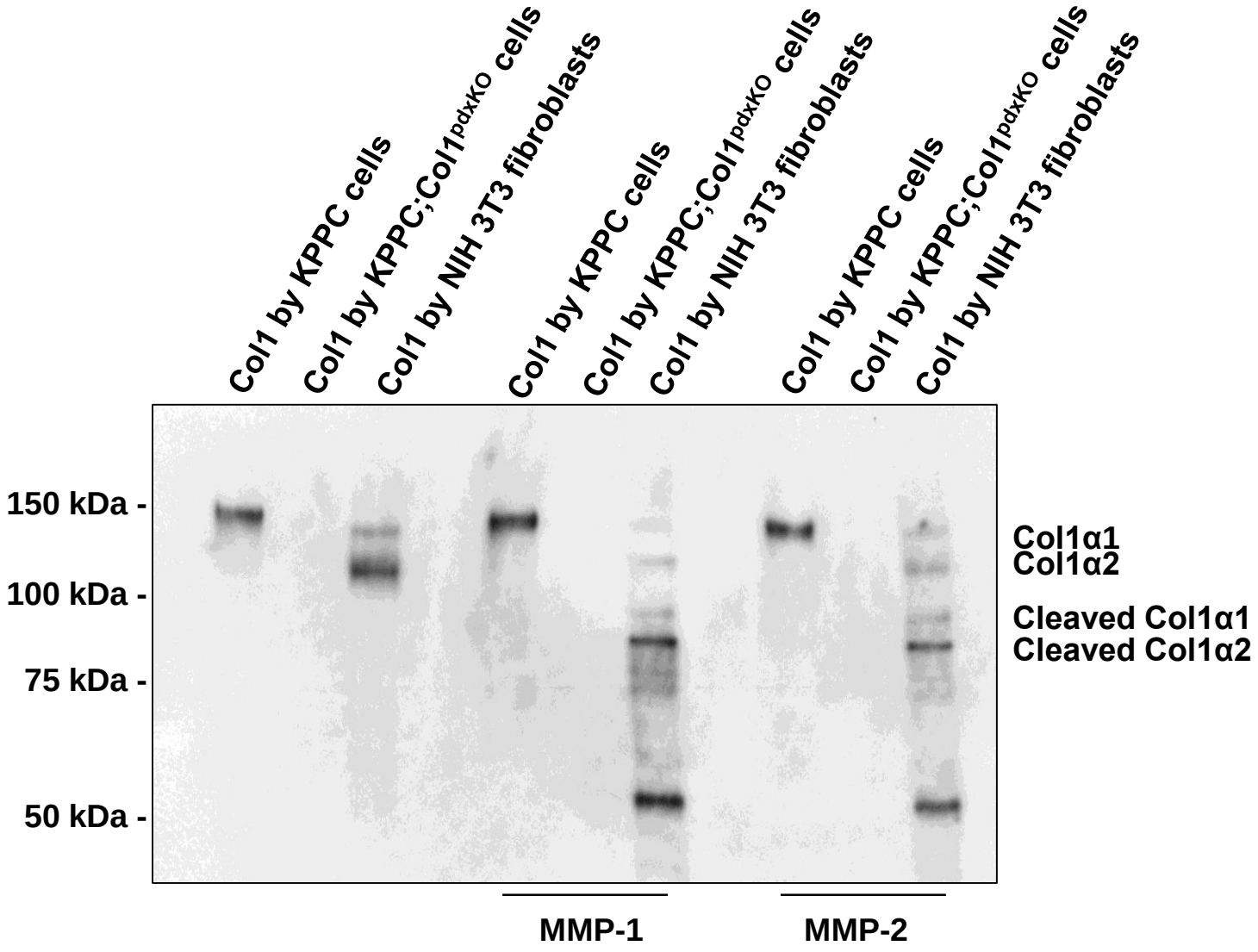




Circular Dichorism (CD) shows that col1 homotrimers denature about 75 –fold slower than col1 heterotrimers

Han, S., McBride, D.J., Losert, W., and Leikin, S. (2008) J Mol Biol *383*, 122-132

Type I collagen homotrimers generated by cancer cells are resistant to proteolysis by MMPs

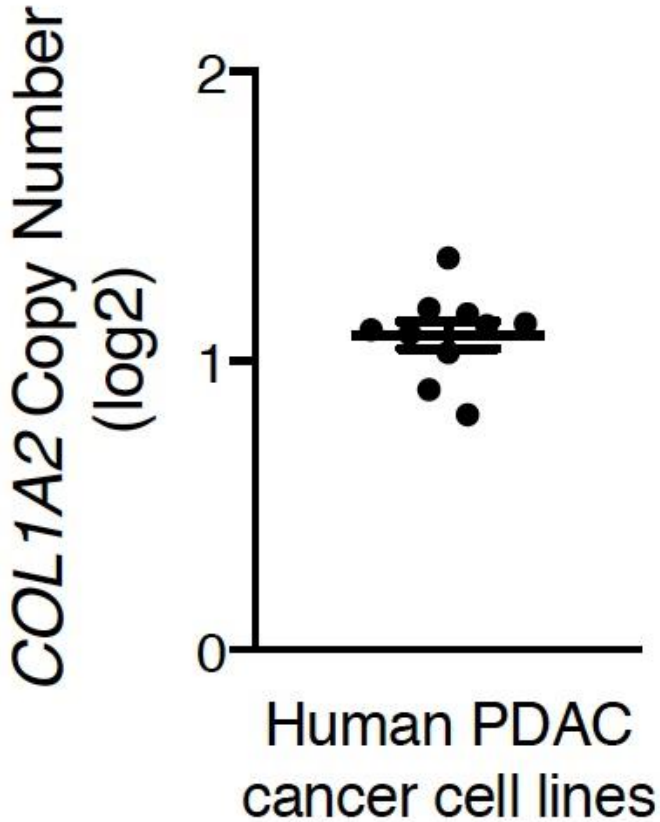


Type I Homotrimers resist local unwinding by MMP-1 because of higher triple helix stability near the cleavage site

Han, S et al (Leikin, S) (2010) JBC *285*, 22276-22281
Makareeva, E et al (2010). Cancer research *70*, 4366-4374

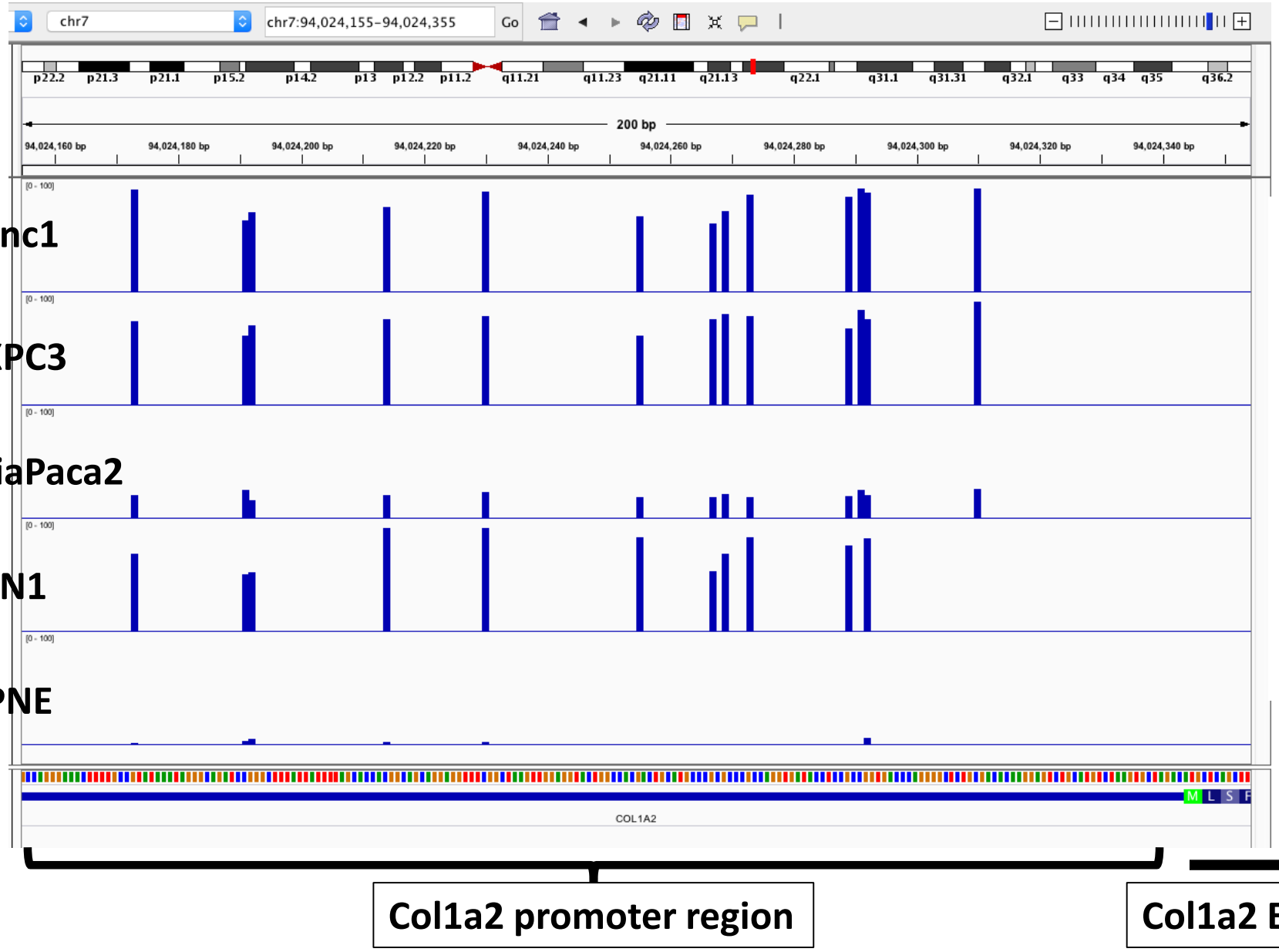
Col1a2 gene analysis

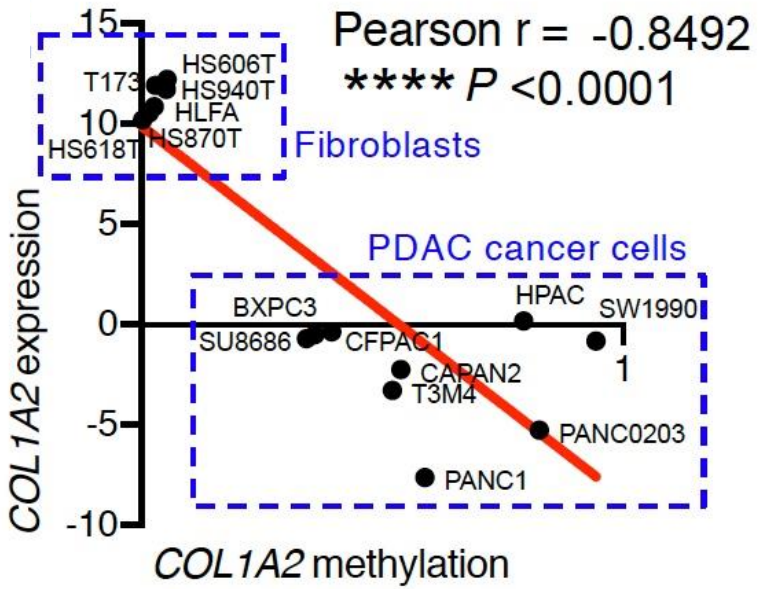
Cell line ID	Copy number alteration	Copy number (log2)
PANC1	not available	1.130
BXPC3	no alteration	1.163
HPAC	not available	1.095
T3M4	no alteration	0.814
CAPAN1	no alteration	1.356
CAPAN2	no alteration	1.108
CFPAC1	no alteration	1.123
PANC0203	no alteration	0.901
SU8686	no alteration	1.030
SW1990	no alteration	1.181



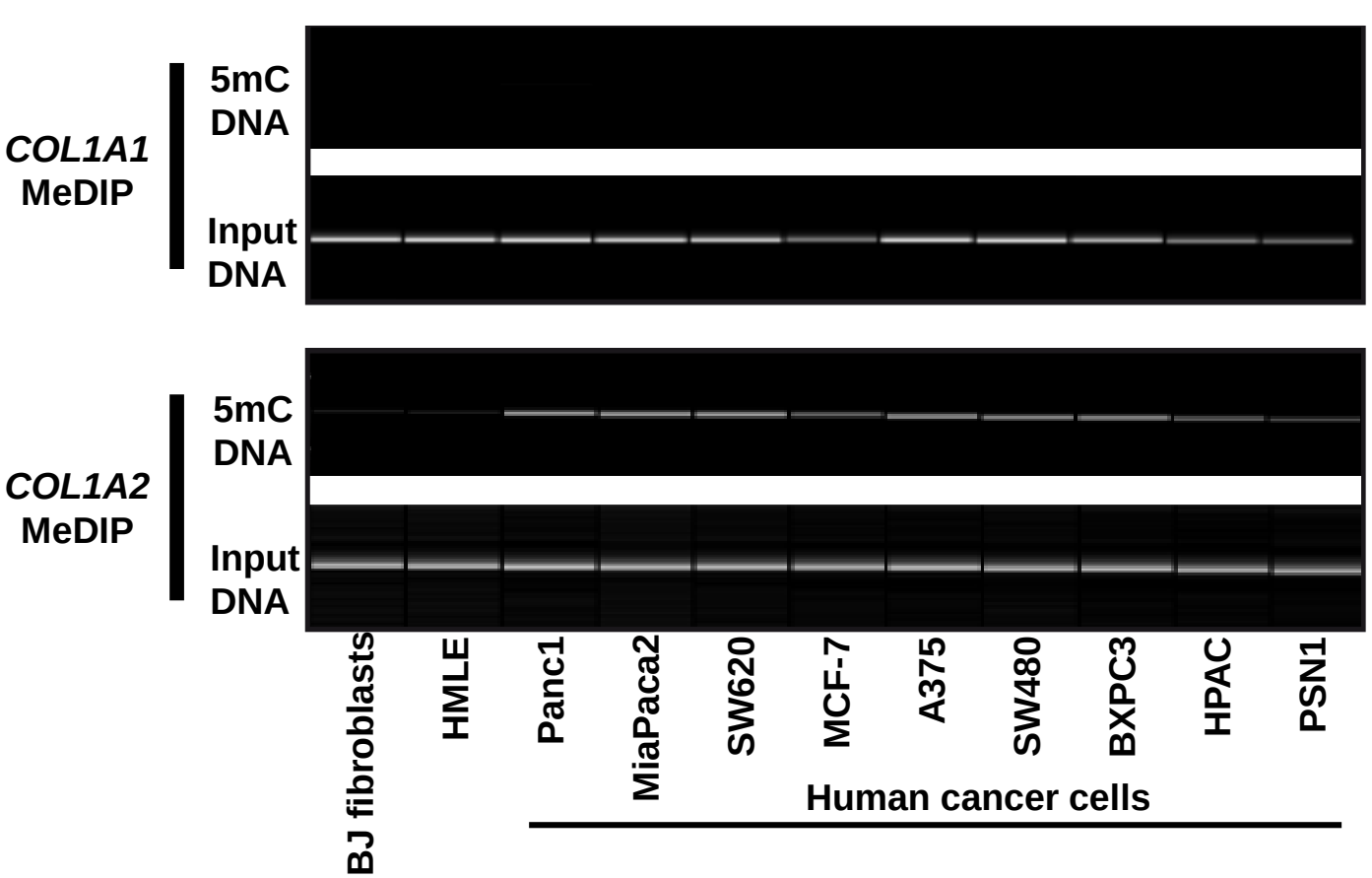
Global Methylation Analysis

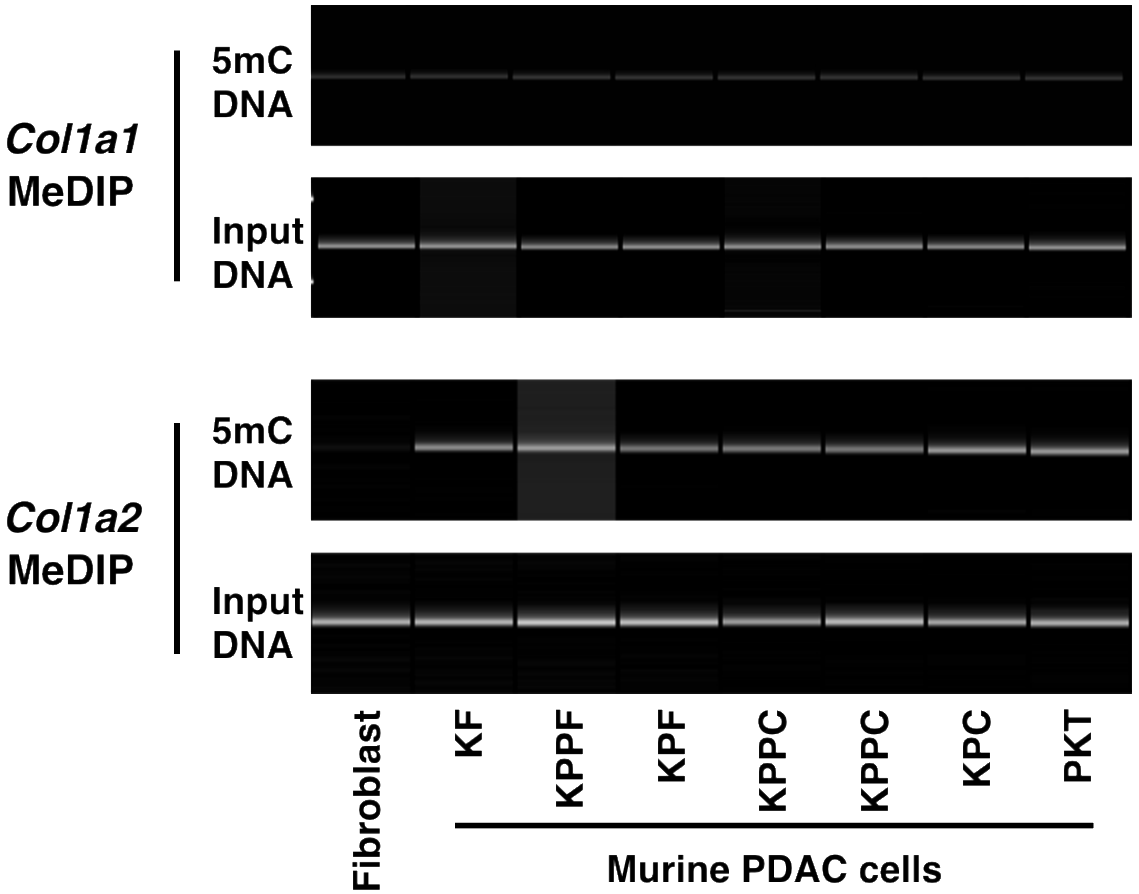
Jena Tavormina





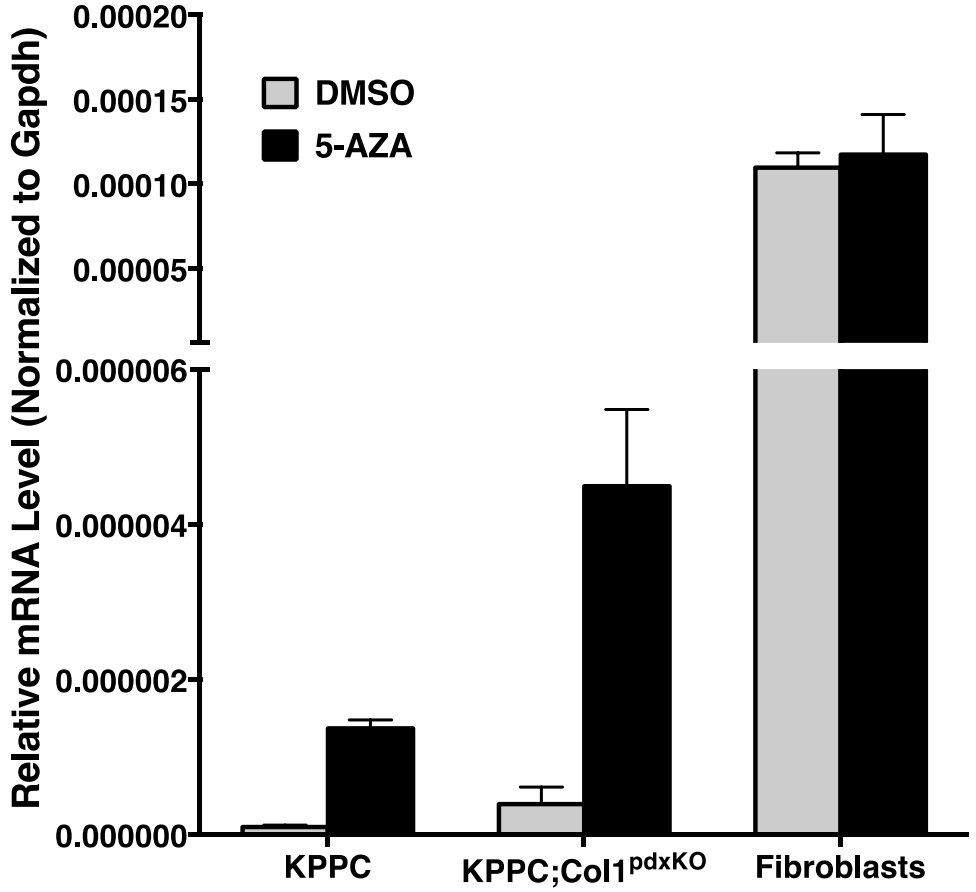
Hypermethylation of COL1A2 in human and mouse cancer cells

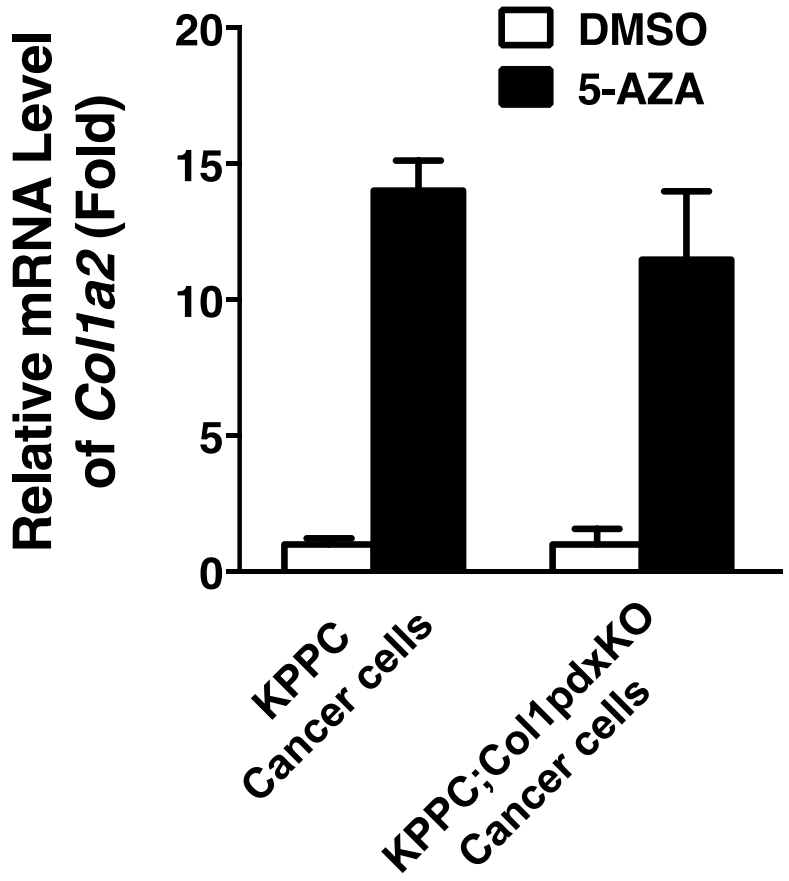




Misawa, K. et al (2011) Cancer Biomark *10*, 135-144.
Sengupta, P.K. et al (2003) Cancer research *63*, 1789-1797.

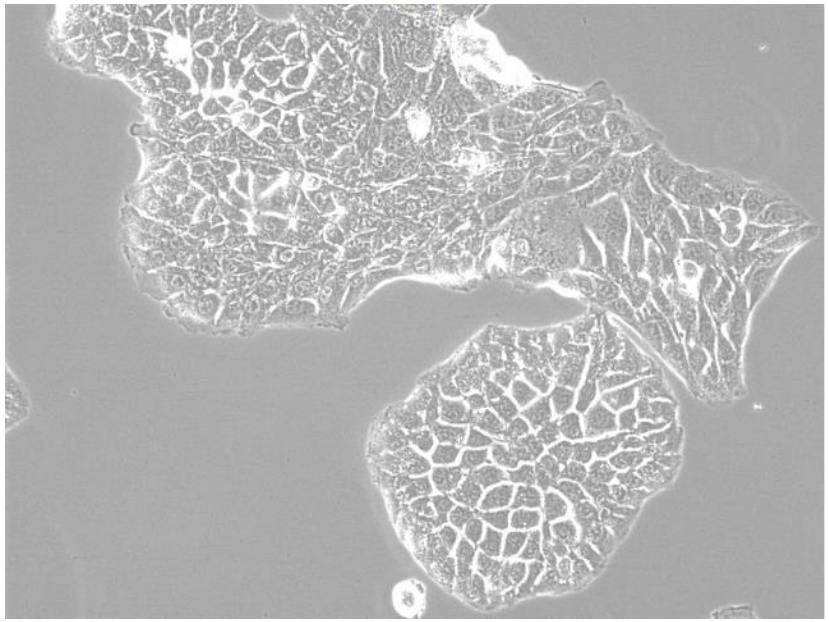
Col1a2 gene hypermethylation in PDAC cells can be reversed by 5-AZA, resulting in increased Col1α2 mRNA



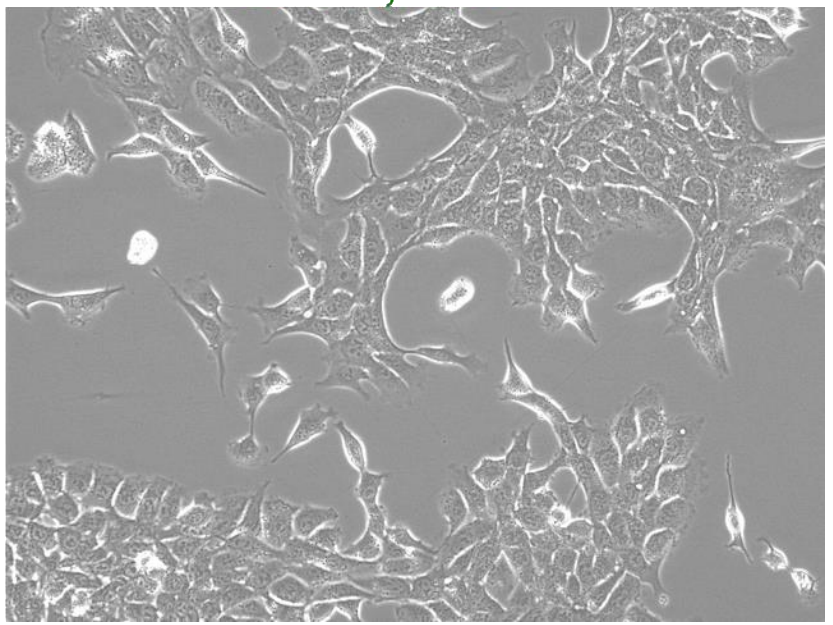


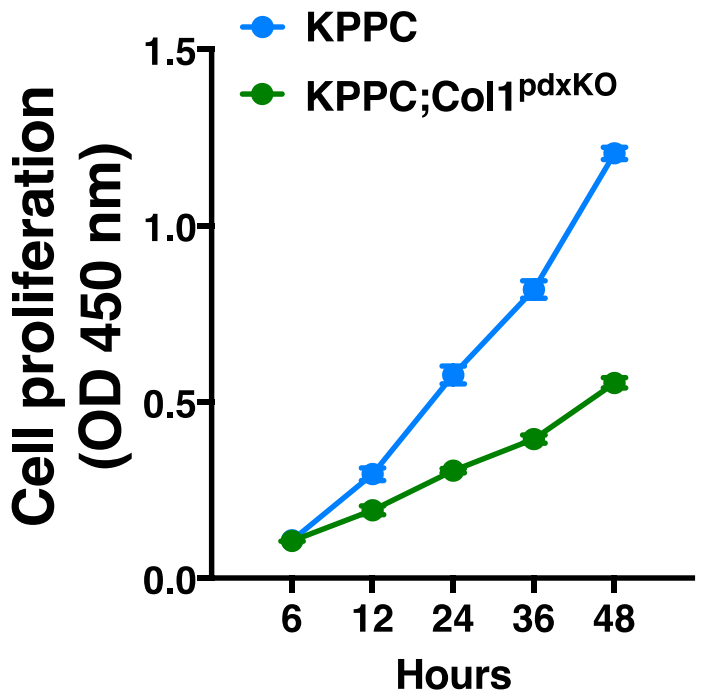
Col1 homotrimer deletion leads to suppressed proliferation of KPPC cancer cells

KPPC

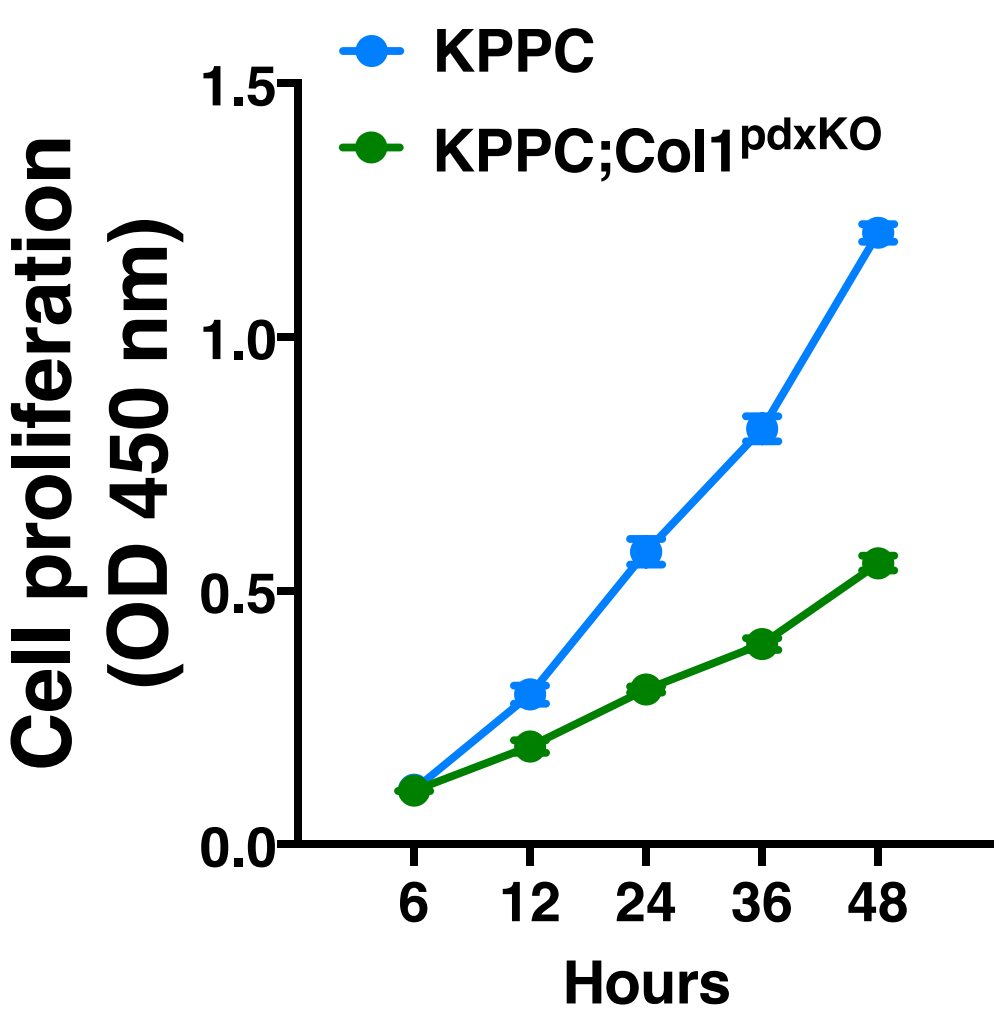


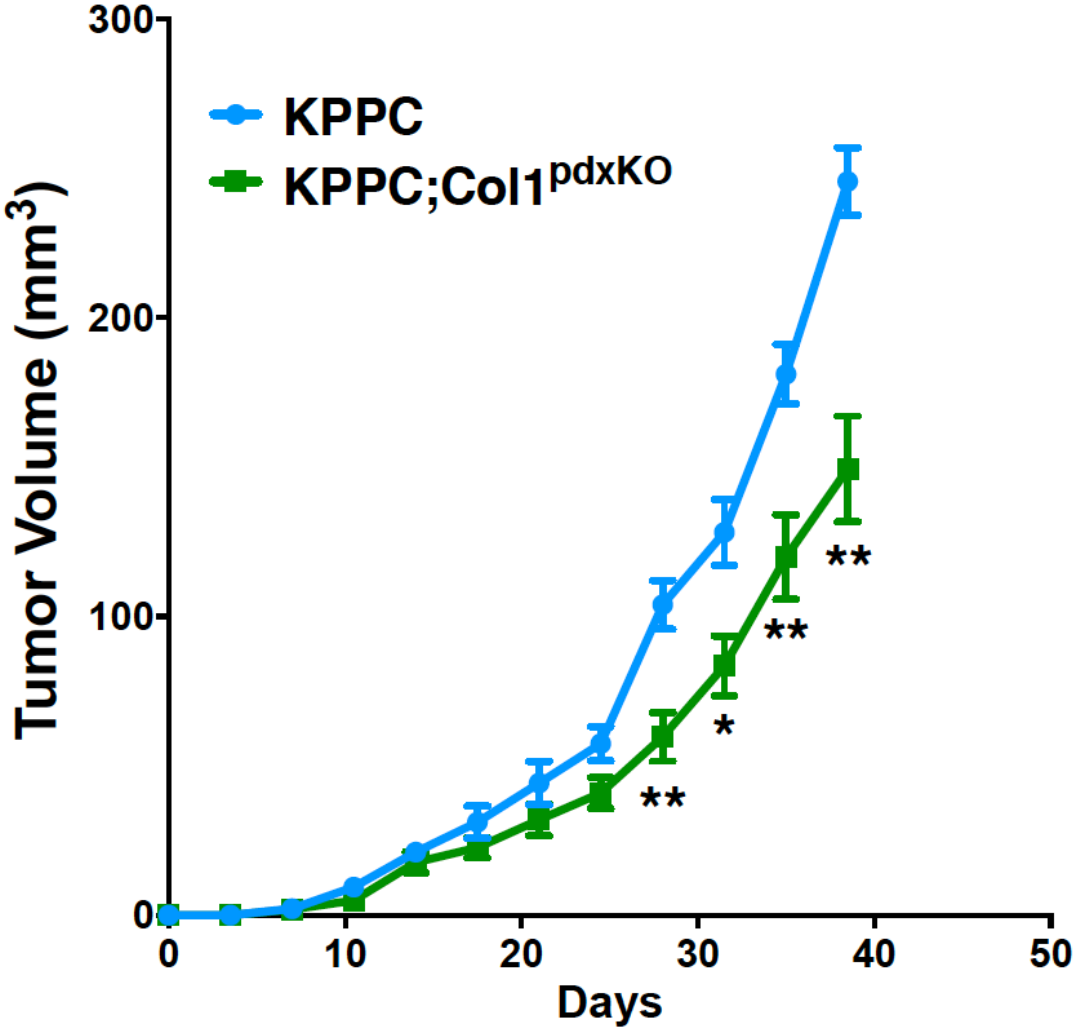
KPPC;Col1^{pdxKO}



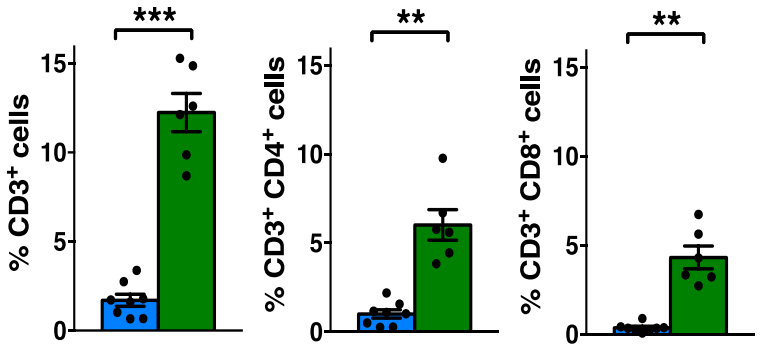


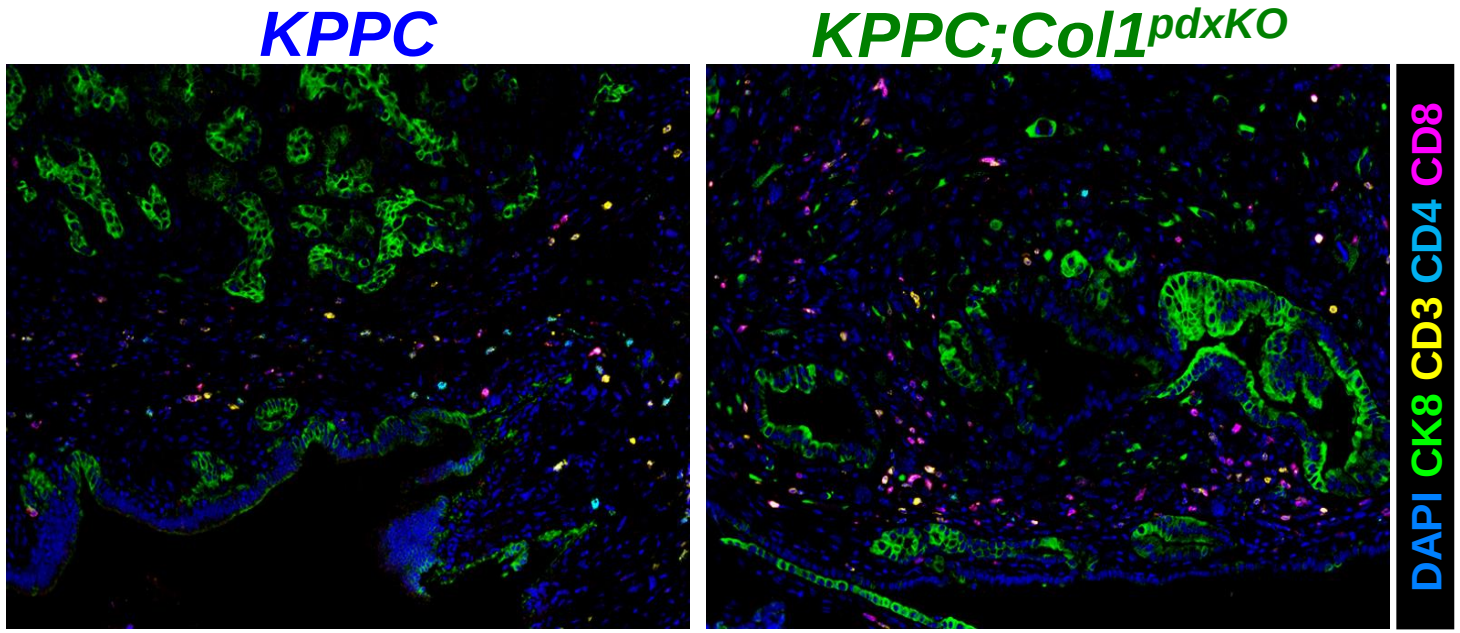
Col1 homotrimer deletion in cancer cells leads to suppressed growth of tumors



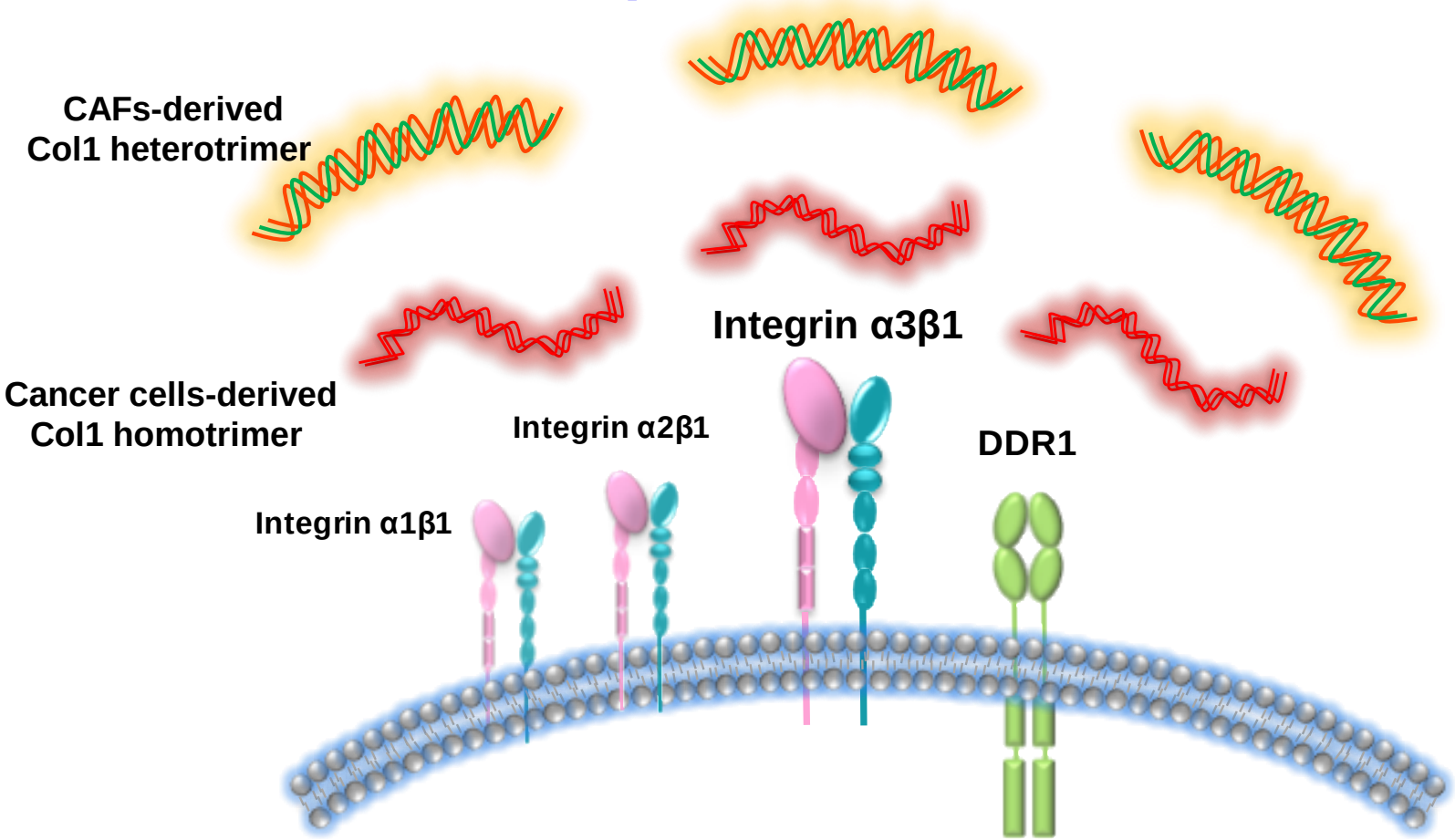


Deletion of type I collagen in cancer cells of KPPC mice increases $CD4^+$ and $CD8^+$ T cells



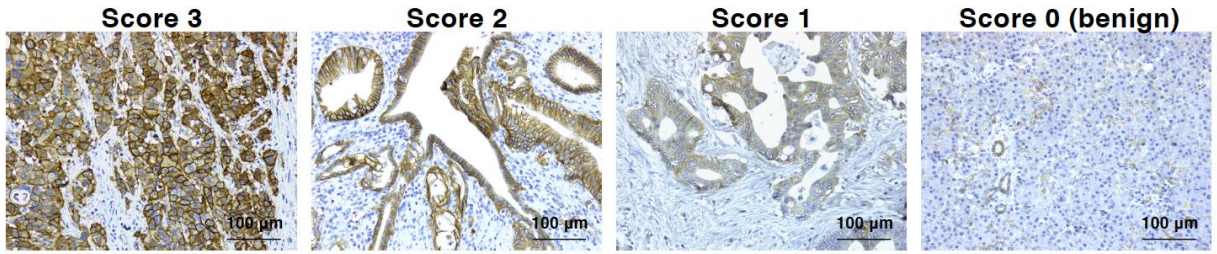


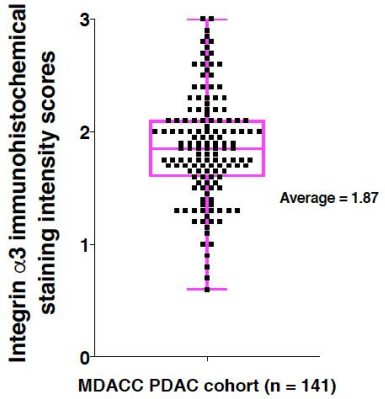
PDAC cancer cells express Col1 binding integrins α1β1, α2β1, α3β1 and DDR1



Col homotrimers promote persistent activation of DDR1/FAK/Akt/ERK signaling pathway via α3β1 integrin

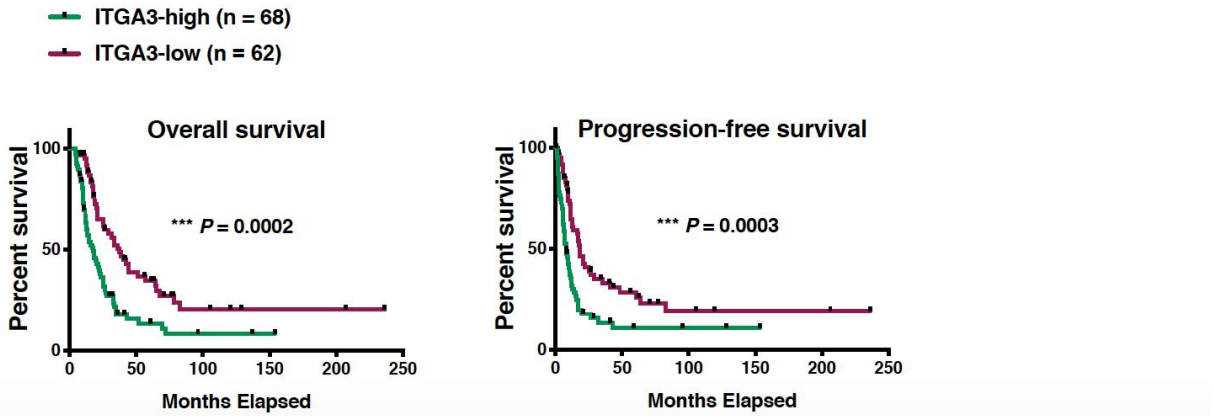
The expression of α3 integrin in tumors correlates with decreased survival of the PDAC patients





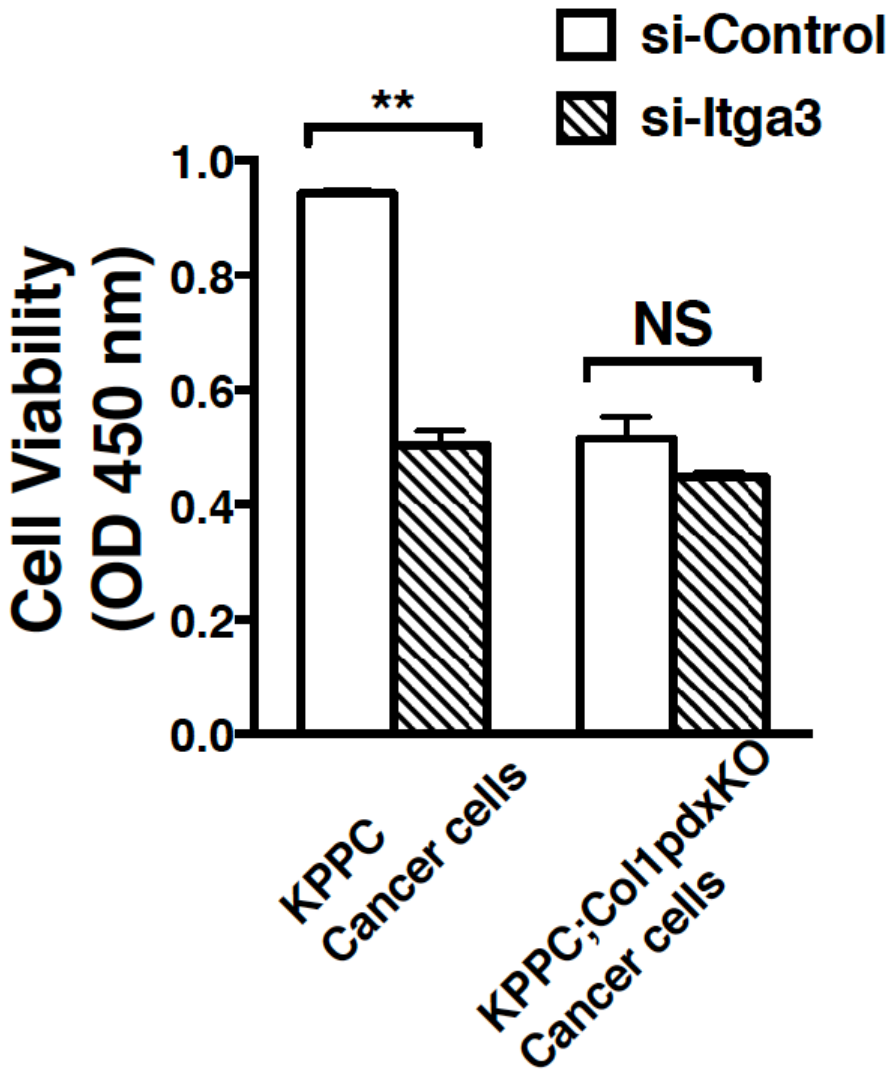
c

Integrin α3 level	# of Patients	Percentage
Very high (score ≥ 2)	55	39%
High (score ≥ 1)	82	58%
Low (score < 1)	4	3%

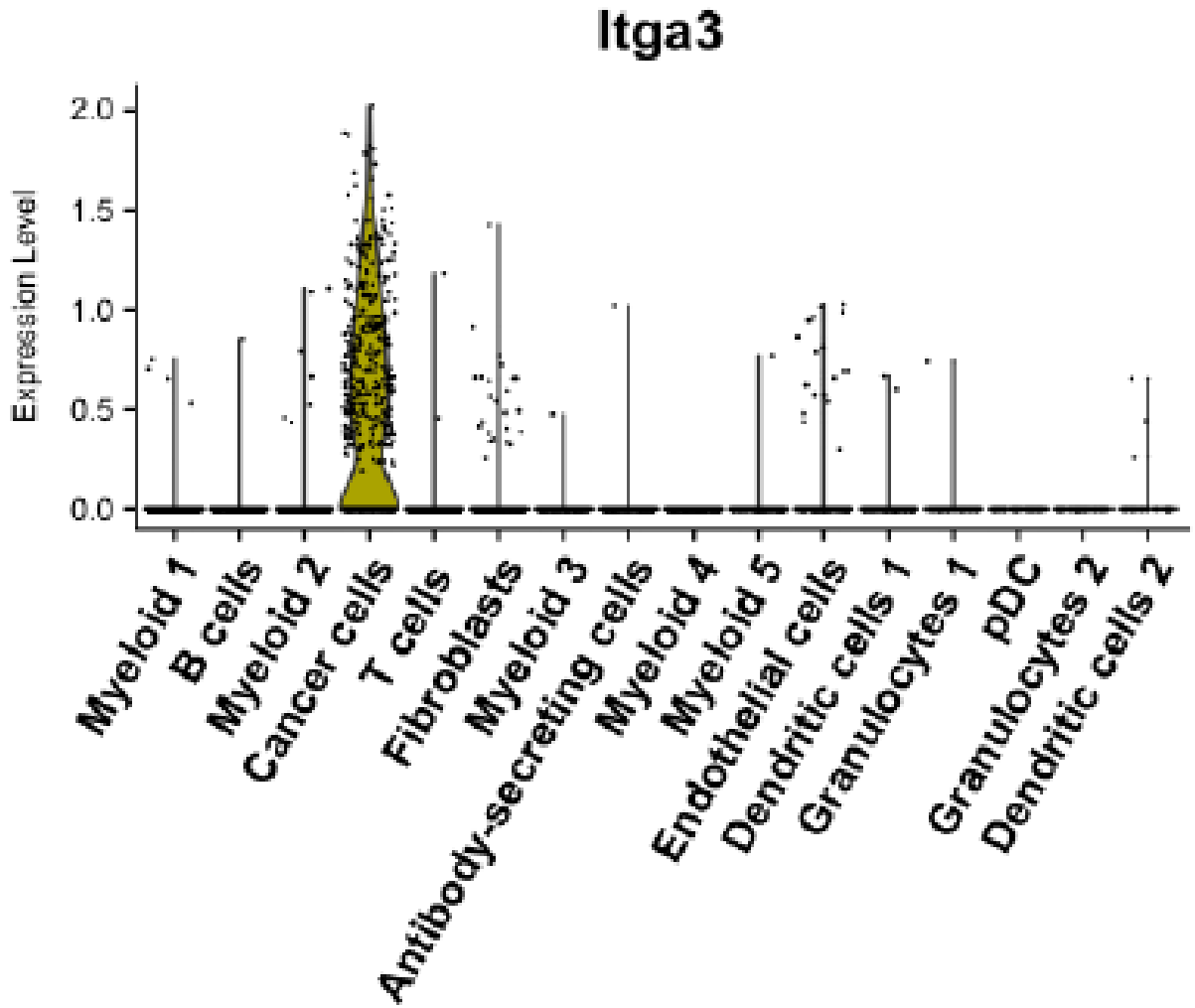


Huamin Wang

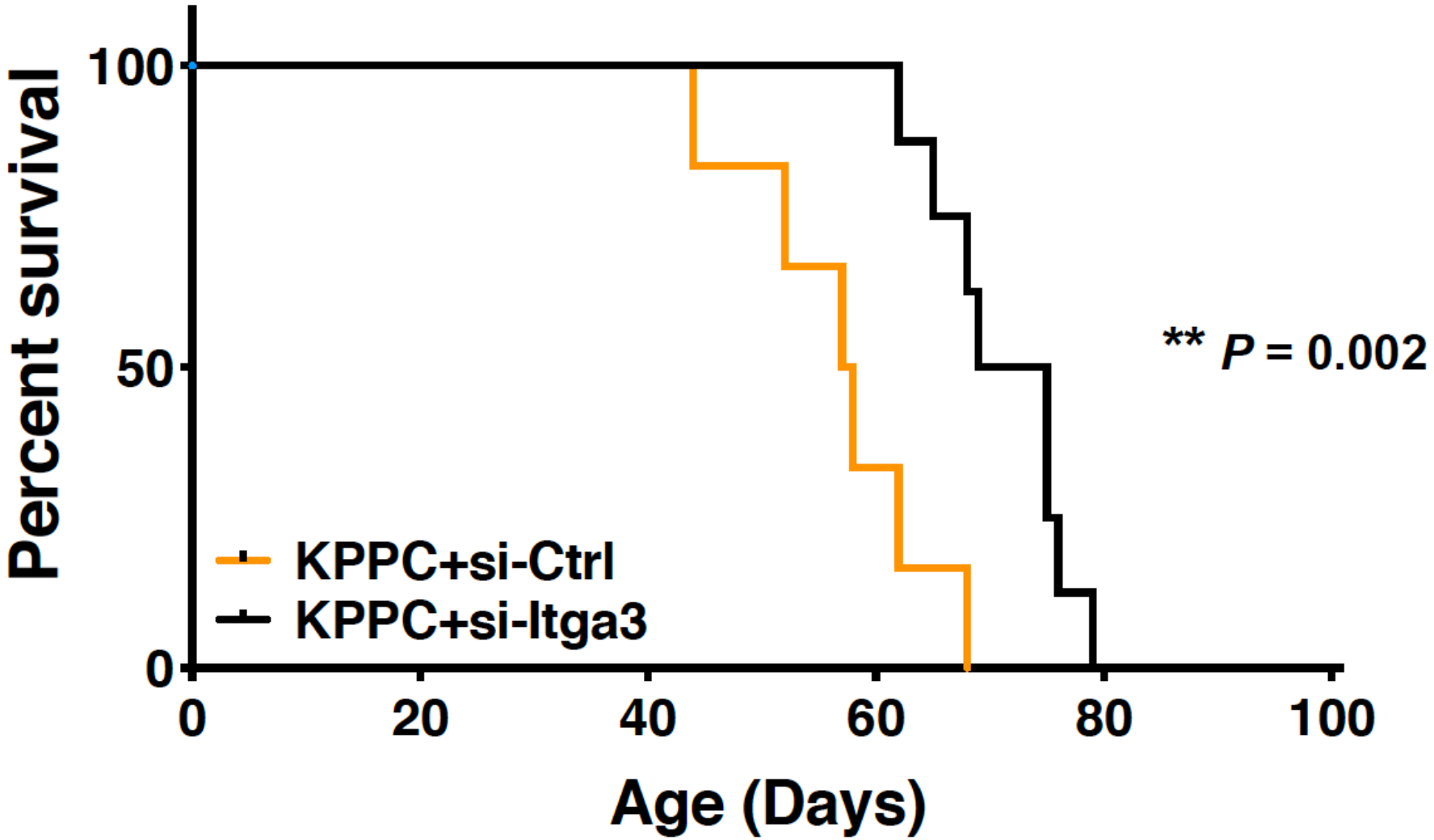
Inhibition of α3(β1) integrin leads to suppression of PDAC cell proliferation



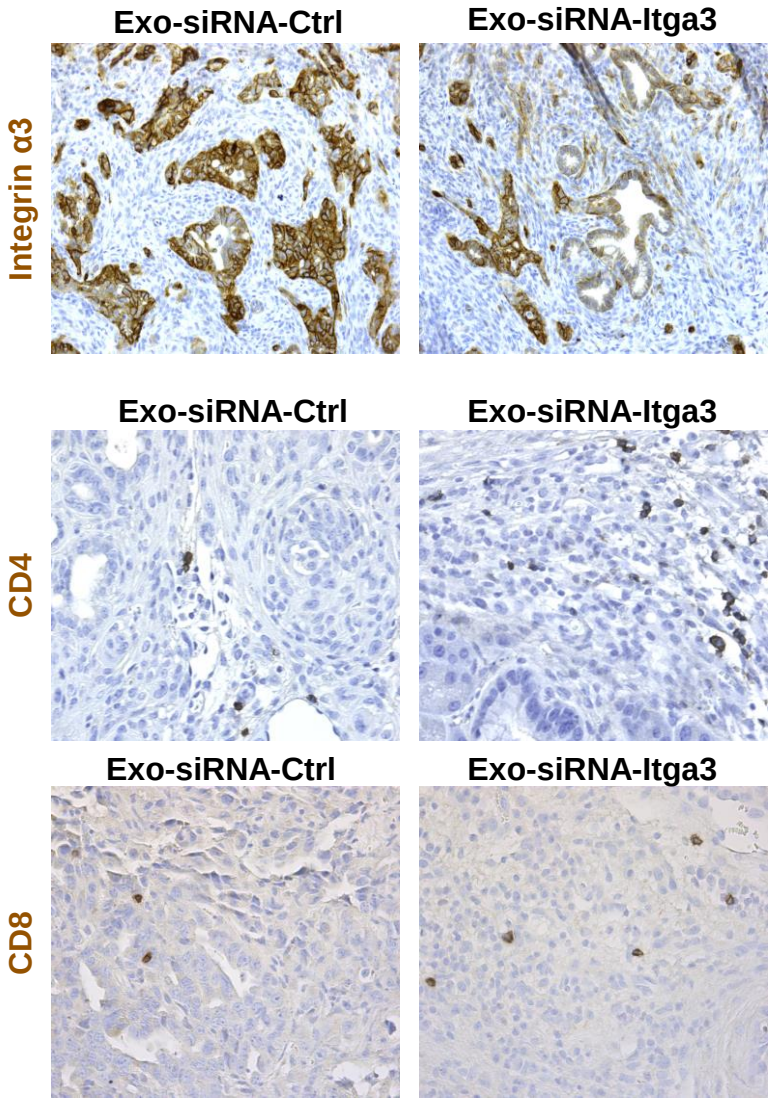
Predominant expression of integrin α3 in PDAC

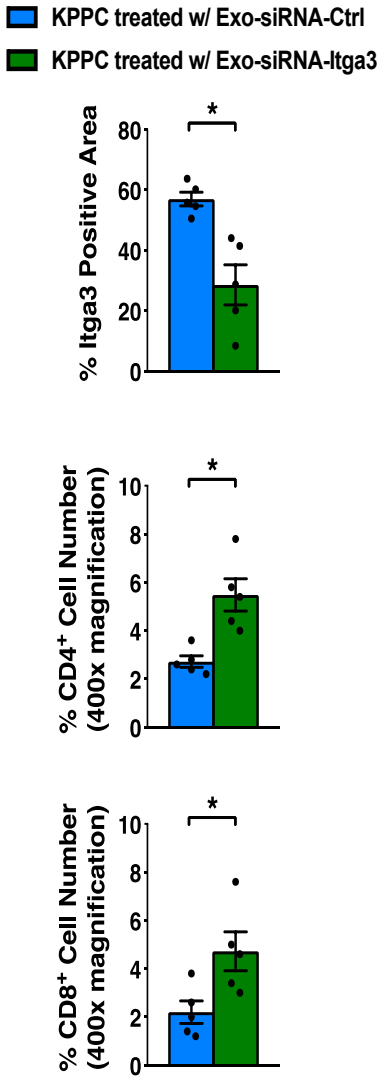


Inhibition of α3(β1) integrin employing iExosomes$^{si\alpha3int}$ leads to suppression of KPPC PDAC

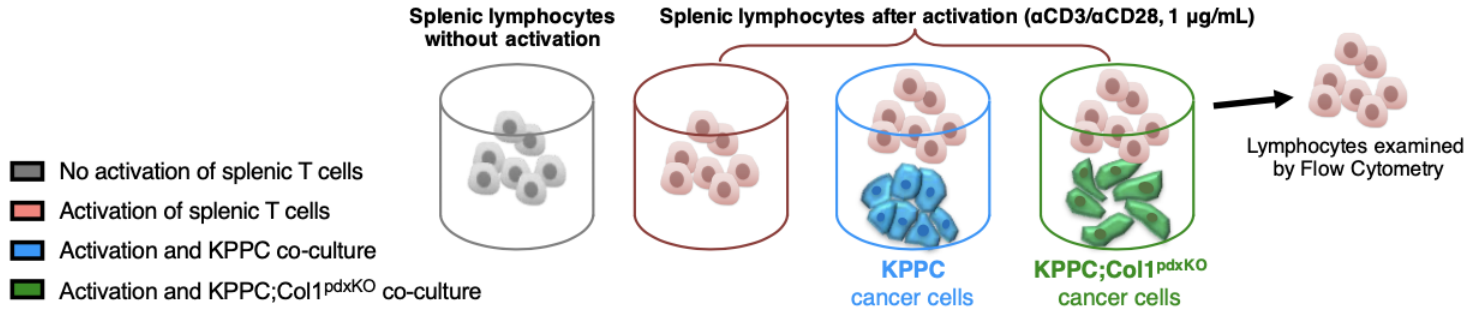


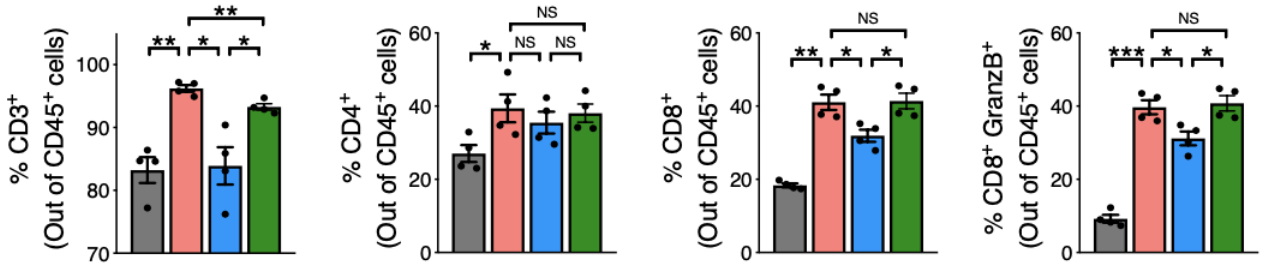
Inhibition of α3(β1) integrin results in increased CD4 and CD8 cells in KPPC PDAC

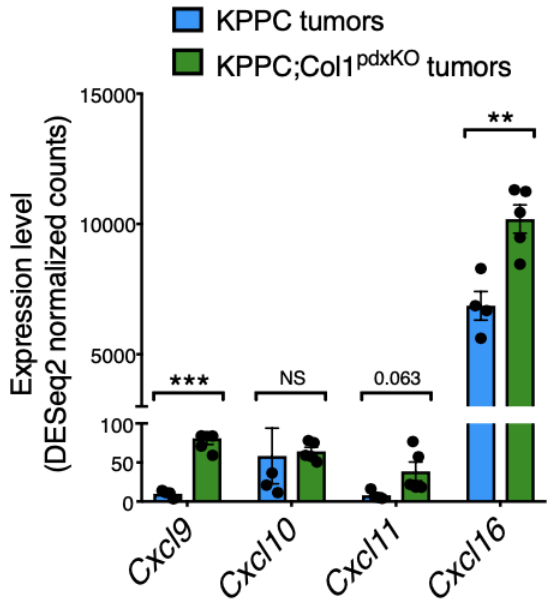


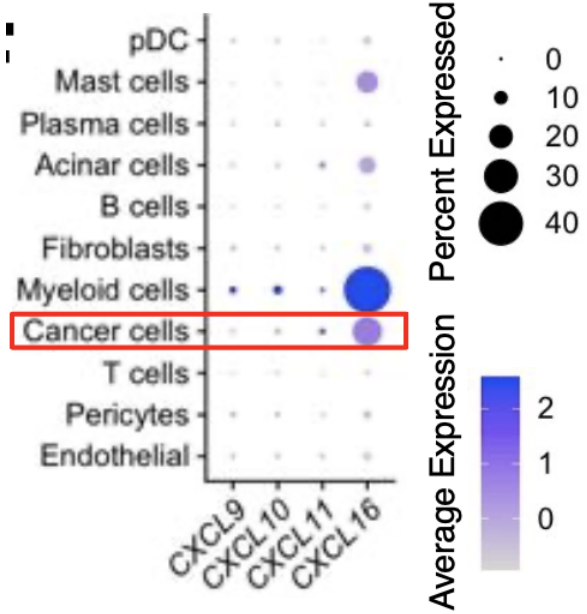


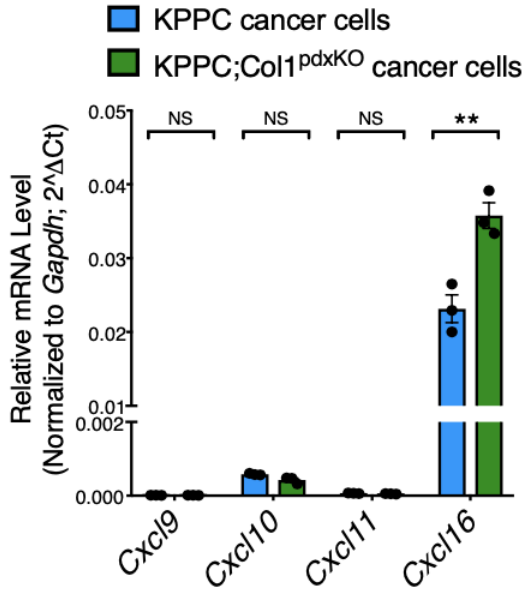
Cxcl16 mediates the recruitment of CD8^{+}GranzB^{+} T cells upon deletion of Col1 homotrimers

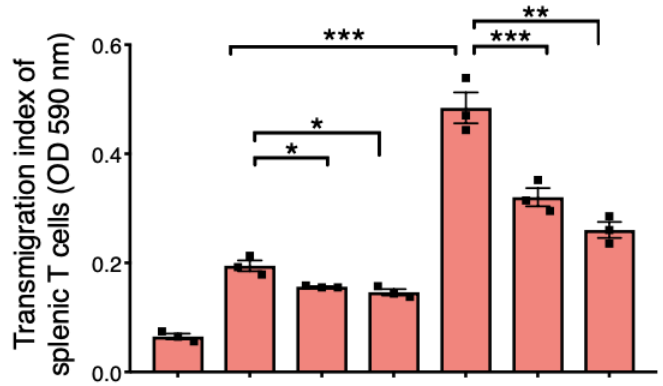






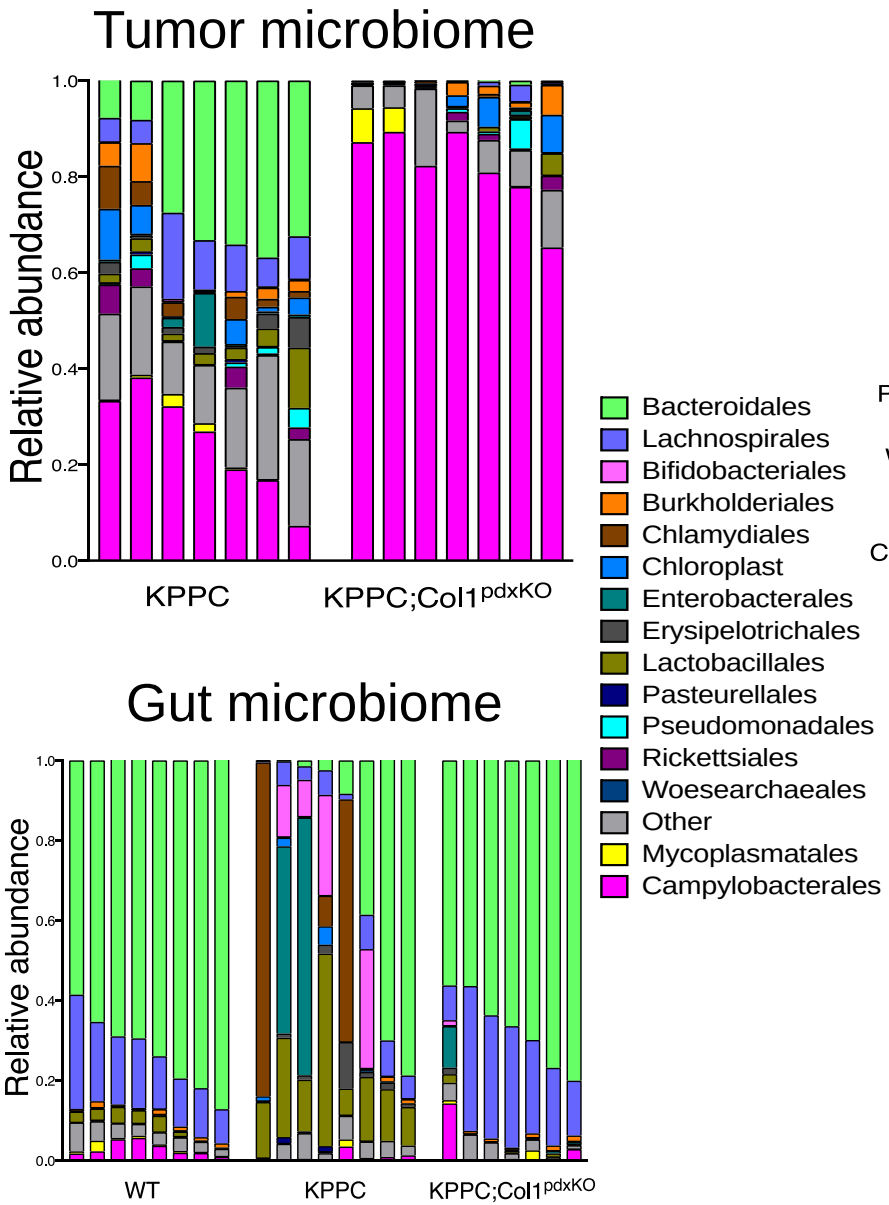


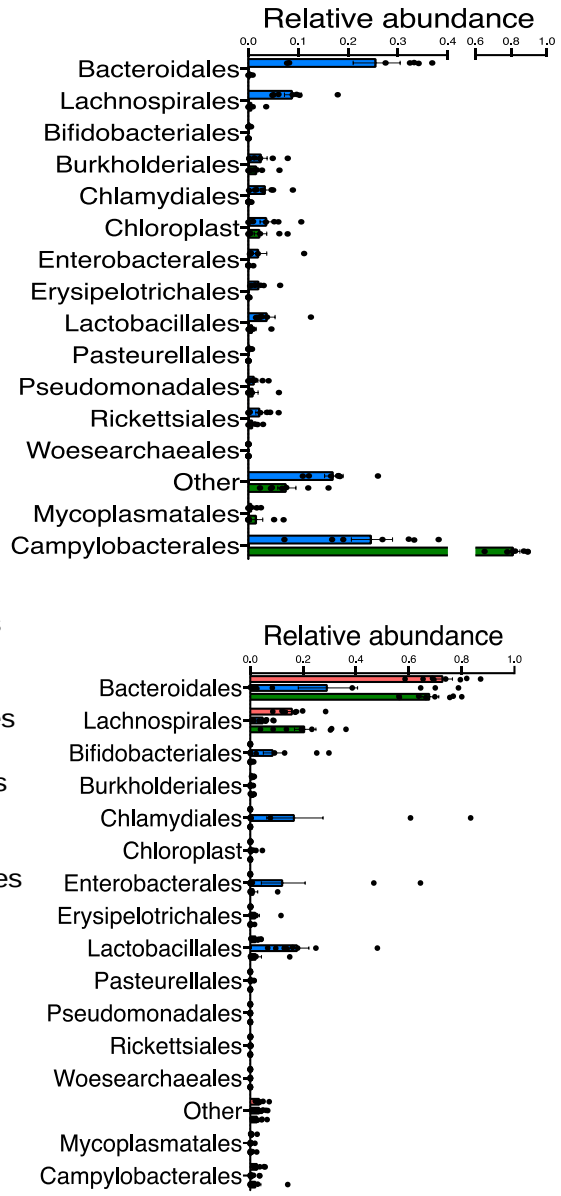


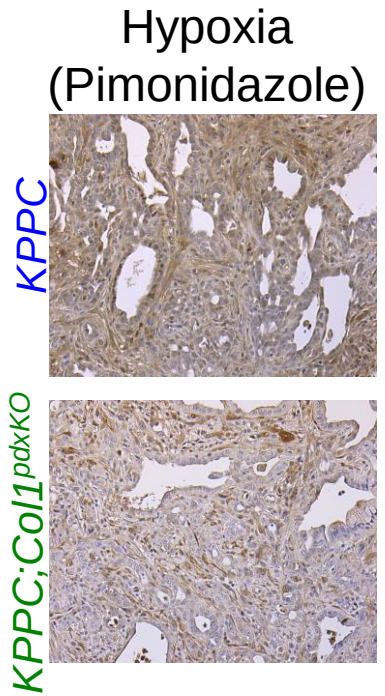


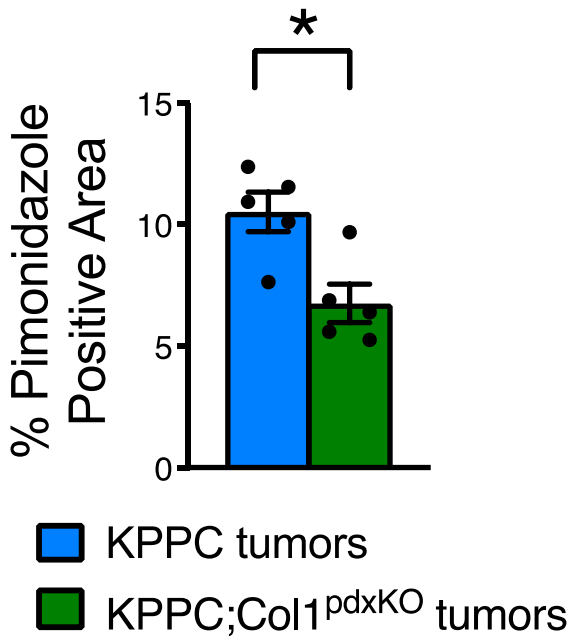
KPPC cancer cell conditioned medium	No	Yes	Yes	Yes	No	No	No
KPPC;Col1pdxKO cancer cell conditioned medium	No	No	No	No	Yes	Yes	Yes
Anti mouse CXCL16 neutralizing antibody (μg/mL)	No	No	10	30	No	10	30

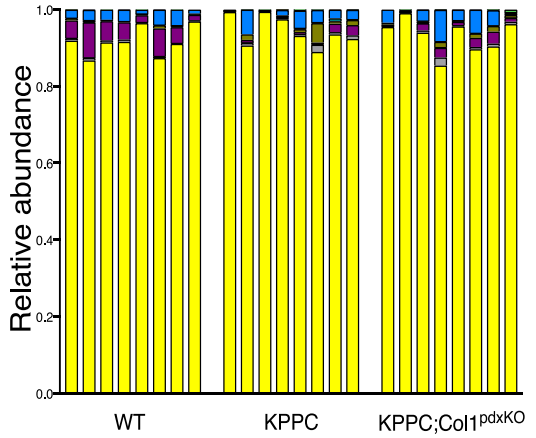
Col1 homotrimers recruit a unique tumor microbiome



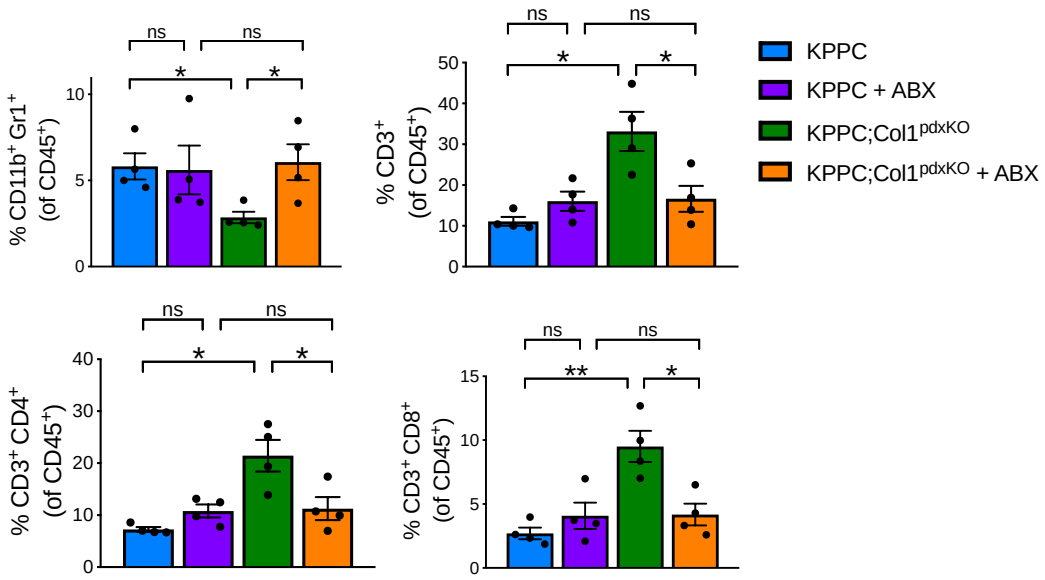


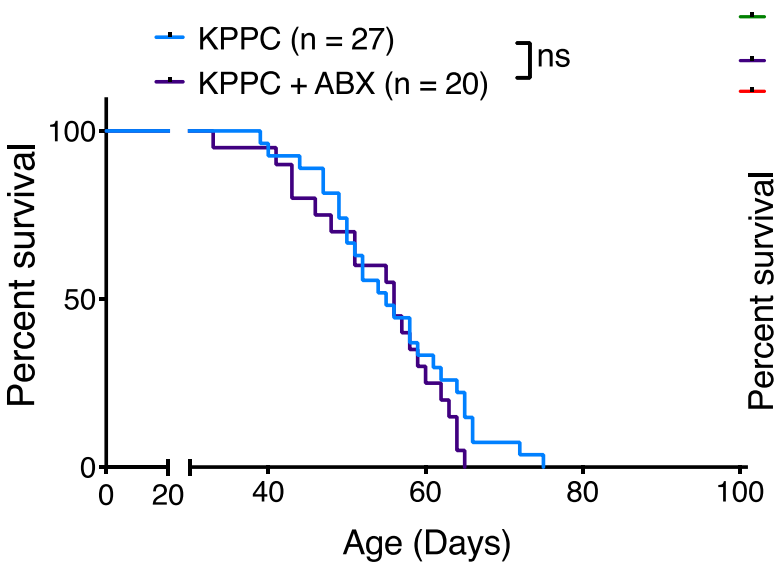


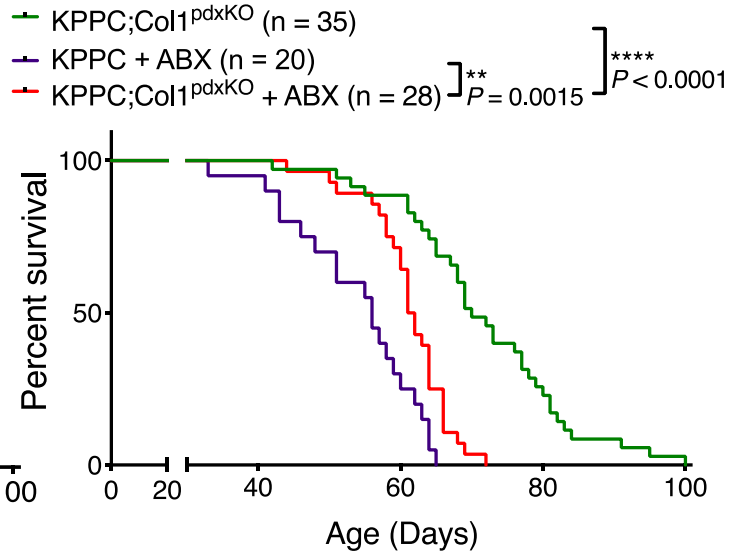




Col1 homotrimers recruit a unique tumor microbiome

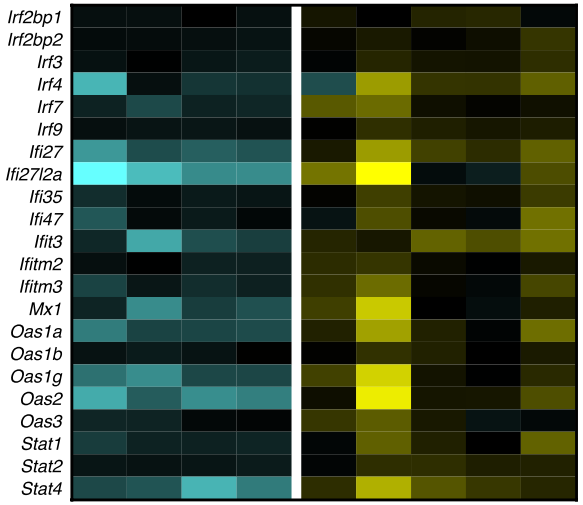




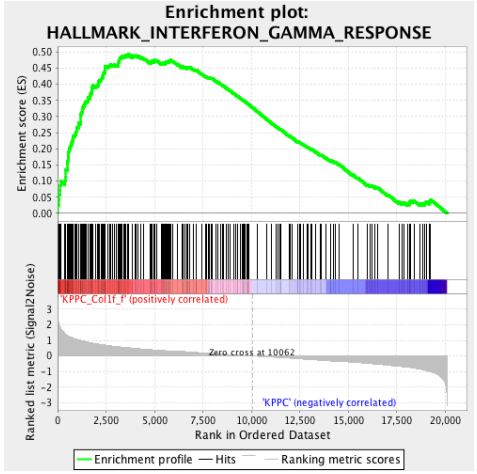


KPPC tumors

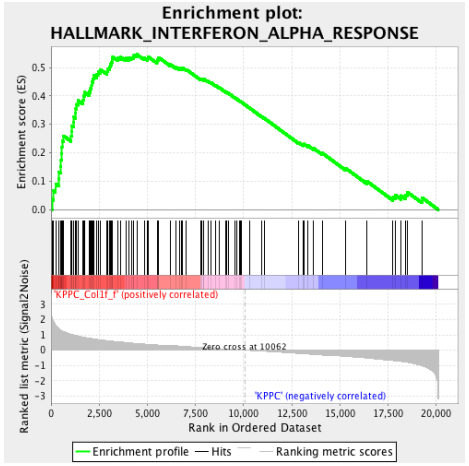
KPPC;Col1^{pdxKO} tumors



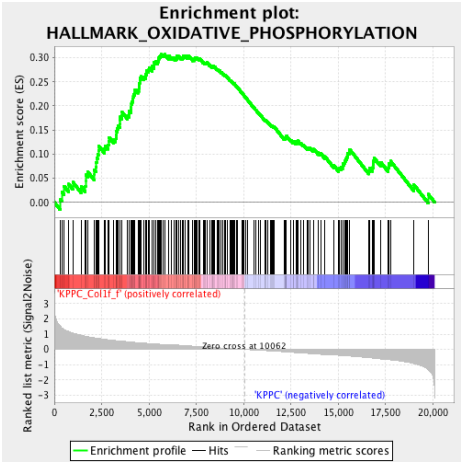
Interferon-γ response



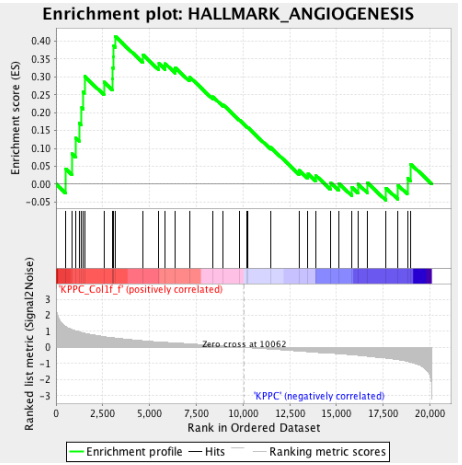
Interferon-α response



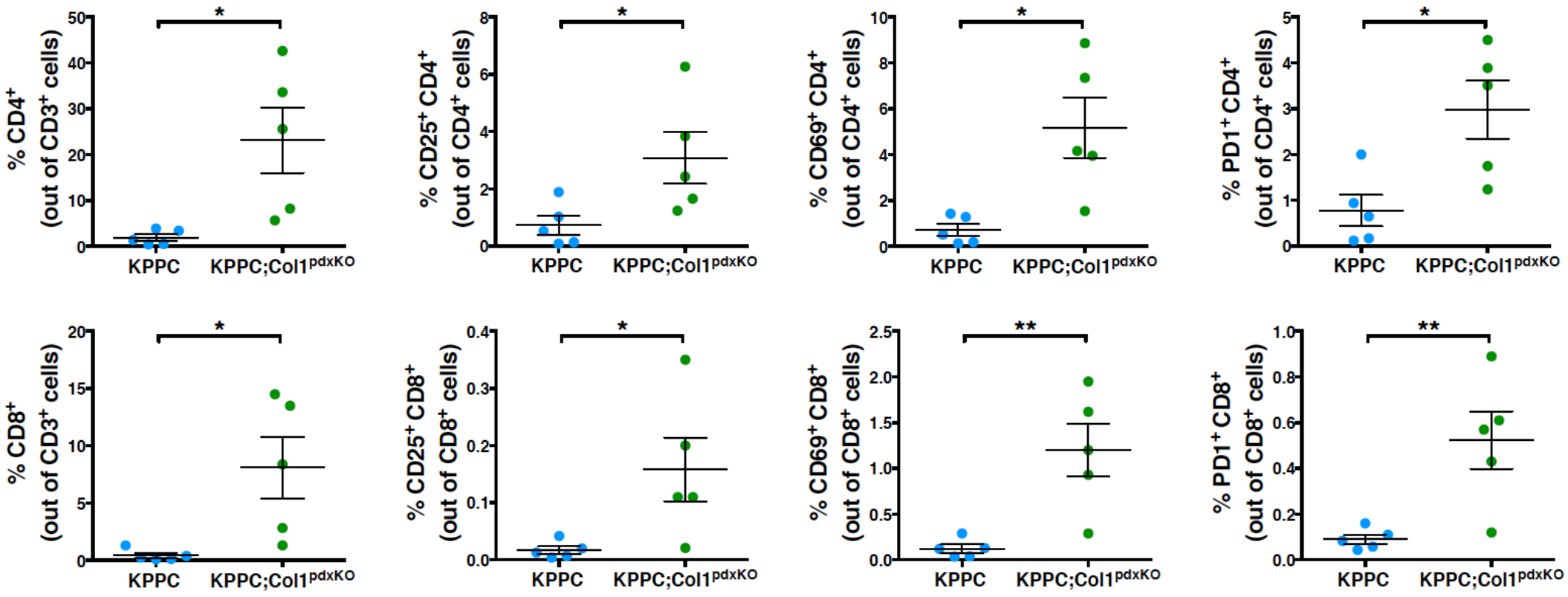
OXPHOS



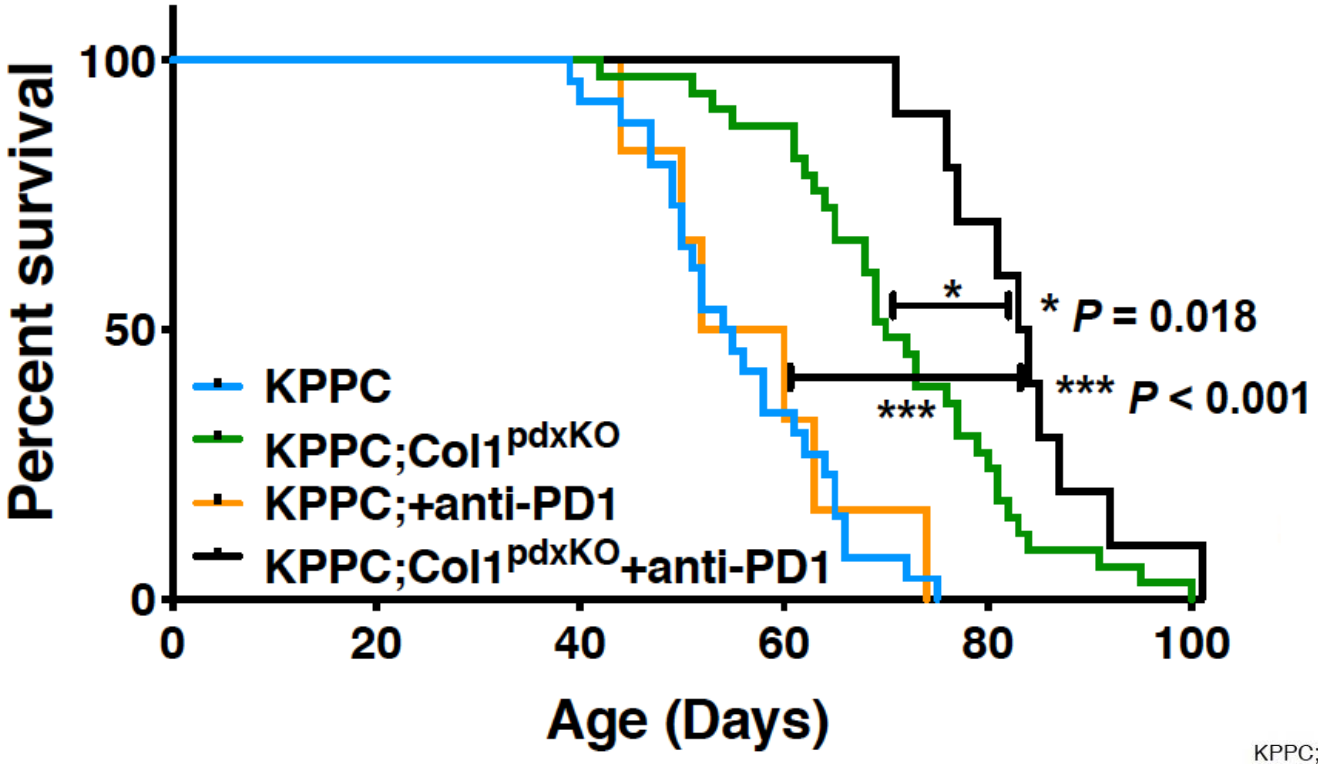
Angiogenesis

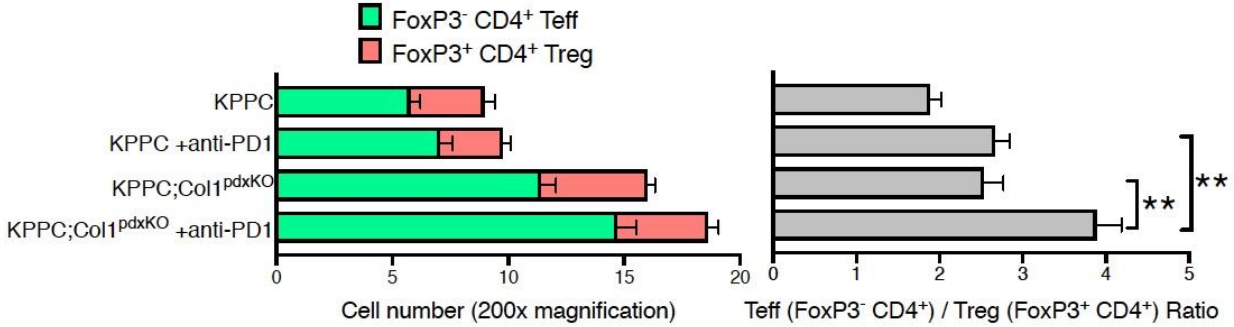


Col1 deletion in cancer cells is associated with an increase in CD8^{+}/PD-1^{+} cells

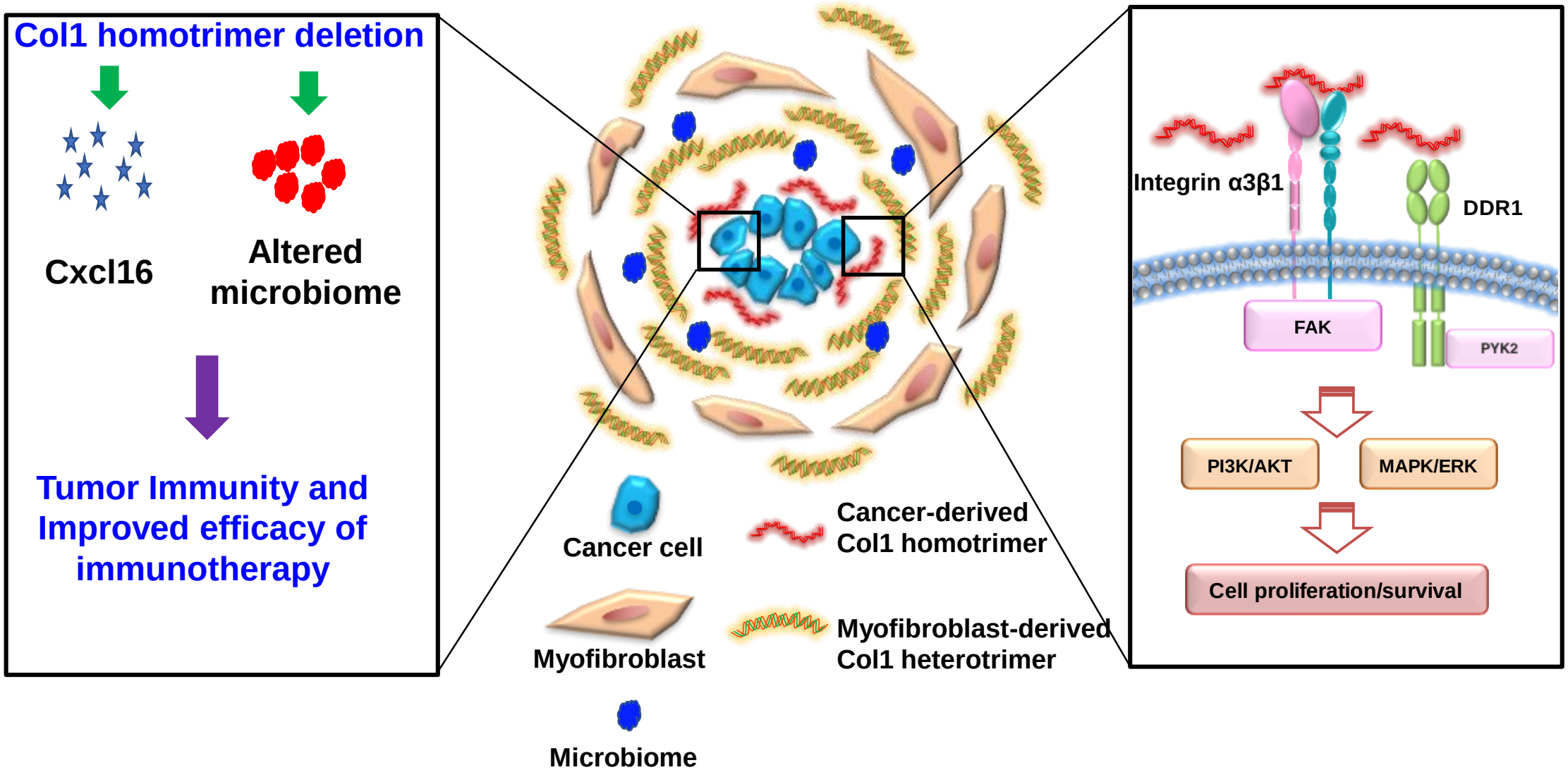


Anti-PD-1 treatment further increases the overall survival of the KPPC mice with Col1 deletion in cancer cells





Col1 homotrimers induce pro-survival signals in and impacts tumor microbiome and immunity in PDAC



Summary

Fibroblasts are a heterogeneous population in PDAC with tumor restraining and tumor promoting properties with an impact on tumor immunity

An oncogenic variant of type I collagen (α1-homotrimers) is produced by the cancer cells due to hypermethylation of promoter of α2(I) chain and helps initiate and promote PDAC

Type I collagen homotrimers contribute to altered tumor microbiome and immune suppression in PDAC

Lab Members and Collaborators

Yang Chen
Kate McAndrews
Jiha Kim
Sujuan Yang
Kebbeh Darpolor
Xiaofeng Zhang
Hikaru Sugimoto
Jena Tavormina
Julie Carsten
Krishnan Mahadevan

Valerie LeBleu
Chia-Chin (Per) Wu
Michael Kim
Huamin Wang
Michael Zeisberg
Deiter Saur
Jim Allison

Funding: NCI, CPRIT, MDACC


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
South Campus
Research Building 3