Biomaterials: basic biology
Reconstruction after tumor resection and modeling the tumor microenvironment

J H Elisseeff
Morton Goldberg Professor

SITC Session 306
Engineering Immunity
November 2020

@JHElisseeff

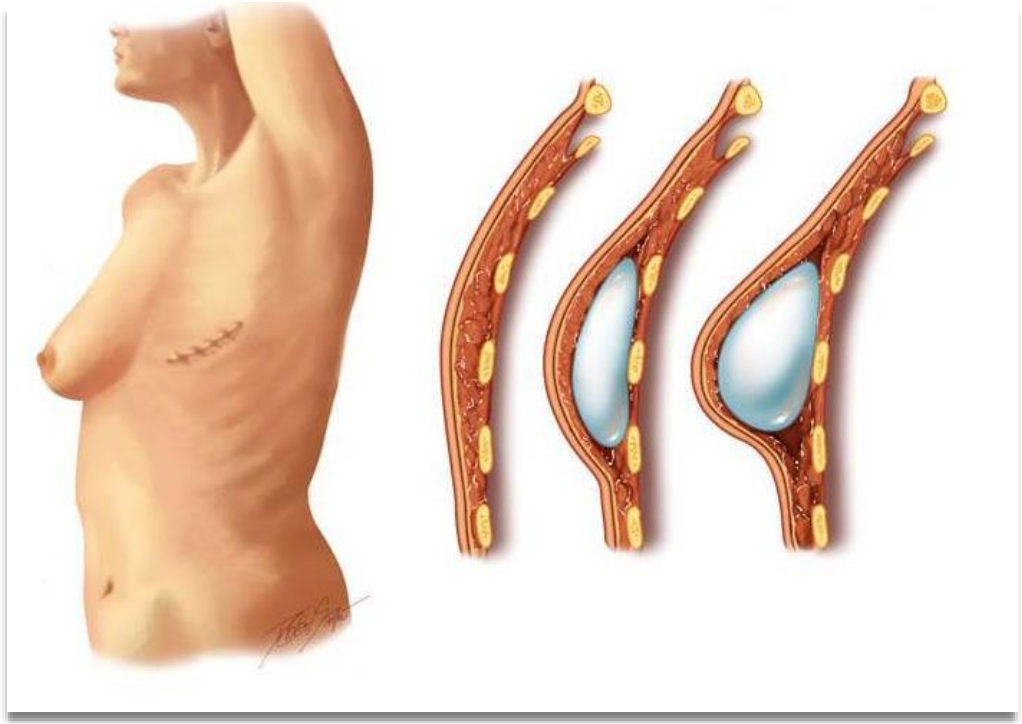
Disclosures

- Founder, Aegeria Soft Tissue
- Former consultant/SAB, Unity Biotechnology and Acell Inc
- Research Funding from BMS and Allergan

BIOMATERIALS FOR RECONSTRUCTION

Rebuilding tissue after tumor resection

SYNTHETIC IMPLANTS

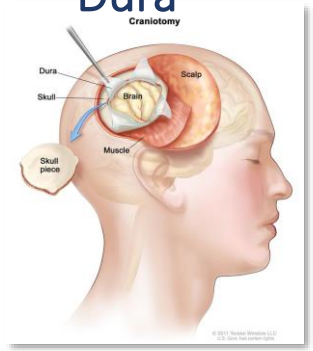


BIOLOGICAL SCAFFOLDS

Breast

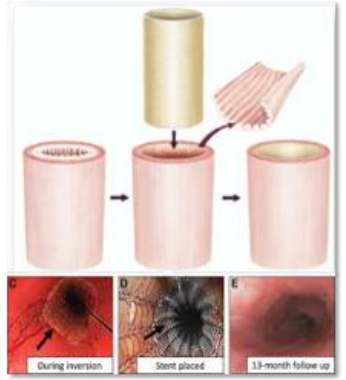
AlloDerm™
Permacol™

Dura



Biodesign® Dural Graft
Durepair™

Esophagus

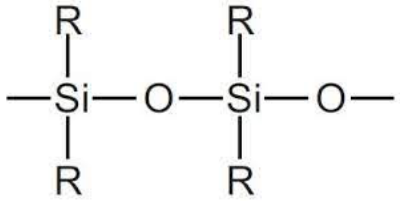


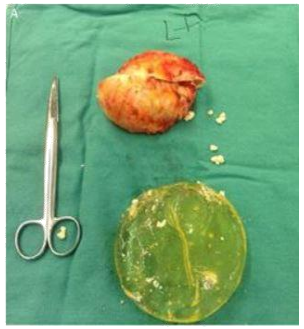
Surgisis®

SYNTHETIC AND BIOLOGICAL MATERIALS

Replacing physical structure versus re-growing tissue

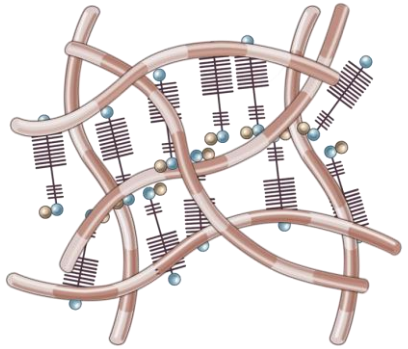
SYNTHETIC

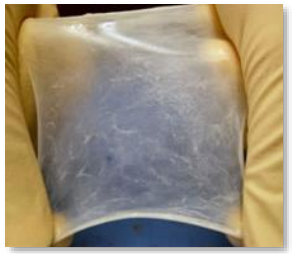




Synthetic implants induce a foreign body response (fibrotic capsule)

BIOLOGICAL

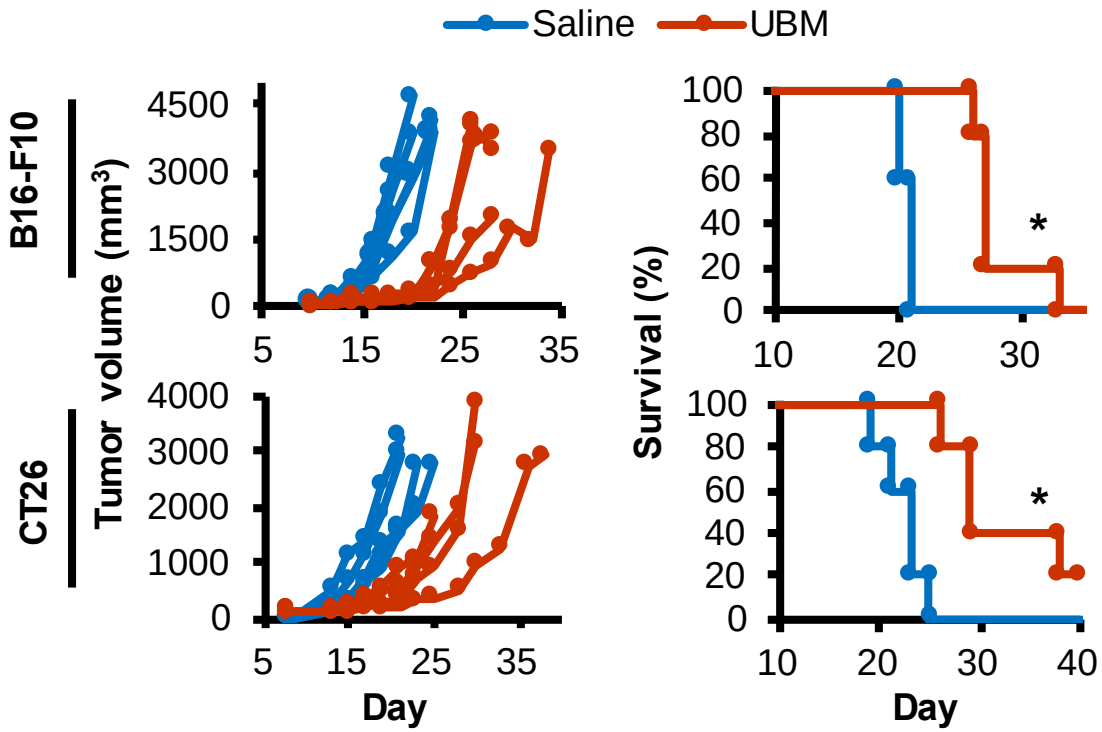


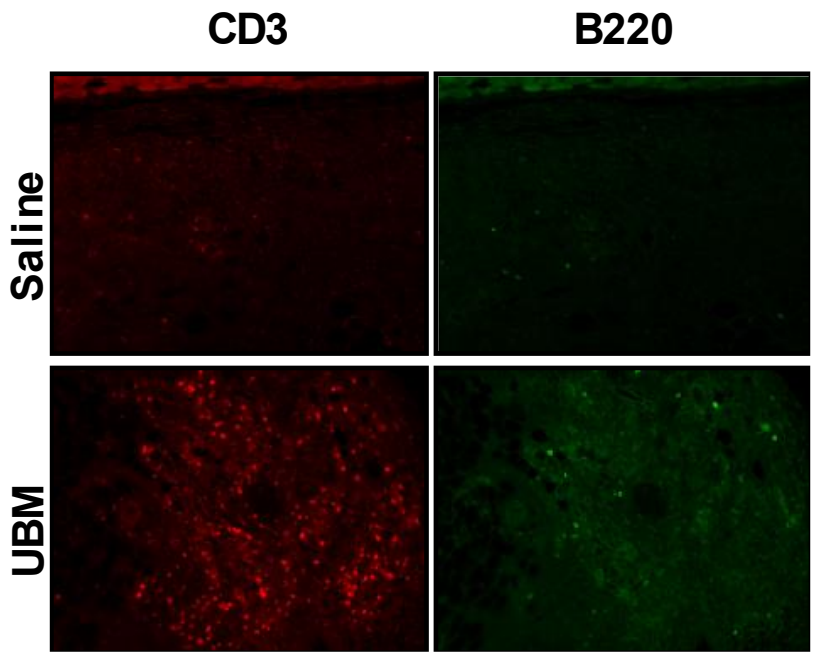


Do biological scaffolds that support tissue repair promote tumor growth?

Biological scaffold co-implantation with tumor cells

Replacing physical structure versus re-growing tissue





Wolf, et al, *Science Translational Medicine,* 2019

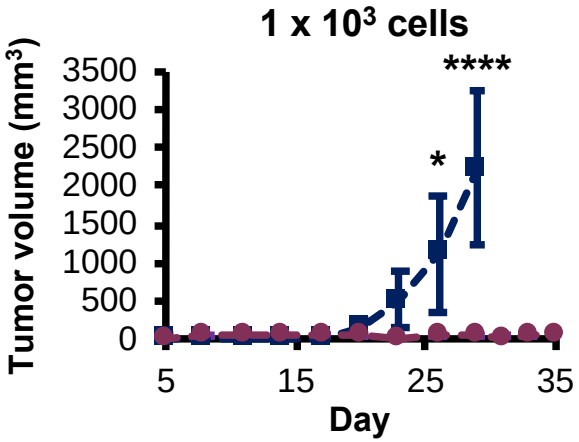
Biological scaffolds reduce tumor growth

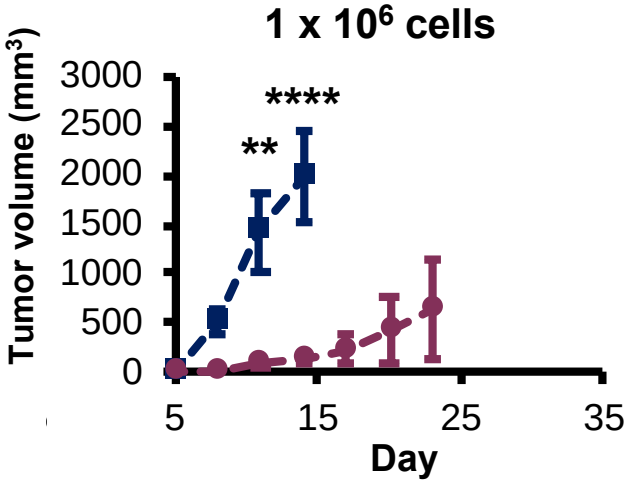
Biological scaffolds synergize with checkpoint blockade

T_H2/M2 with biomaterials differs from tumor

Saline + αPD-1

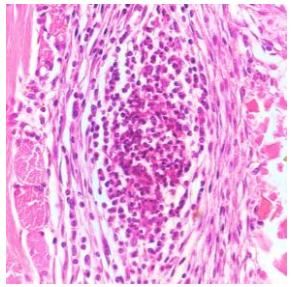
UBM + αPD-1



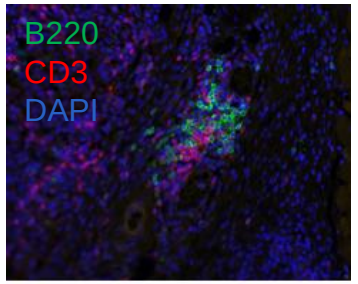


Lymphoid aggregates

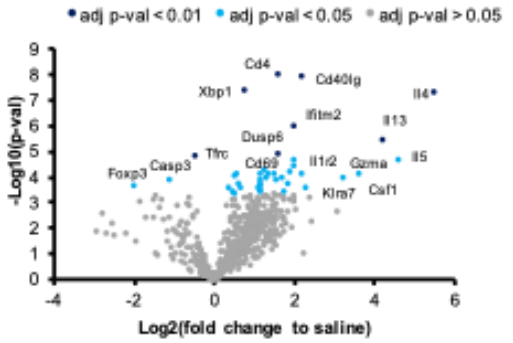
SubQ ECM



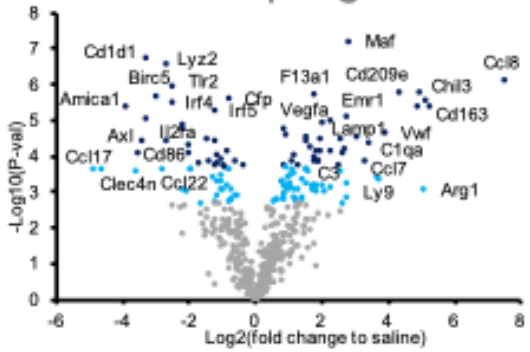
Tumor ECM

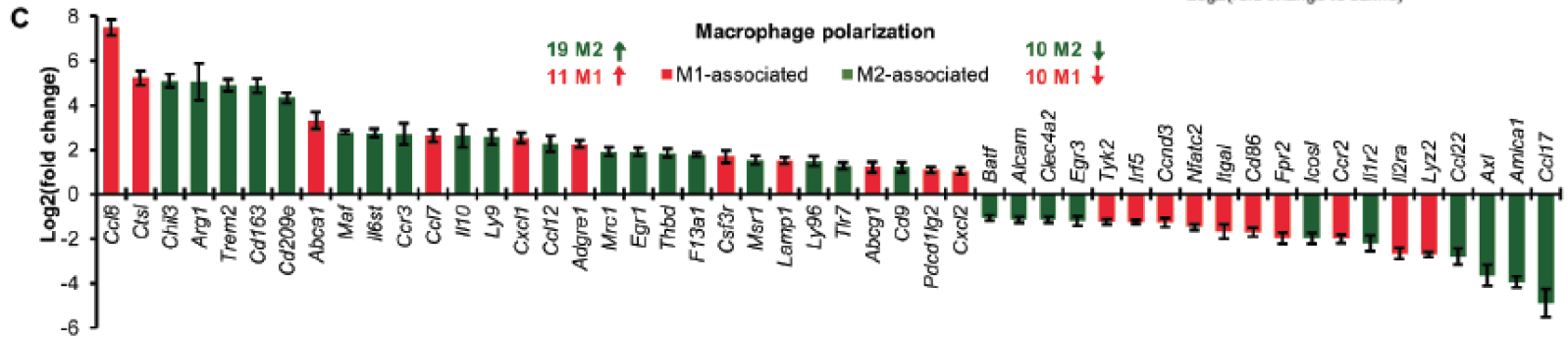


T cells



Macrophages





The NEW ENGLAND JOURNAL of MEDICINE
SEMINARS IN MEDICINE OF THE BETH ISRAEL HOSPITAL, BOSTON ARCHIVE
December 25, 1986
N Engl J Med 1986; 315:1650-1659
DOI: 10.1056/NEJM198612253152606

Tumors: Wounds That Do Not Heal

Masters of Immunology

Cancer Immunology Research 2015

Tumors: Wounds That Do Not Heal—Redux

Harold F. Dvorak

Abstract

Similarities between tumors and the inflammatory response associated with wound healing have been recognized for more than 150 y
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VEGF, I
heal. Mo
wound-he
maintena
plasma proteins; activation of the clotting system outside the vascular system; deposition of an extravascular fibrin gel that

REVIEW

Parallels
and solid

Alan Y. Wong[1]

147, dev181636

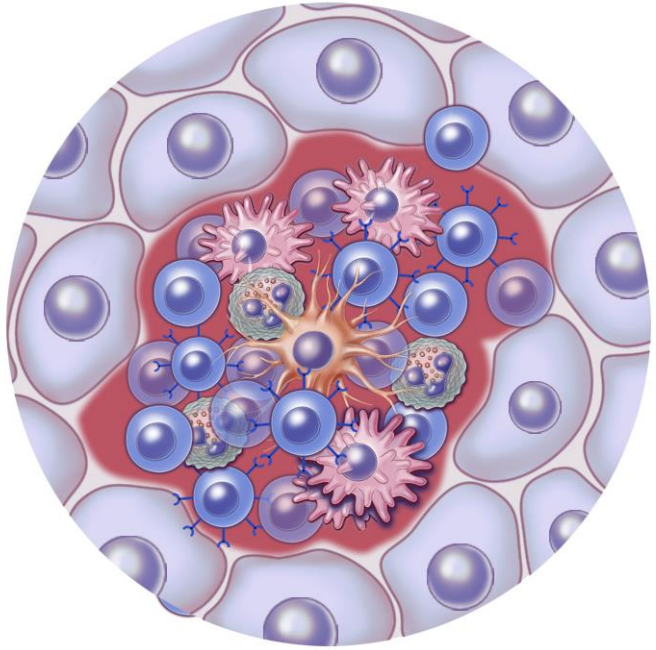
neration

ABSTRACT

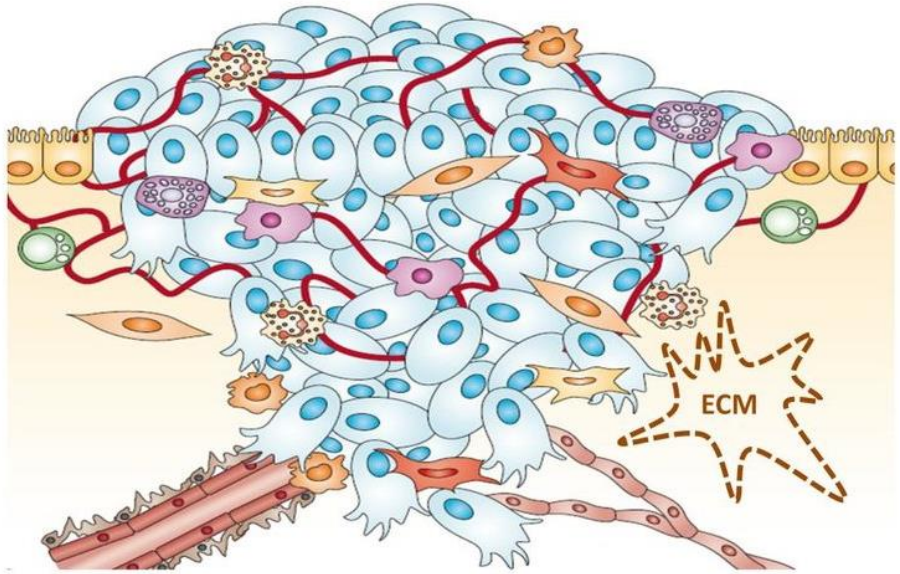
Striking similarities between wound healing, epimorphic regeneration and the progression of solid tumors have been uncovered by recent studies. In this Review, we discuss systemic effects of tumorigenesis that are now being appreciated in epimorphic regeneration, including genetic, cellular and metabolic heterogeneity, changes in circulating factors, and the complex roles of immune cells and immune modulation at systemic and local levels. We suggest that certain mechanisms ~~enabling regeneration~~ involved in healing/fibrosis may be co-opted by cancer to promote growth at primary and metastatic sites. Finally, we advocate that working with a unified approach could complement research in both fields.

BIOMATERIALS AS MODELS FOR THE TUMOR MICROENVIRONMENT

Wound microenvironment



Tumor microenvironment

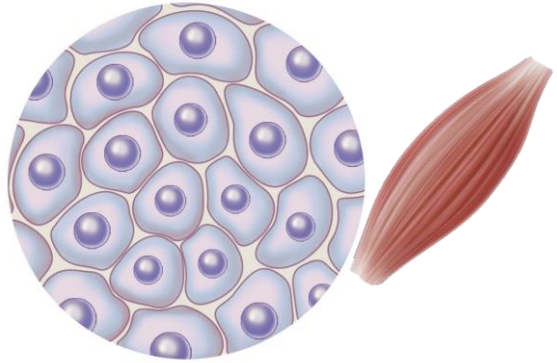


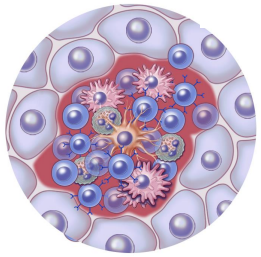
There is a continuum of wounds - from healing to non-healing - that are regulated by intrinsic and extrinsic factors that correlate with tumor properties

New discoveries in wound environment → implications for tumors and immunotherapy

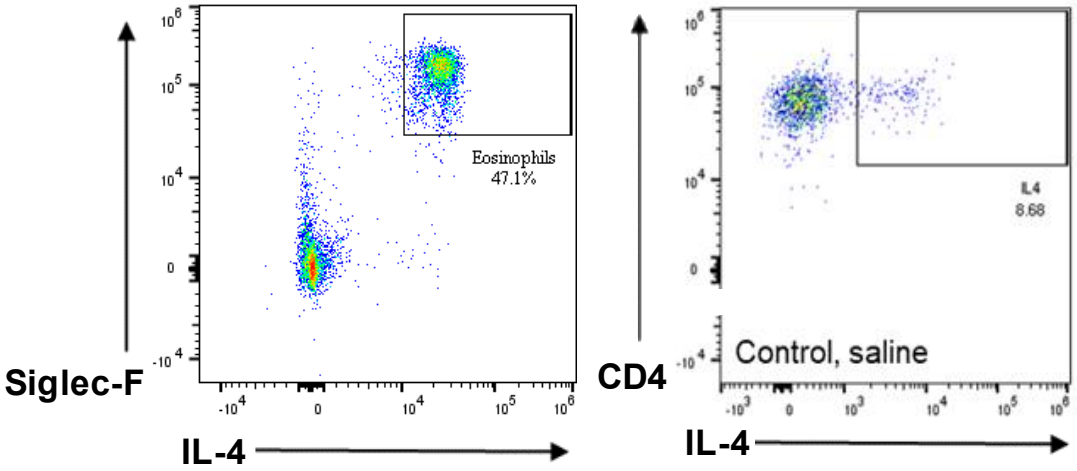
Healing wound

Inflammation→resolution





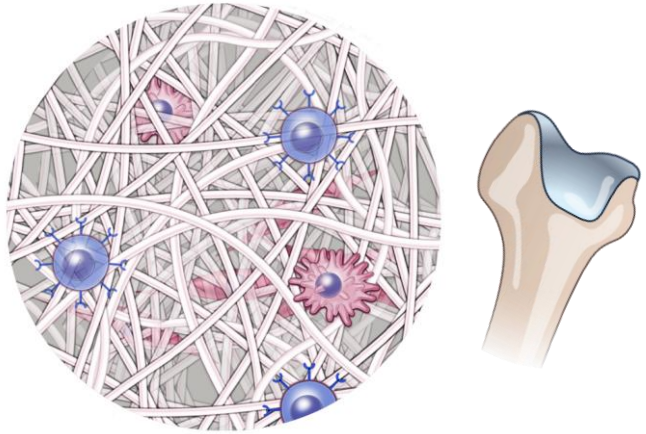
Muscle wound



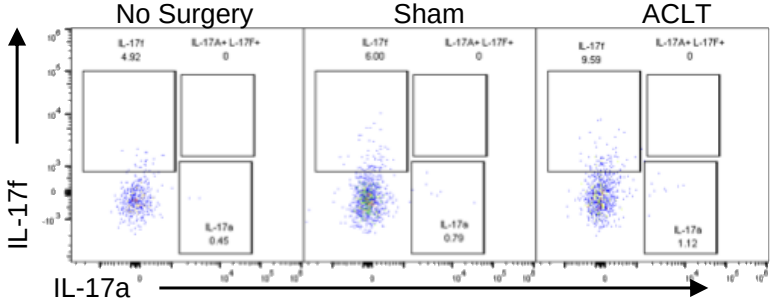
Articular joint /cartilage

Non-healing wound

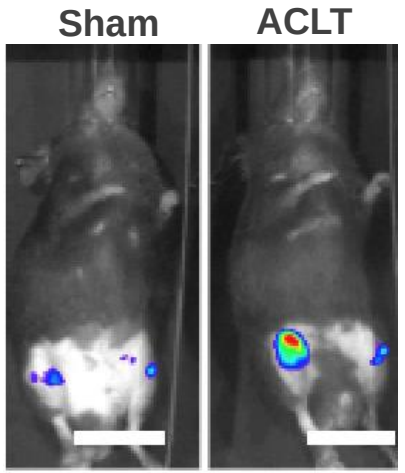
Fibrosis, chronic inflammation



CD4⁺ T cells



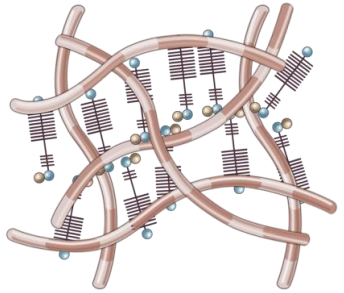
p16^{INK4a} cells (Senescence)

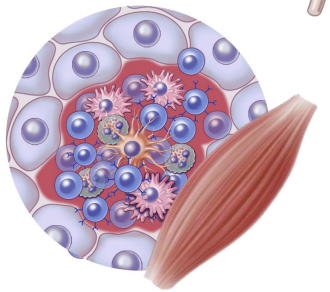


MODELS OF HEALING AND NON-HEALING TISSUE ENVIRONMENTS

Different biomaterials create unique immune and tissue environments

BIOLOGICAL





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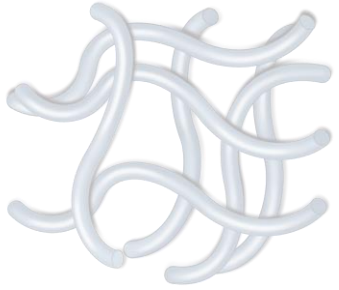
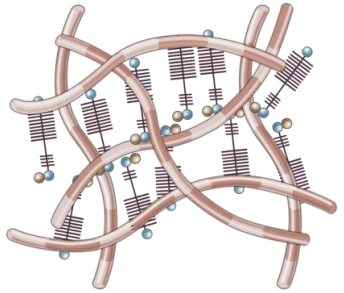
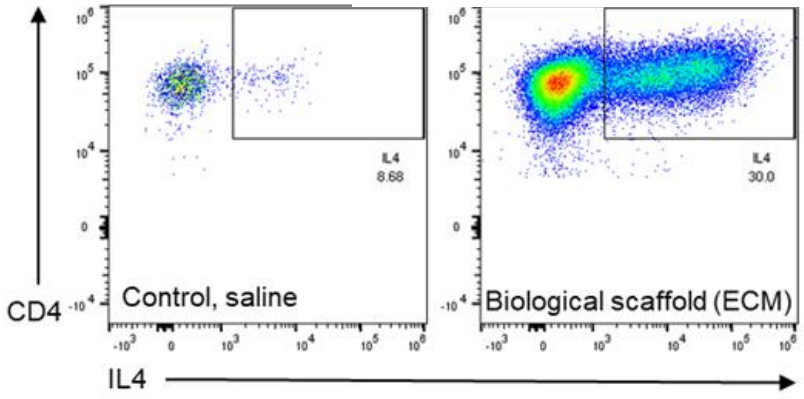


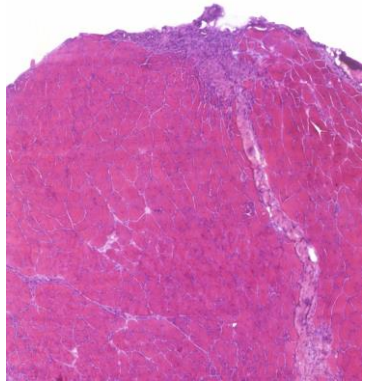
MODELS OF HEALING AND NON-HEALING TISSUE ENVIRONMENTS

BIOLOGICAL

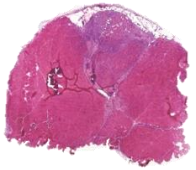


T cells



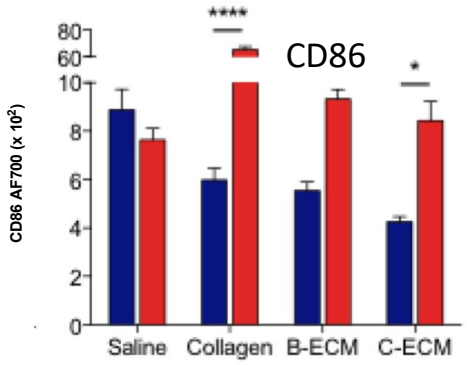


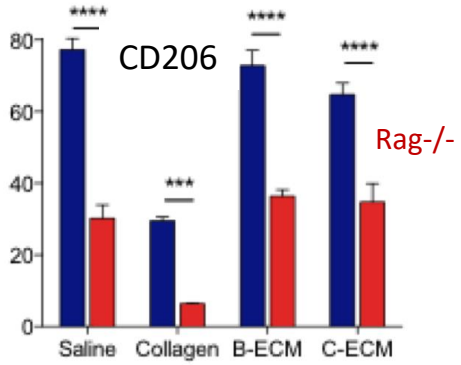
Material



No Treatment

Macrophages

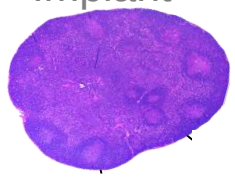




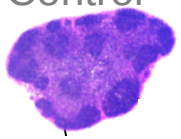
Rag-/-

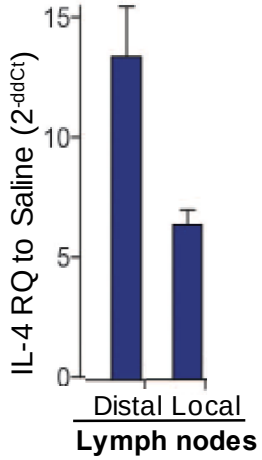
Systemic Changes

Implant



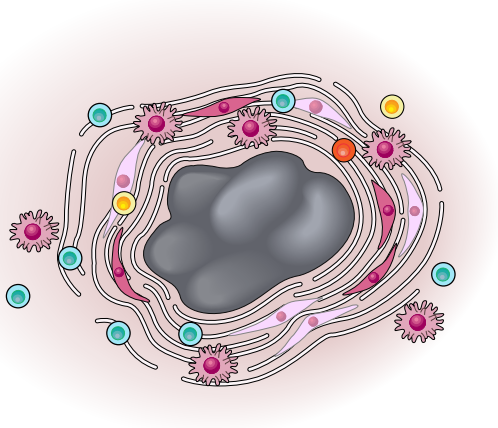
Control



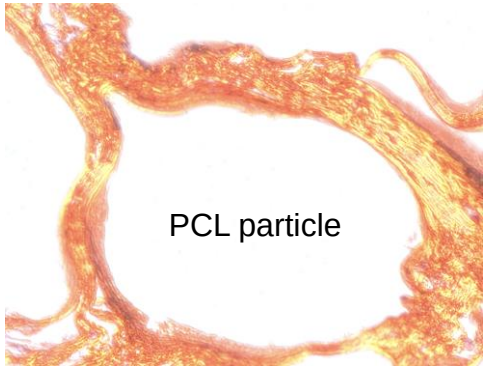


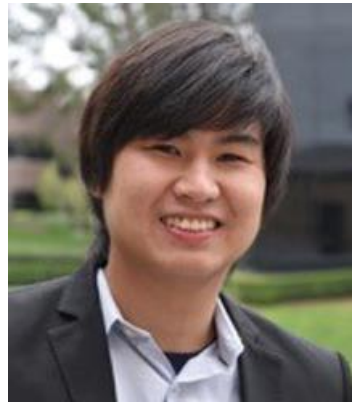
Sadtler et al., *Science*, 2016

MODELS OF HEALING AND NON-HEALING TISSUE ENVIRONMENTS

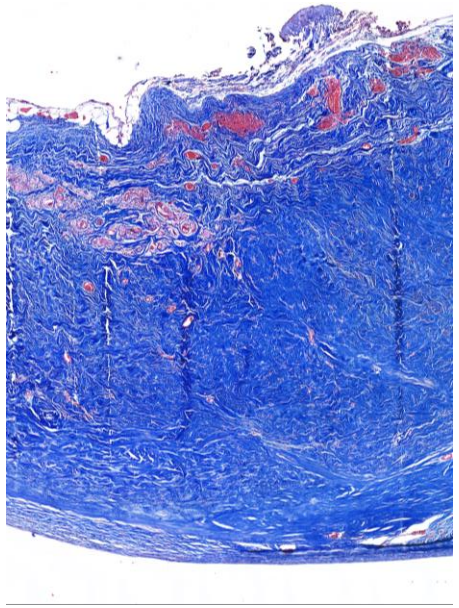


Fibrosis Picrosirius Red

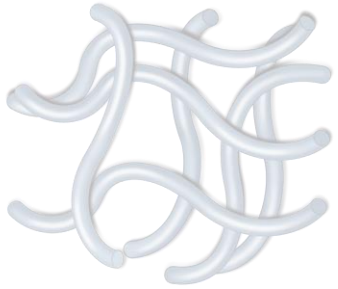


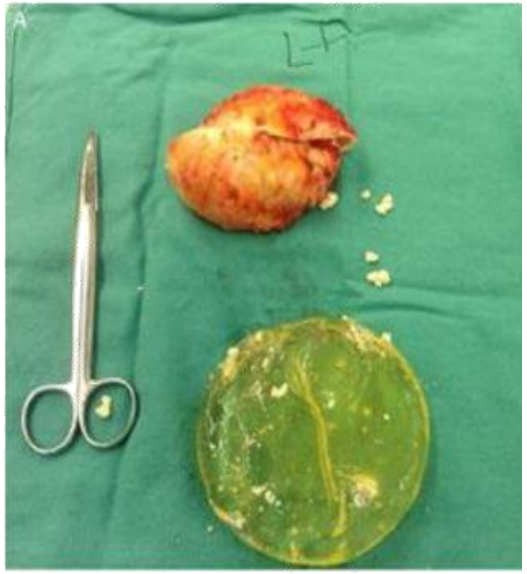


Breast implant Fibrosis



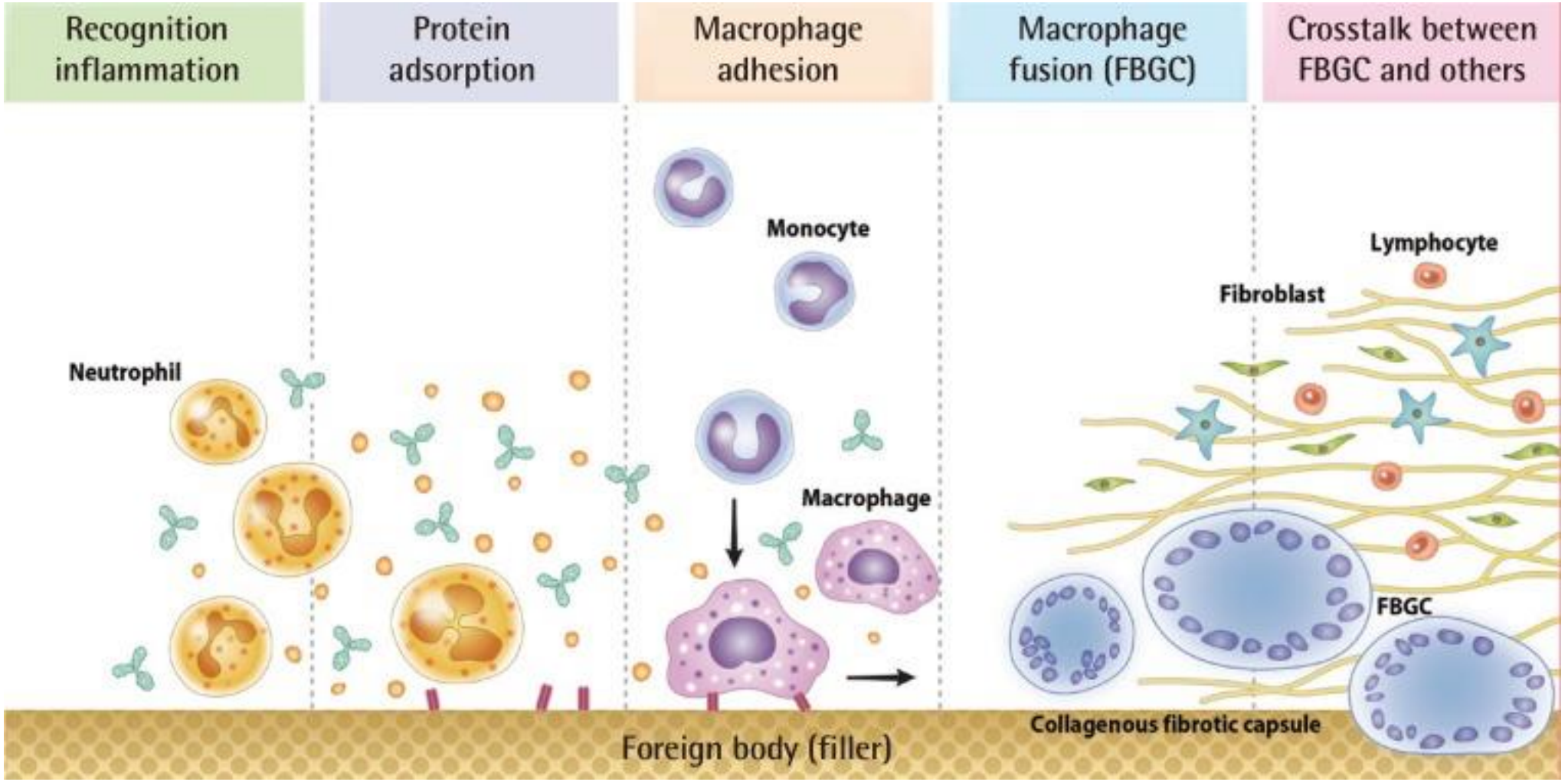
SYNTHETIC





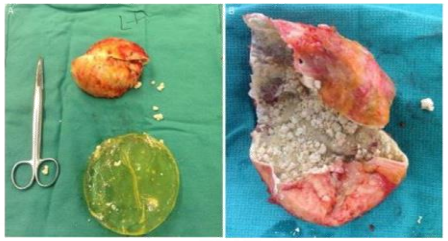
Chung, et al, *Science Translational Medicine,* 2020

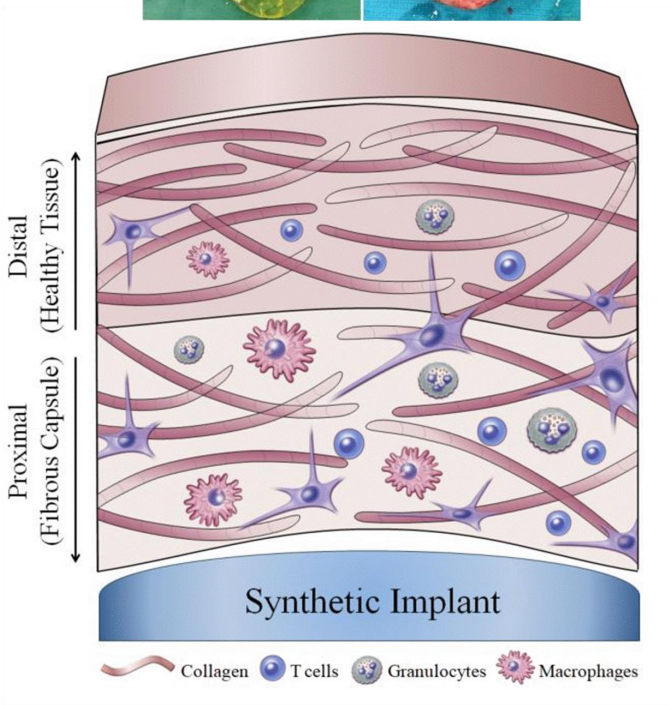
THE IMMUNE RESPONSE TO SYNTHETIC MATERIALS

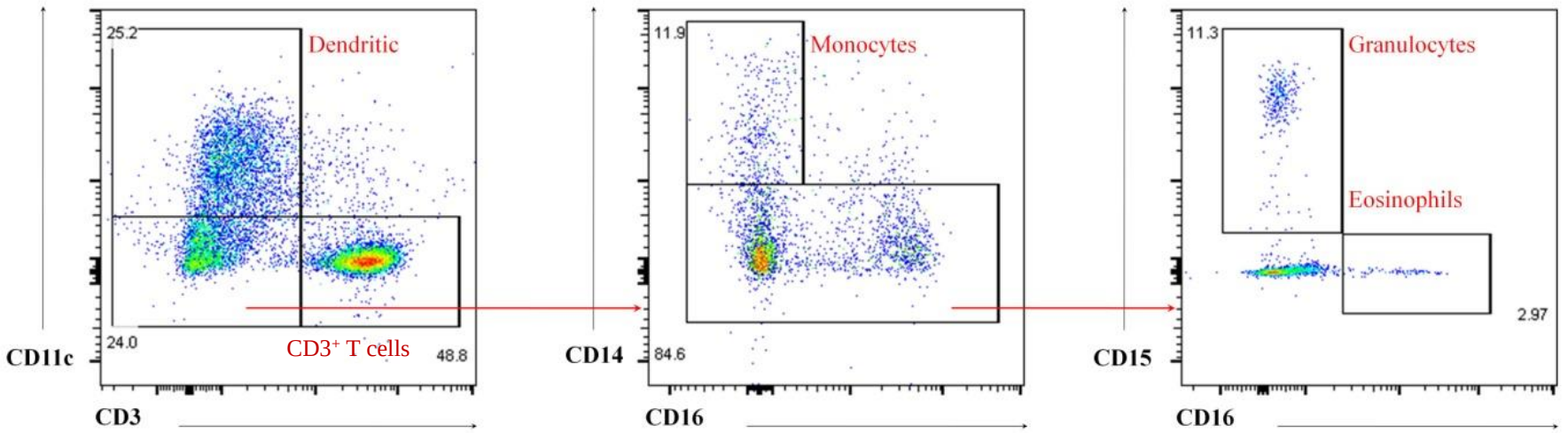


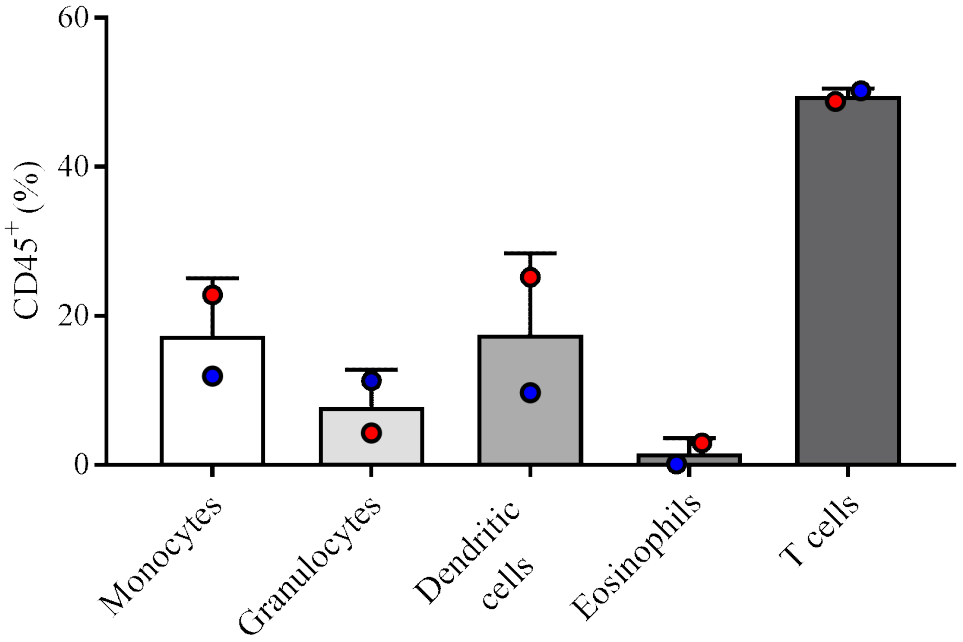
Lee et al, Archives of Plastic Surgery

THE SYNTHETIC IMPLANT RESPONSE



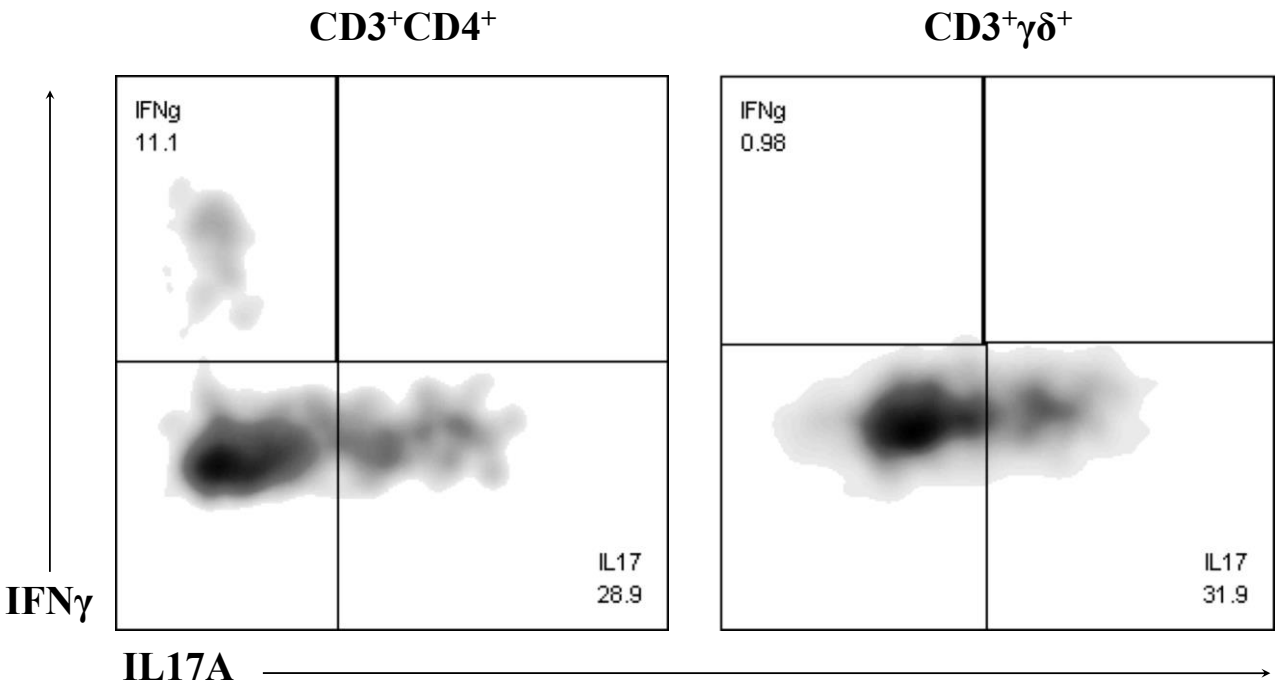






Chung et al., Elisseeff, *Science Translational Medicine,* April 2020.

T CELL RESPONSE TO BREAST IMPLANTS

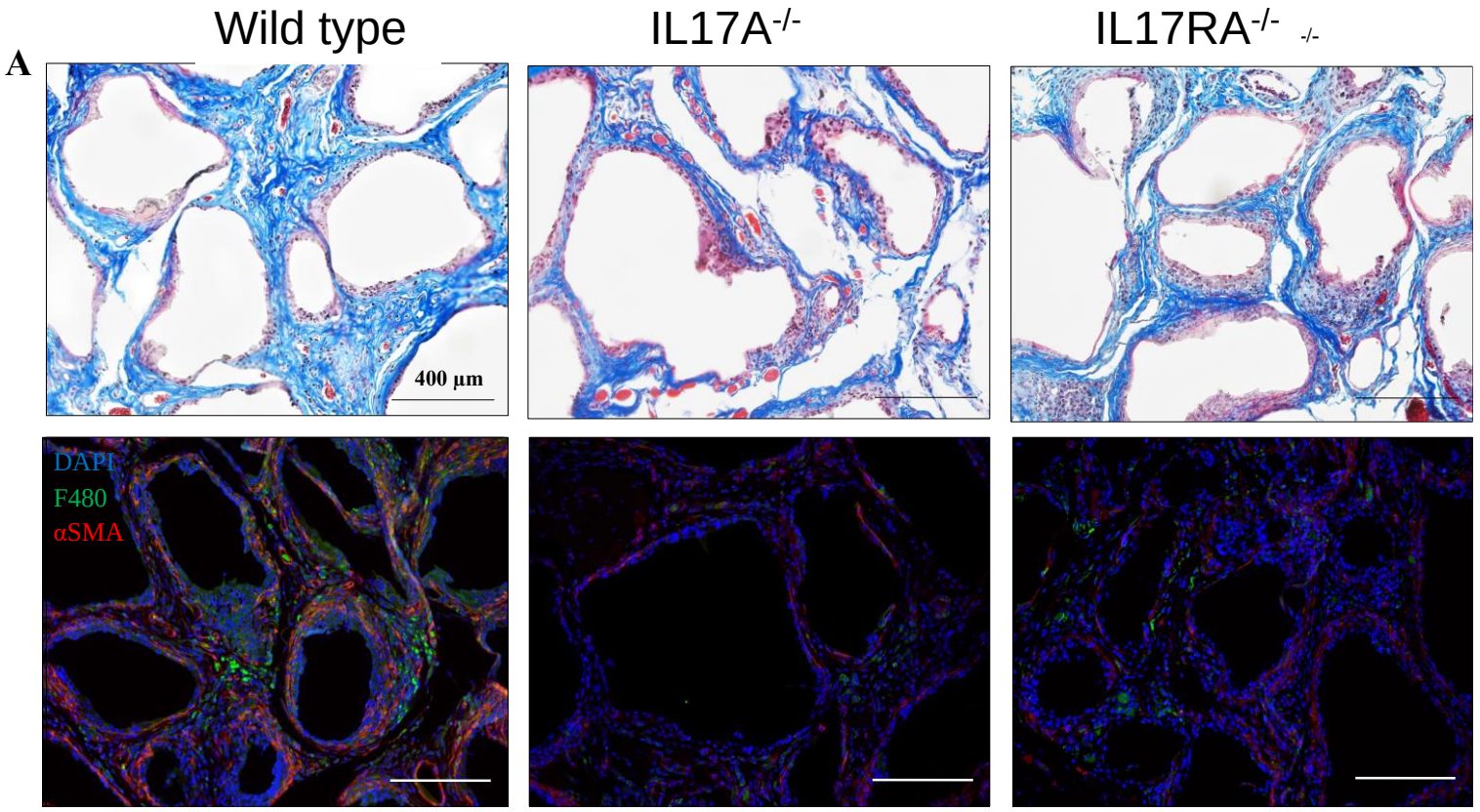


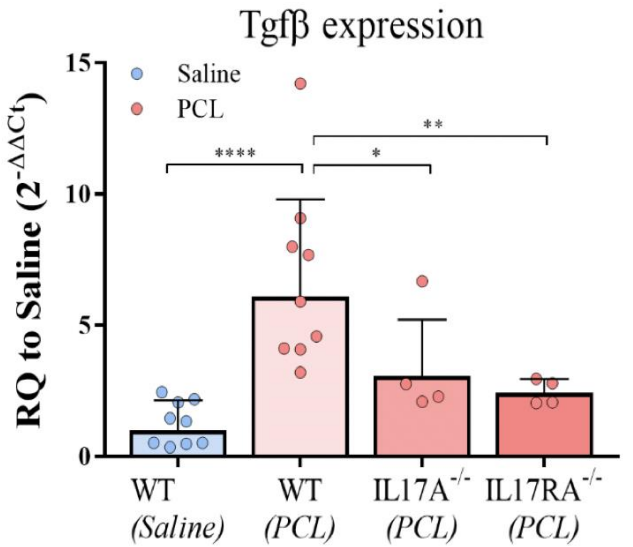
Average patient age was 56 (range of 41-70 years)

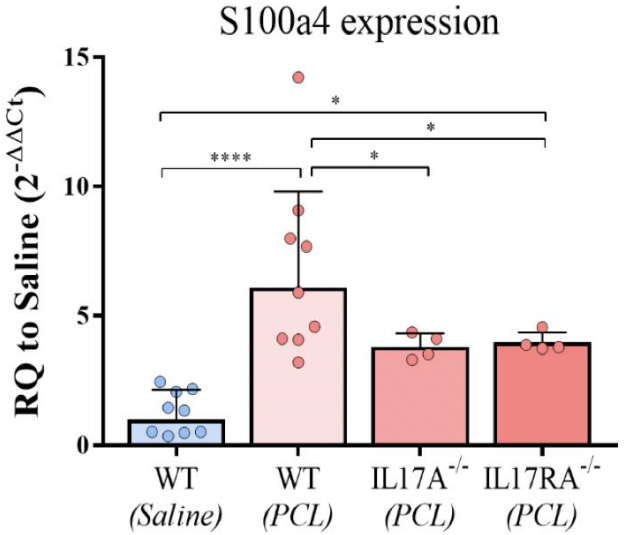
Average implant residence time was 41 months (range of 1-360 months).

Gedge Rosson, MD

Loss of IL-17 signaling reduces macrophages and fibrosis





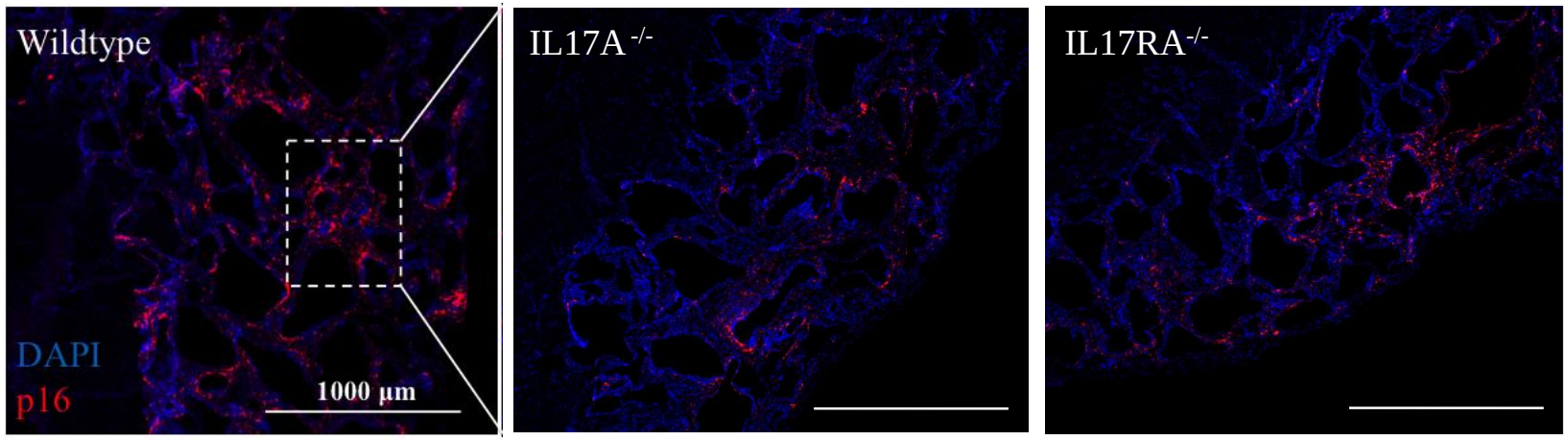


Liam Chung

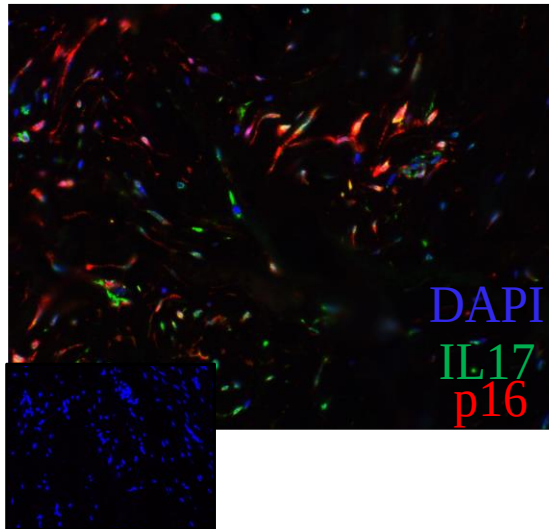
Senescent cells associated with synthetic implants during chronic Th17

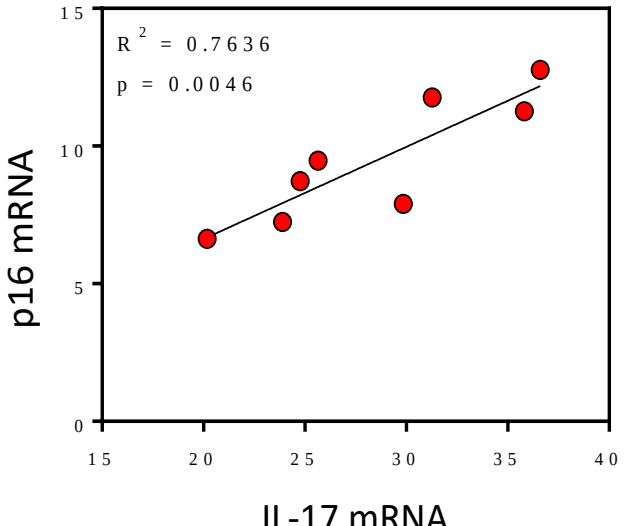
IL-17, fibrosis, and senescent cells

p16 positive cells present in WT but not IL17 transgenic animals



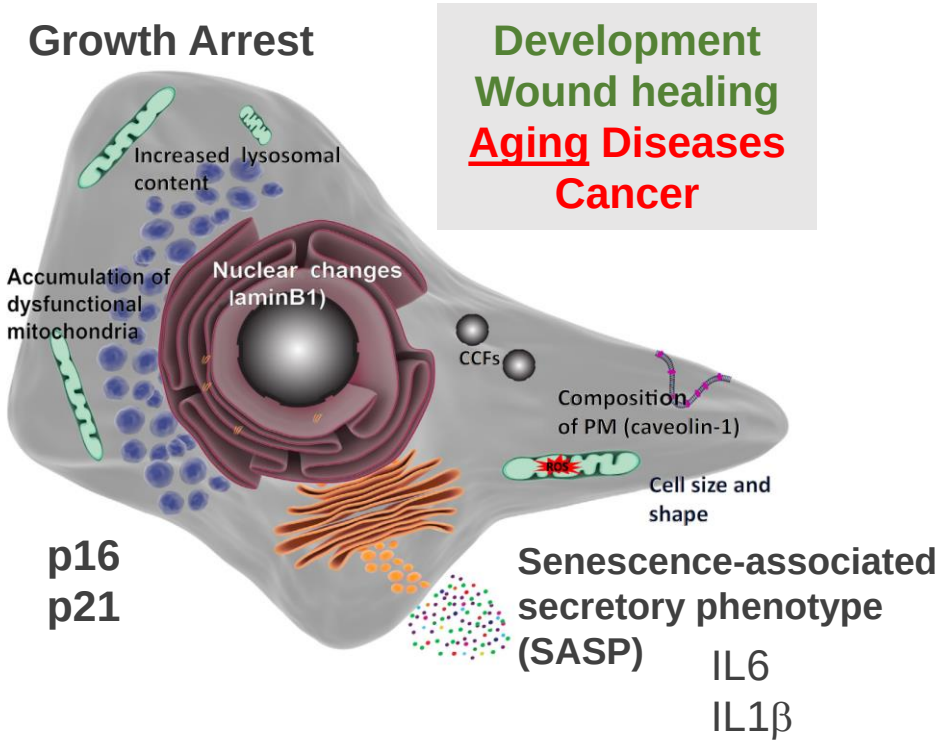
p16 positive cells also present around breast implants





SENESCENT CELLS: a key factor in a non-healing wound?

What is a SnC?

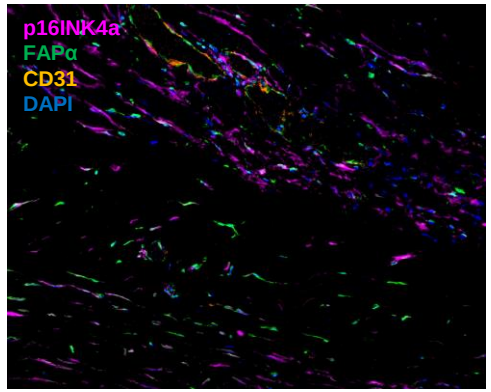


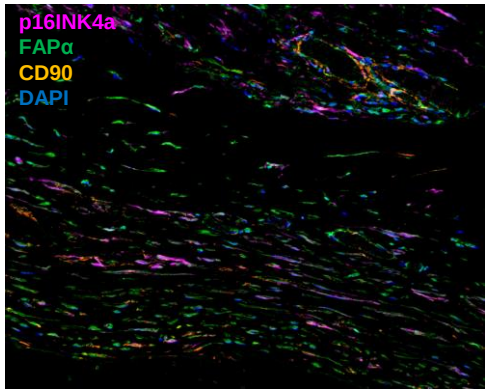
Replicative senescence

Oncogenic senescence

Redox senescence

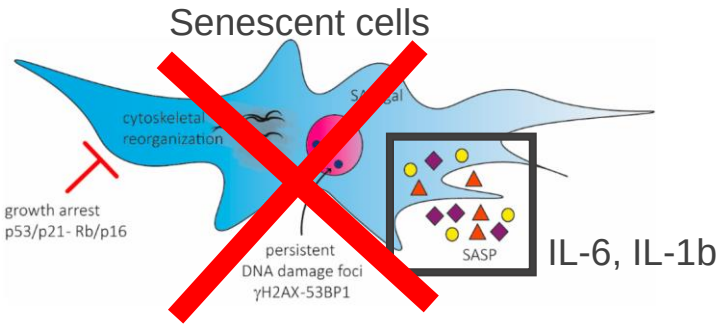
Immunologically-induced senescence?



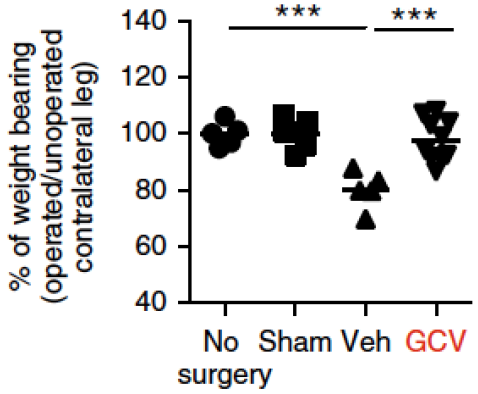


SnCs do NOT overlap with CAF subsets and cannot be detected by single cell

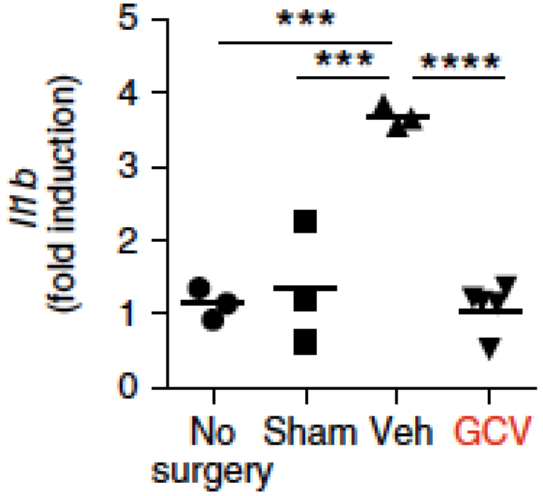
CLEARANCE OF SNC PROMOTES HEALING AND REDUCES FIBROSIS

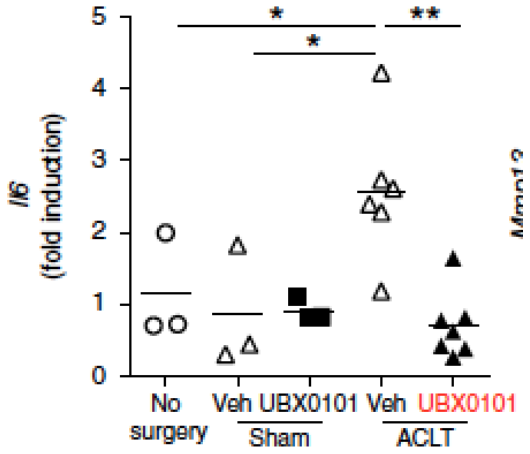


PAIN REDUCED

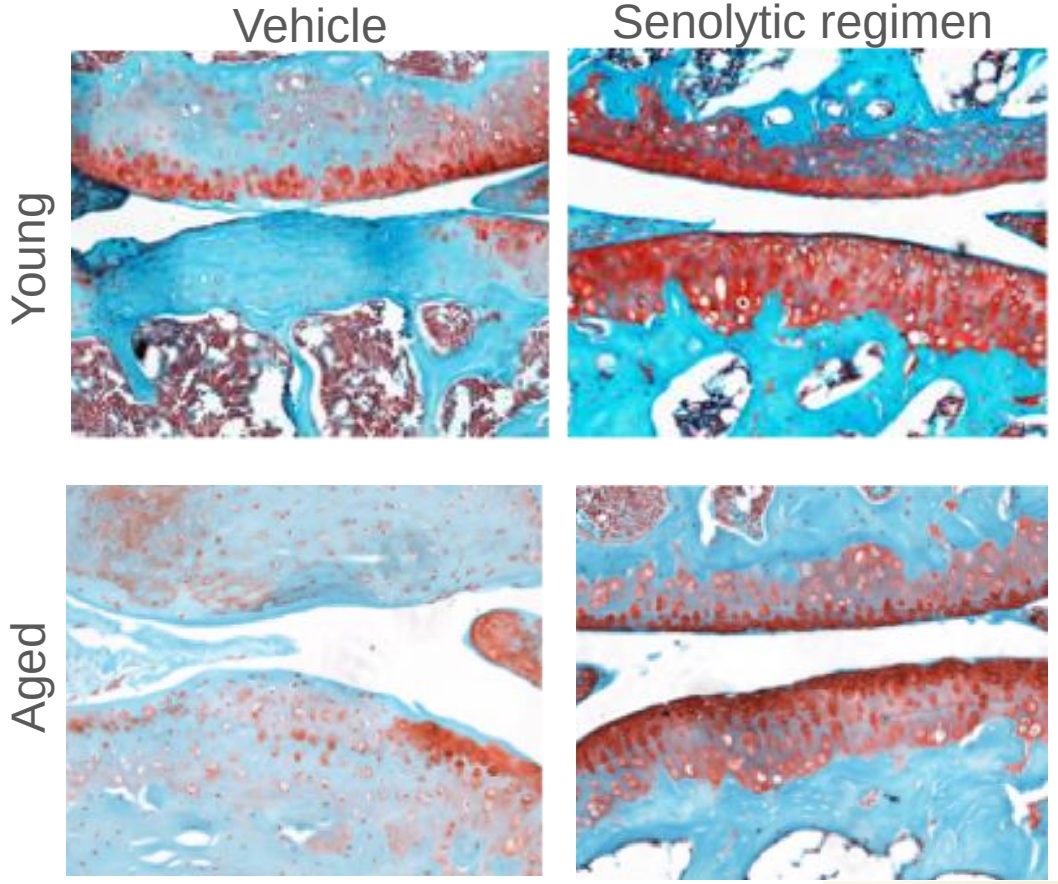


INFLAMMATION REDUCED

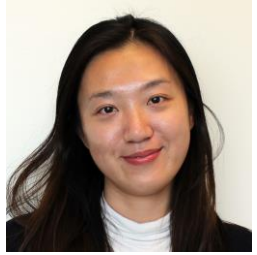




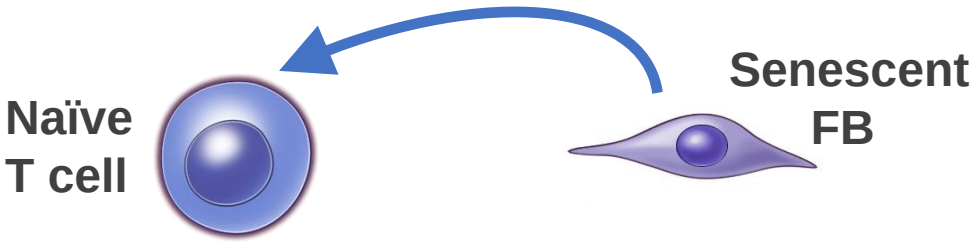
TISSUE REPAIR AFTER SENOLYSIS

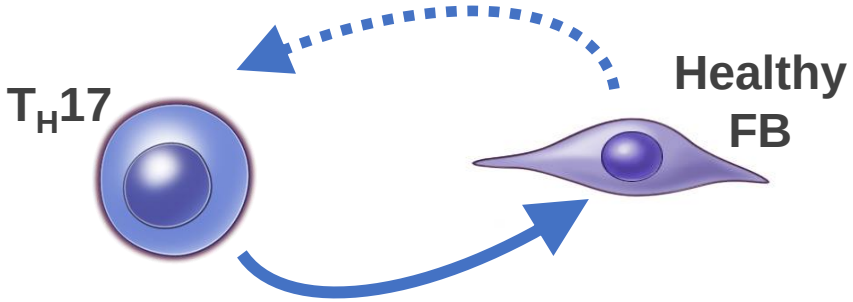


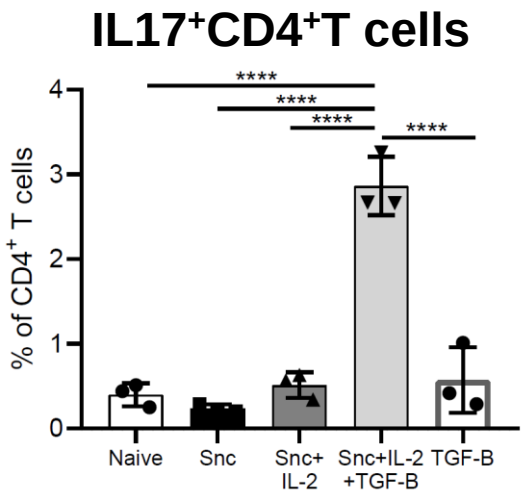
Kim, Jeon et al., *Nature Medicine* 2017

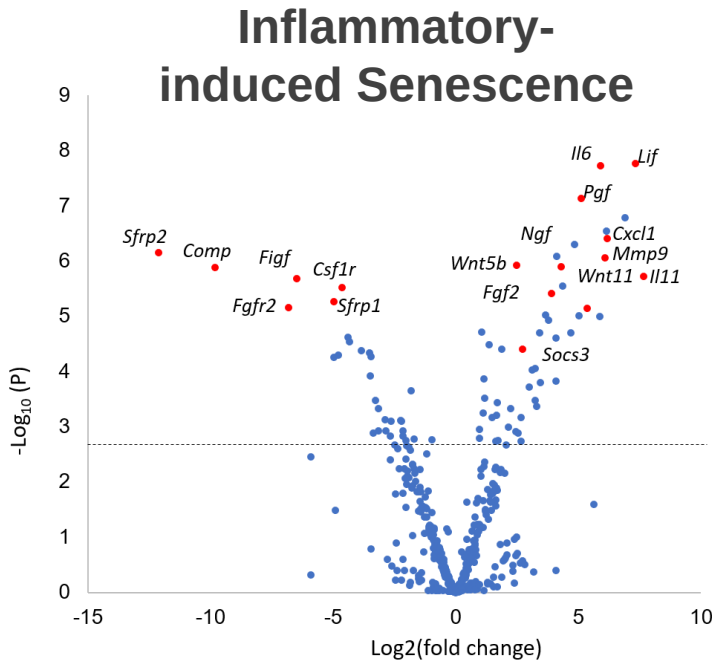


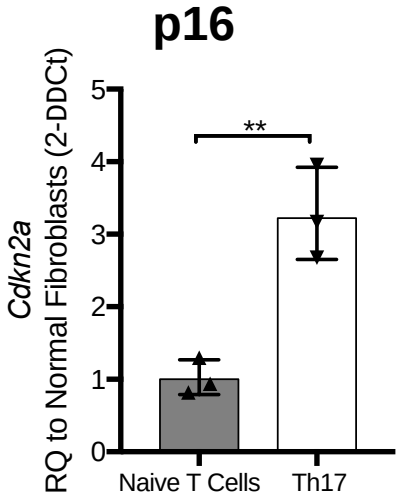
IMMUNOLOGICALLY-INDUCED SENESCENCE

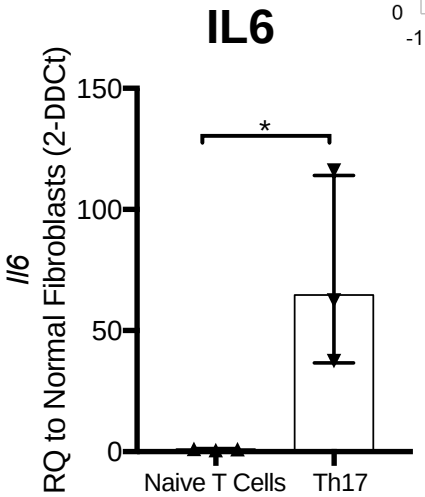








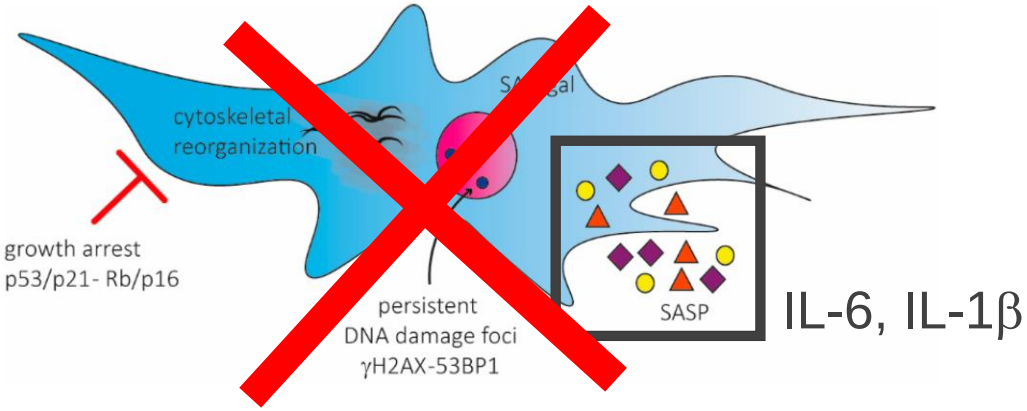




Faust, Zhang, Han, et al., *JCI*, 2020

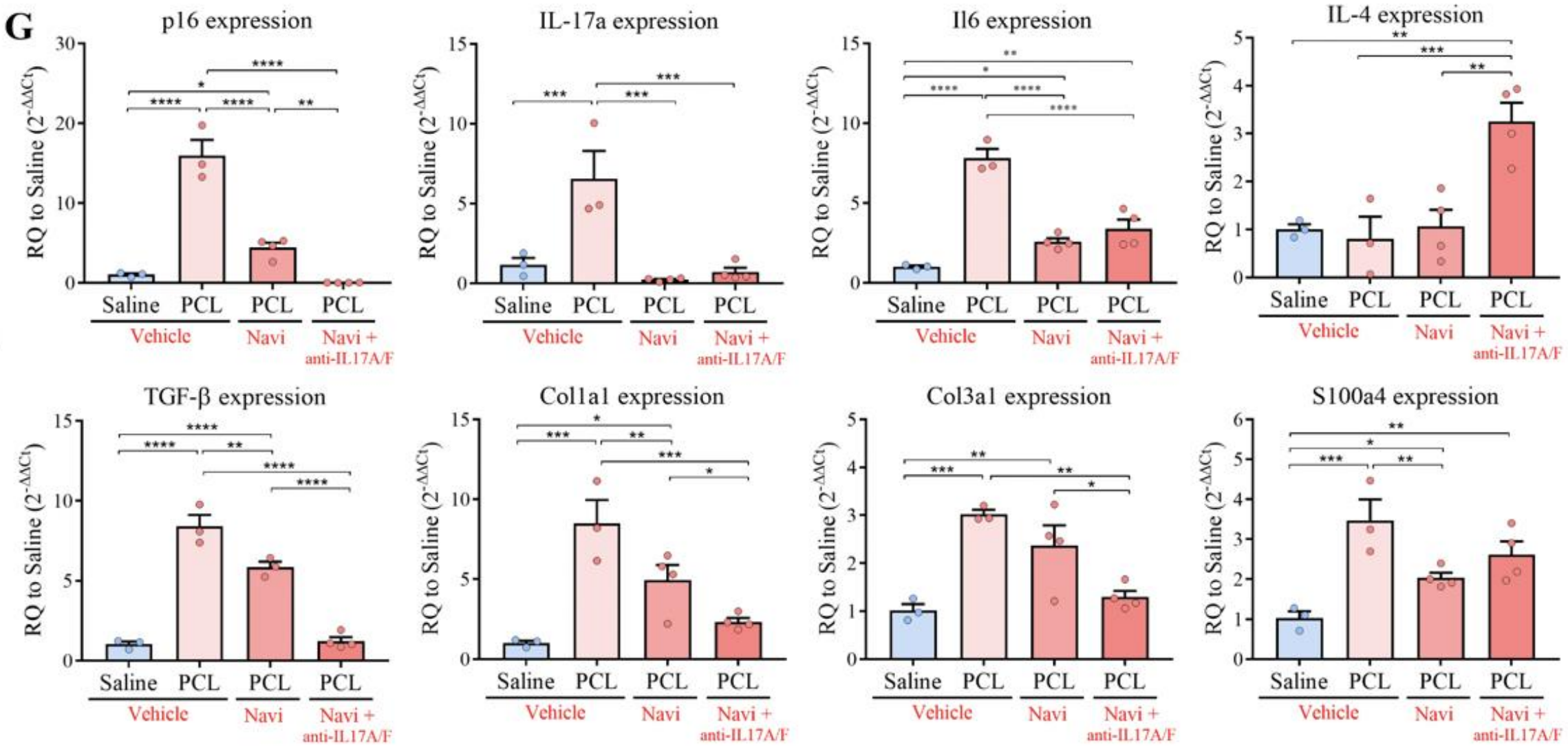
New therapeutic targets for FBR

Senescent cells



Th17

Reduction in the FBR with treatment

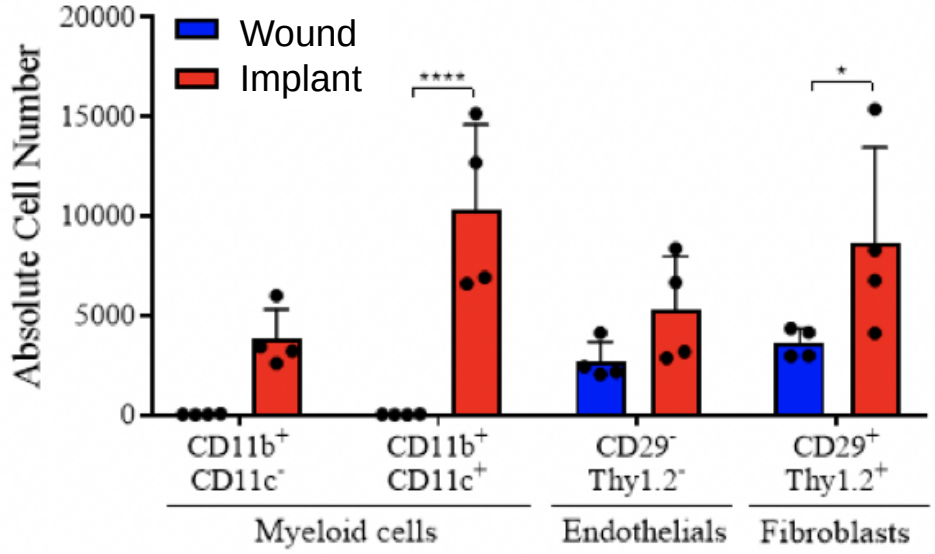


WHICH CELL TYPES ARE SENESCENT IN WOUND AND TUMOR?

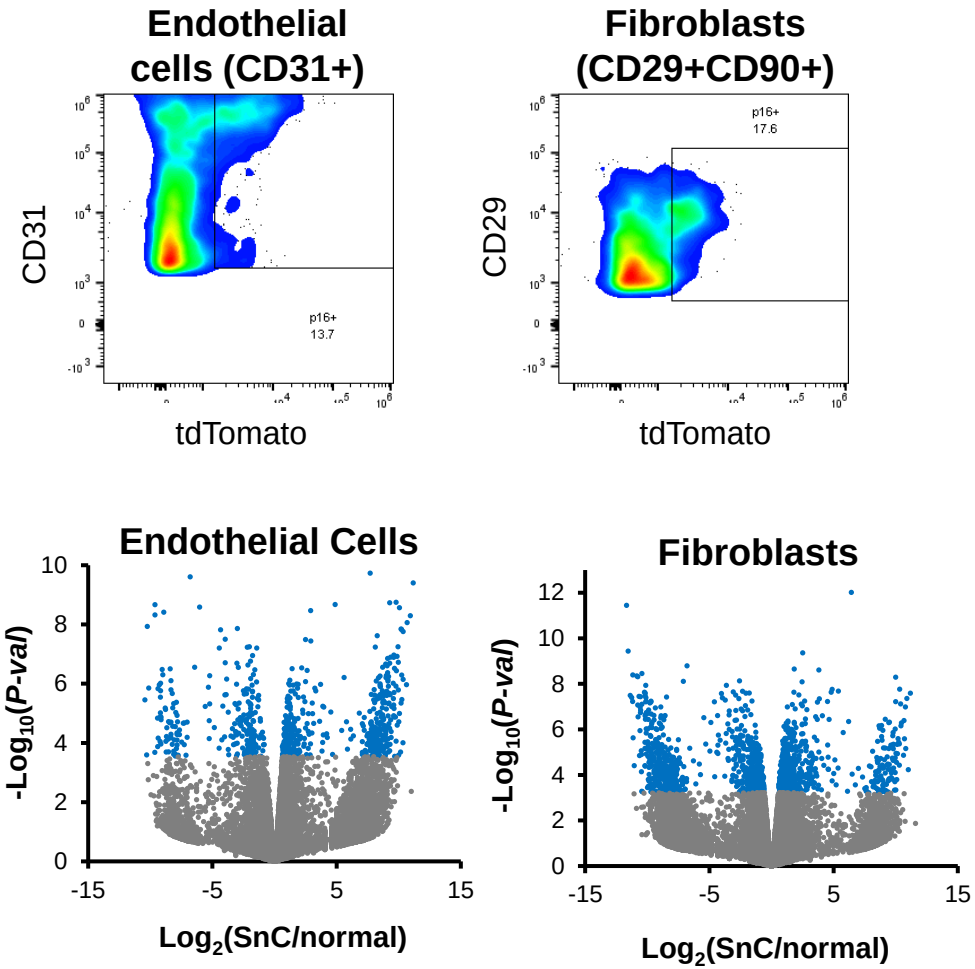
Cdkn2a^{CreErt2}*:LSLtdTomato*
(p16INK4a-tdTomato)
Jan van Deursen

Chronic Wound Model

tdTomato p16^{+} cells



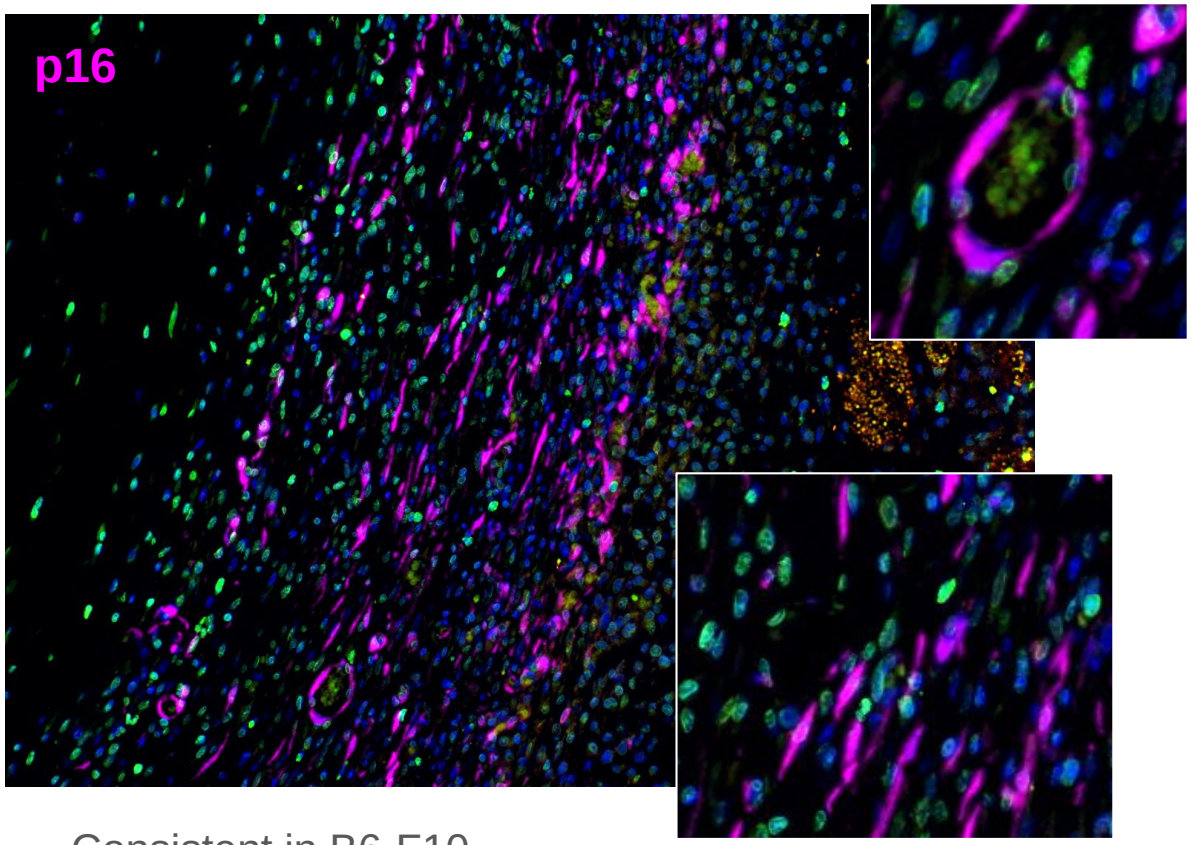
Tumor Model (B16-F10)



Matt Wolf

SENESCENCE IN THE TUMOR MICROENVIRONMENT

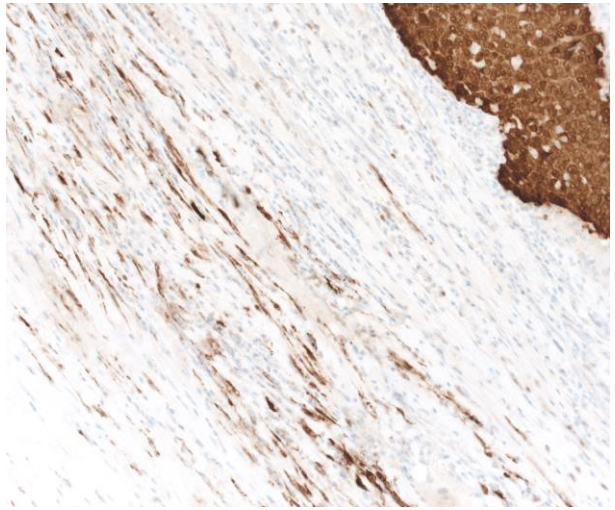
Senescence formation in the TME



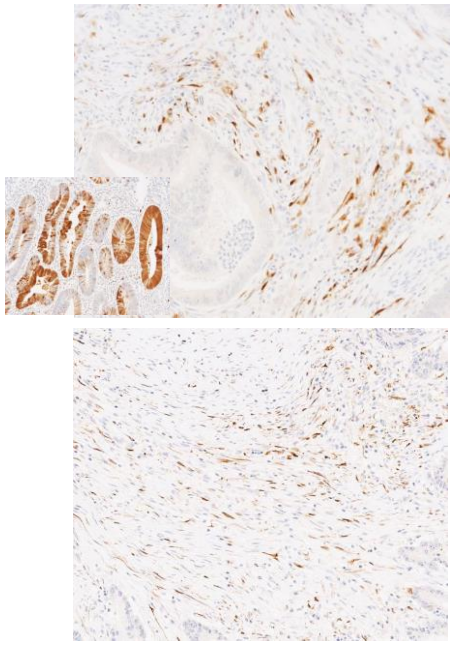
Consistent in B6-F10
Variable in young MC38
Consistent in aged MC38

Human p16

HPV⁺ head/neck metastasis in lymph node

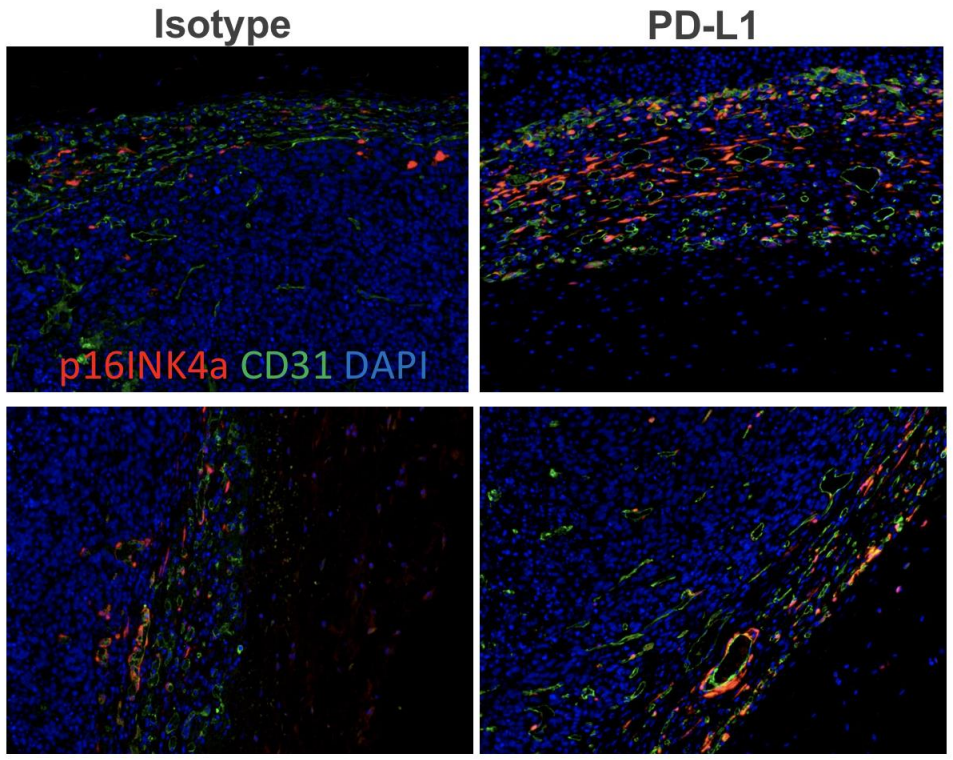


Colon cancer

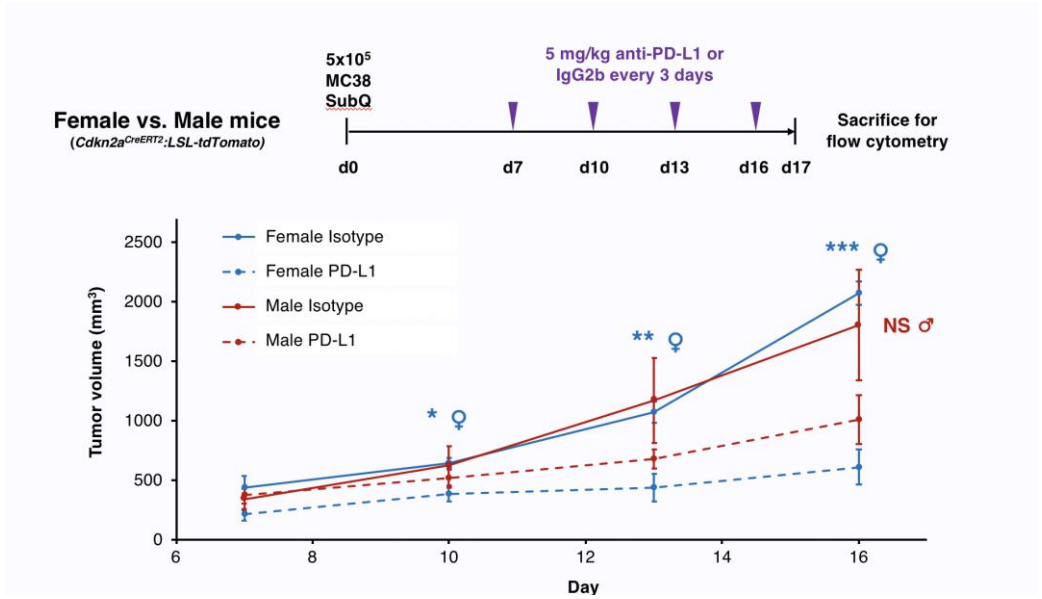


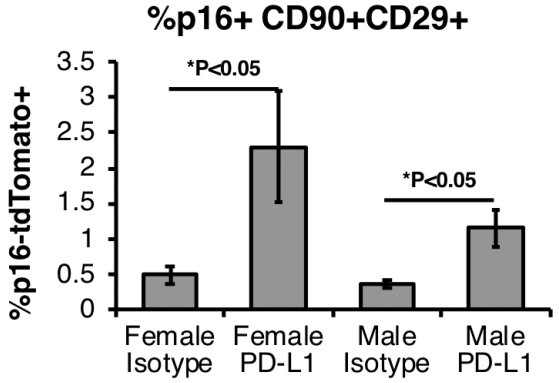
Matt Wolf

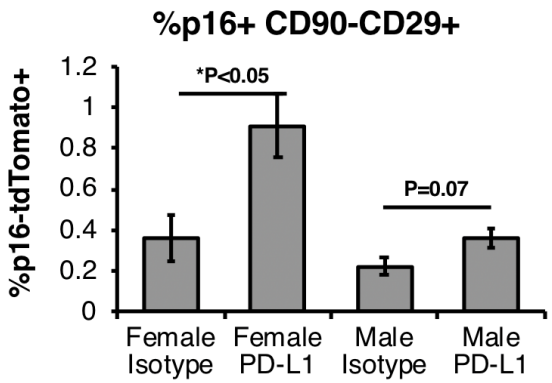
SnC's INCREASE IO-RESPONSIVE TUMORS IN A SEX-DEPENDENT MANNER



MC38 tumors +/- PD-L1, 74 wk old mice

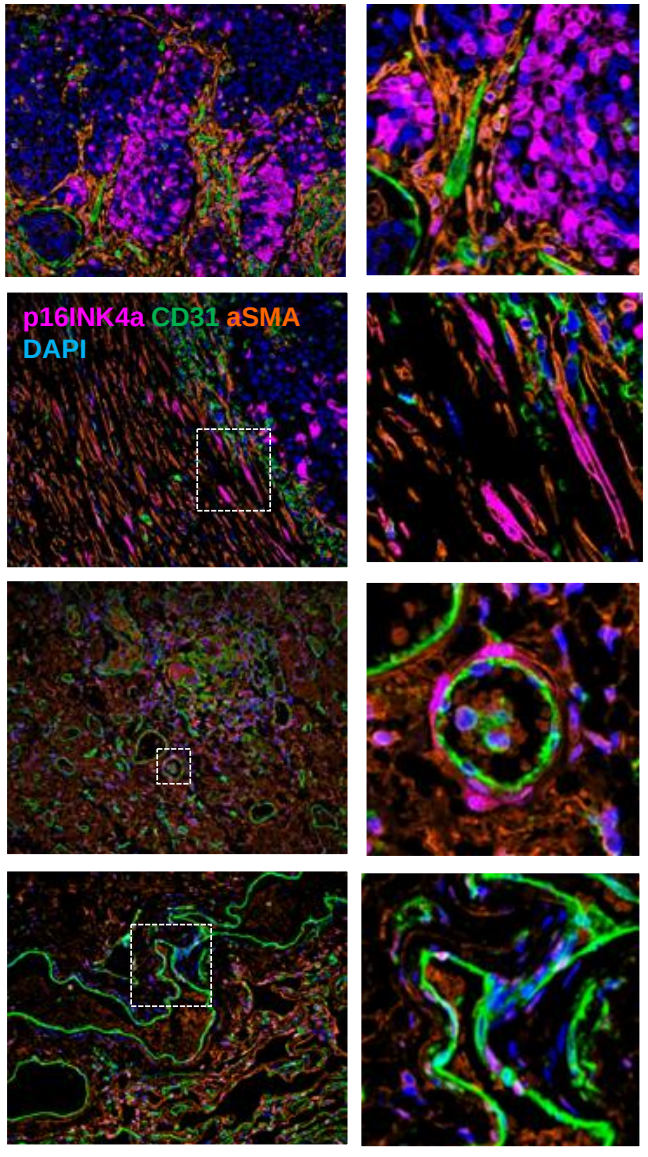


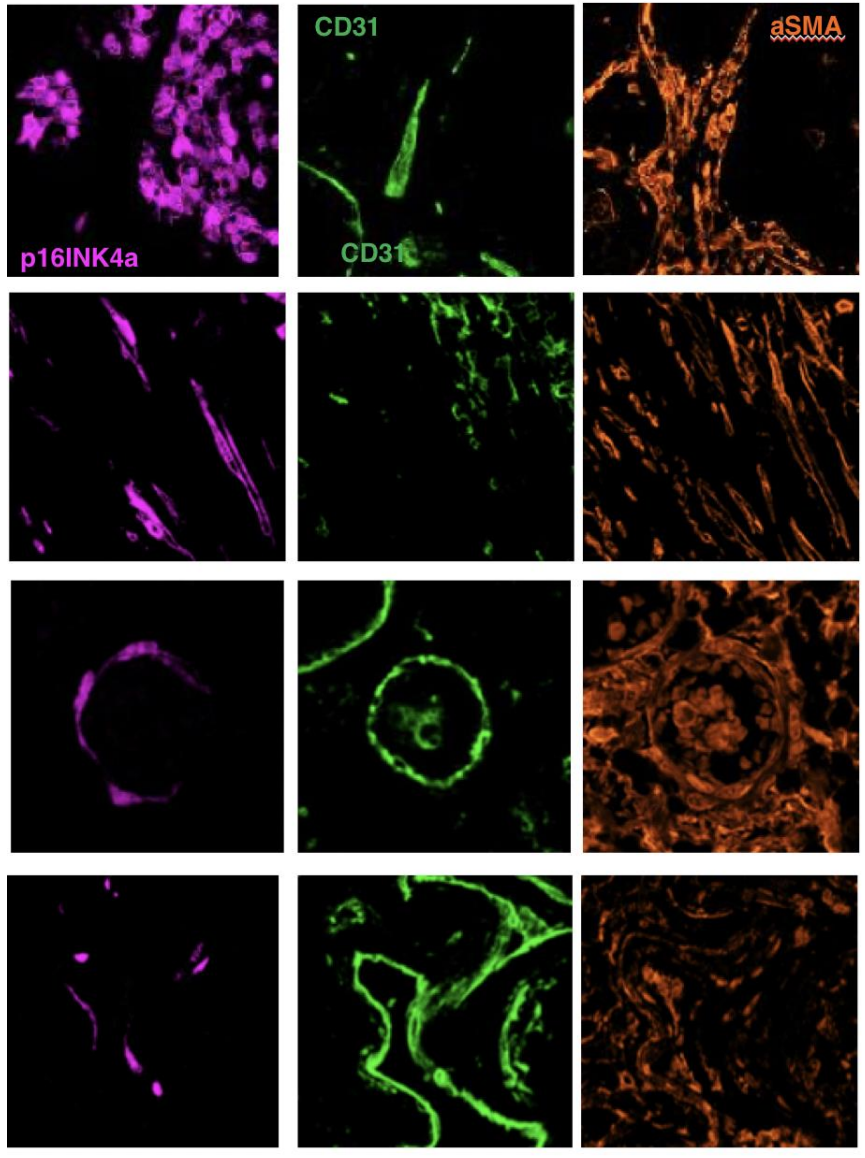




WHAT IS THE SnC PHENOTYPE AND REQUIREMENT FOR RESPONES?

Clinical relevance: SnCs in lung tumor neoadjuvant PD-1 clinical studies

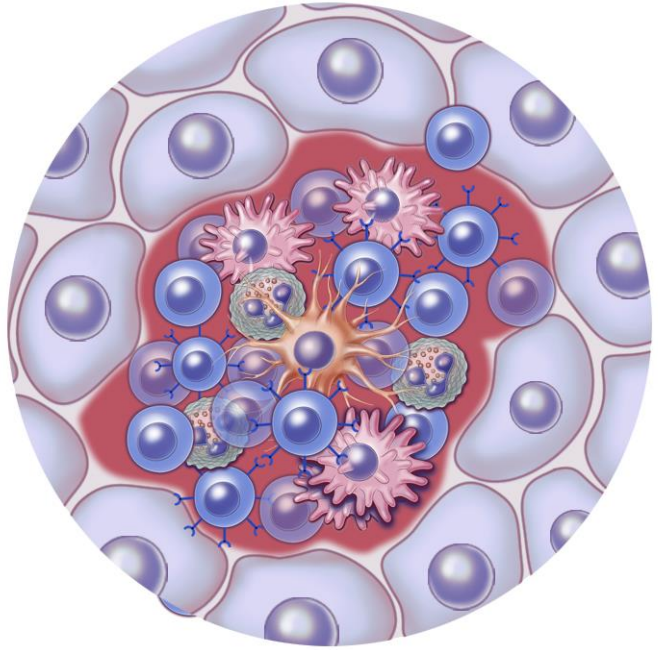




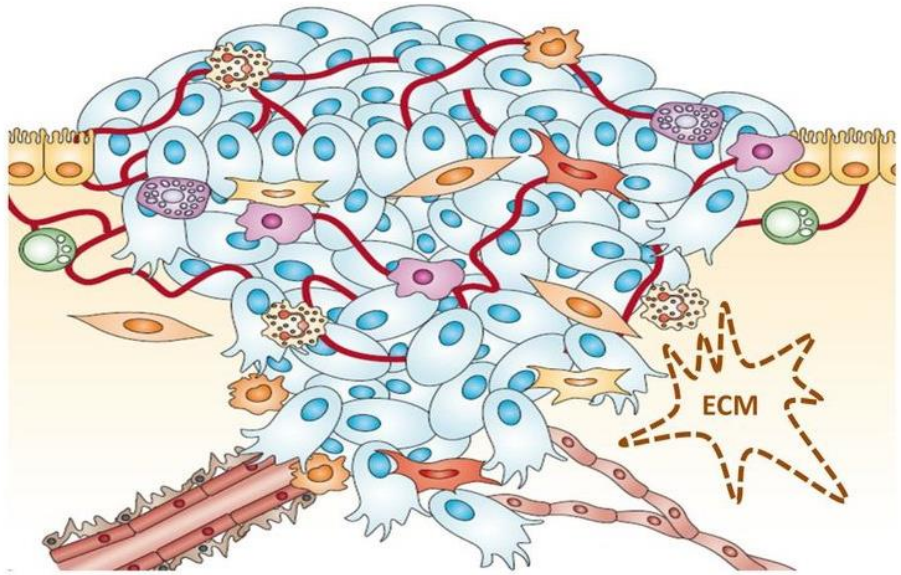
Janis Taube
Tricia Cotrell
Franck Housseau
(colon cancer)

Do SnCs correlate with response/resistance and how does location impact response?

Wound microenvironment



Tumor microenvironment



Healing and non-healing wounds and biomaterial models to define the tumor microenvironment and IO responsiveness

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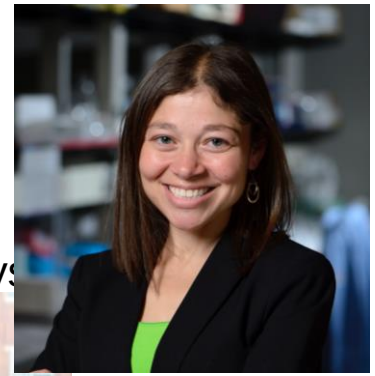
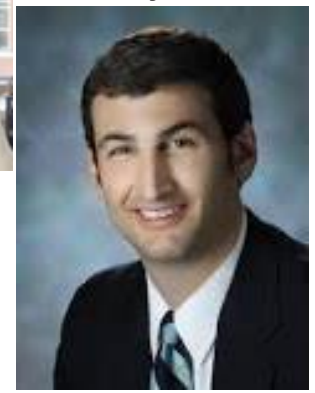
rren Grays

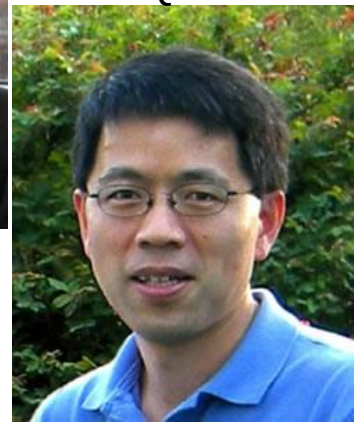


Zandy Hillel

Jordan Green



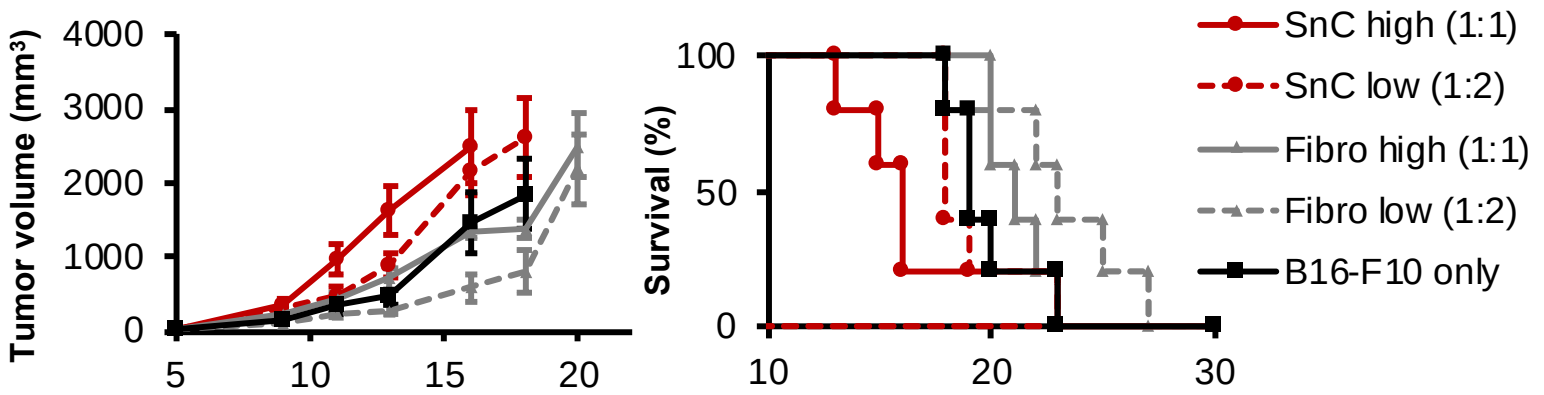
HQ Mao



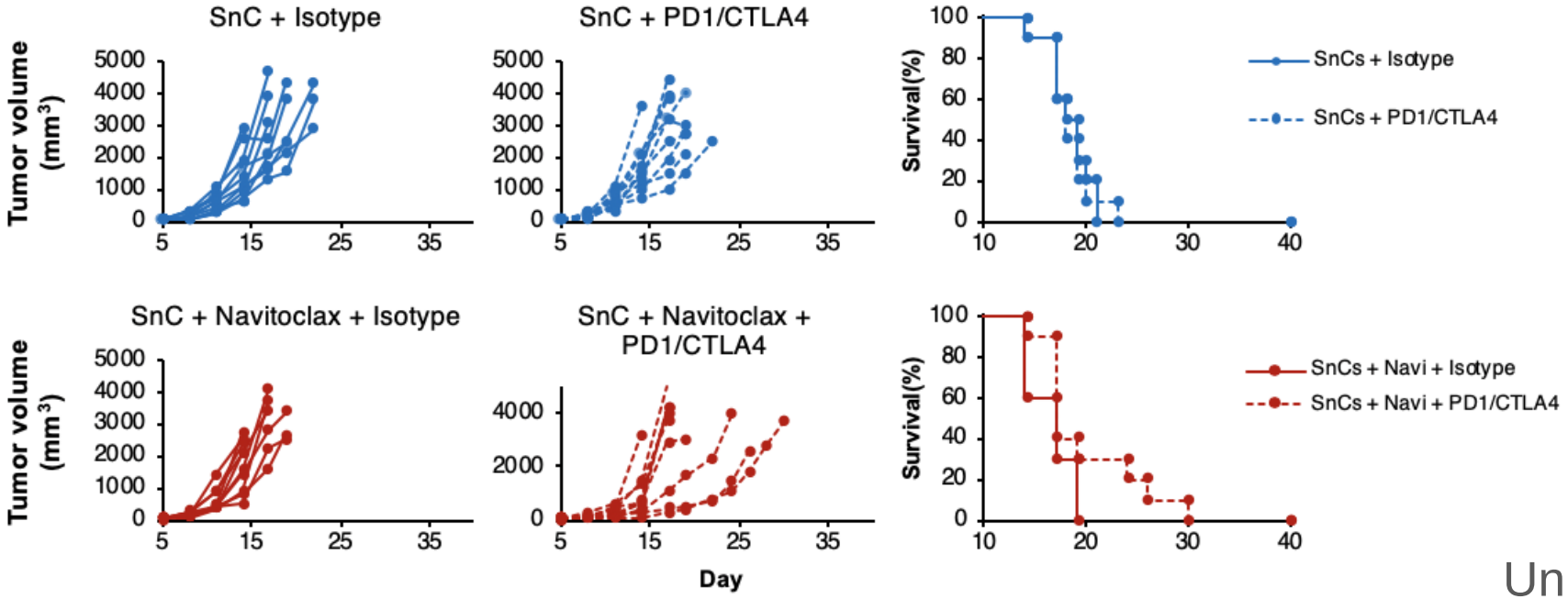
POSTDOC POSITIONS AVAILABLE!

LAB MANAGER/TECH POSITIONS AVAILABLE!

Adding senescent cells (artificial) increases tumor growth



SnC doping and IO responsiveness



Unpublished data