TRANSLATION →
MECHANISM →
UNDERSTANDING
VARIABILITY

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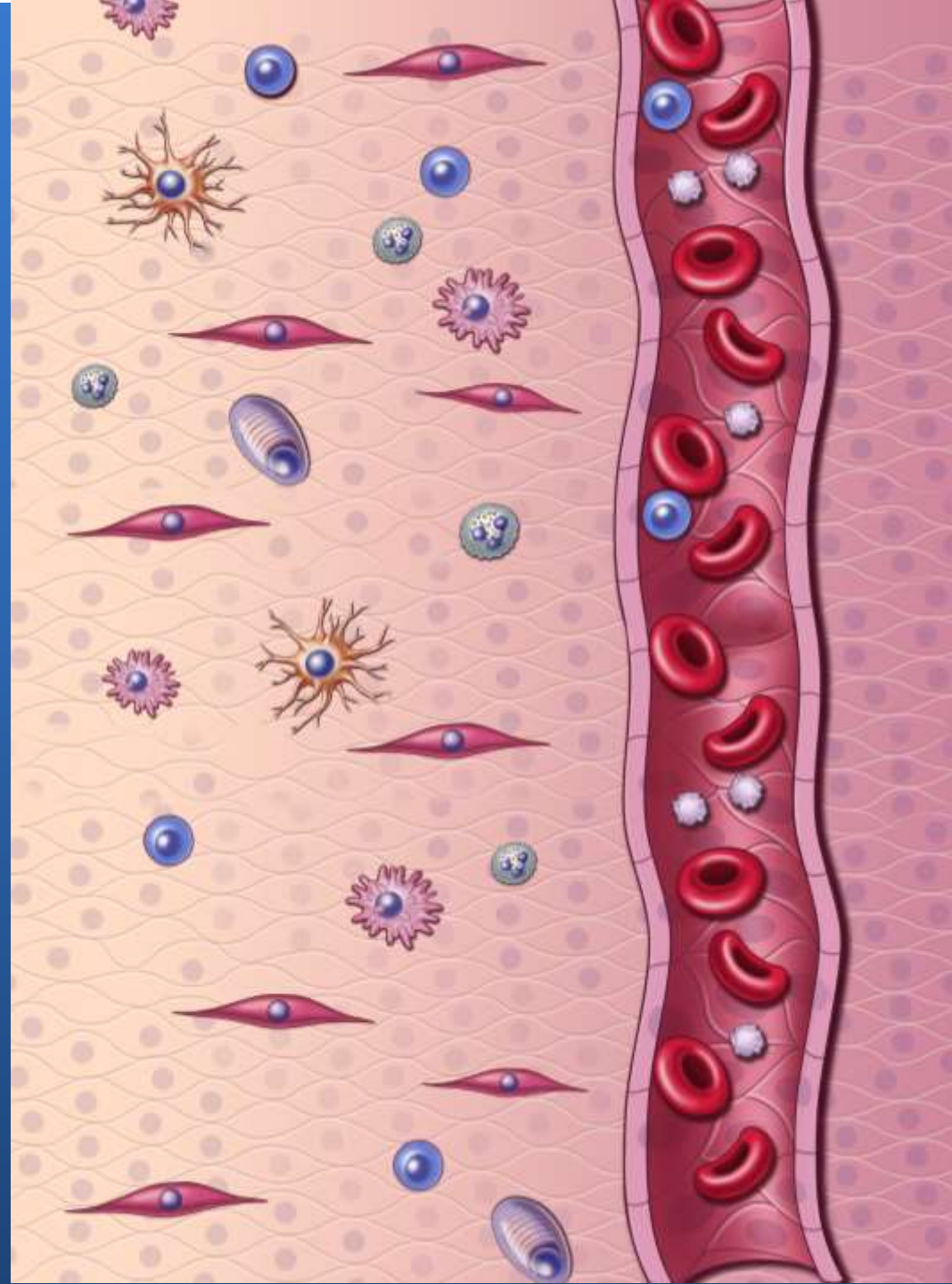
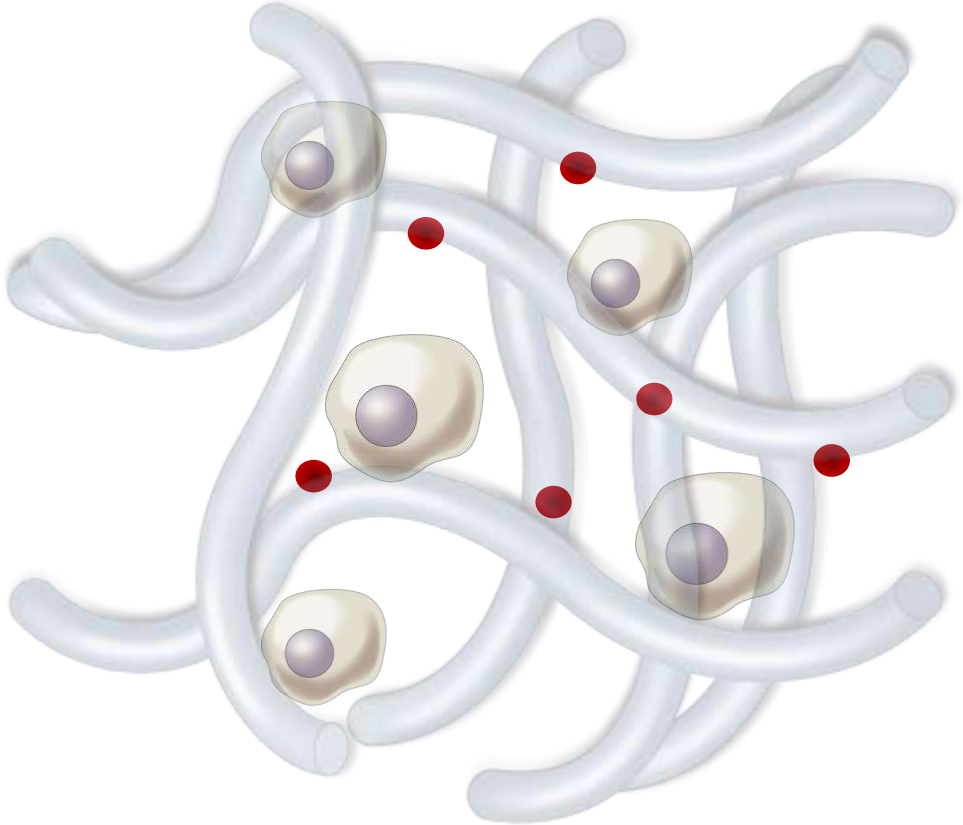
Johns Hopkins University

Forum on Regenerative Medicine
National Academy of Sciences
October 17,2018



TRADITIONAL CELL AND TISSUE ENGINEERING APPROACHES

Engaging and manipulating biology



Cells

+

Signals/Delivery

+

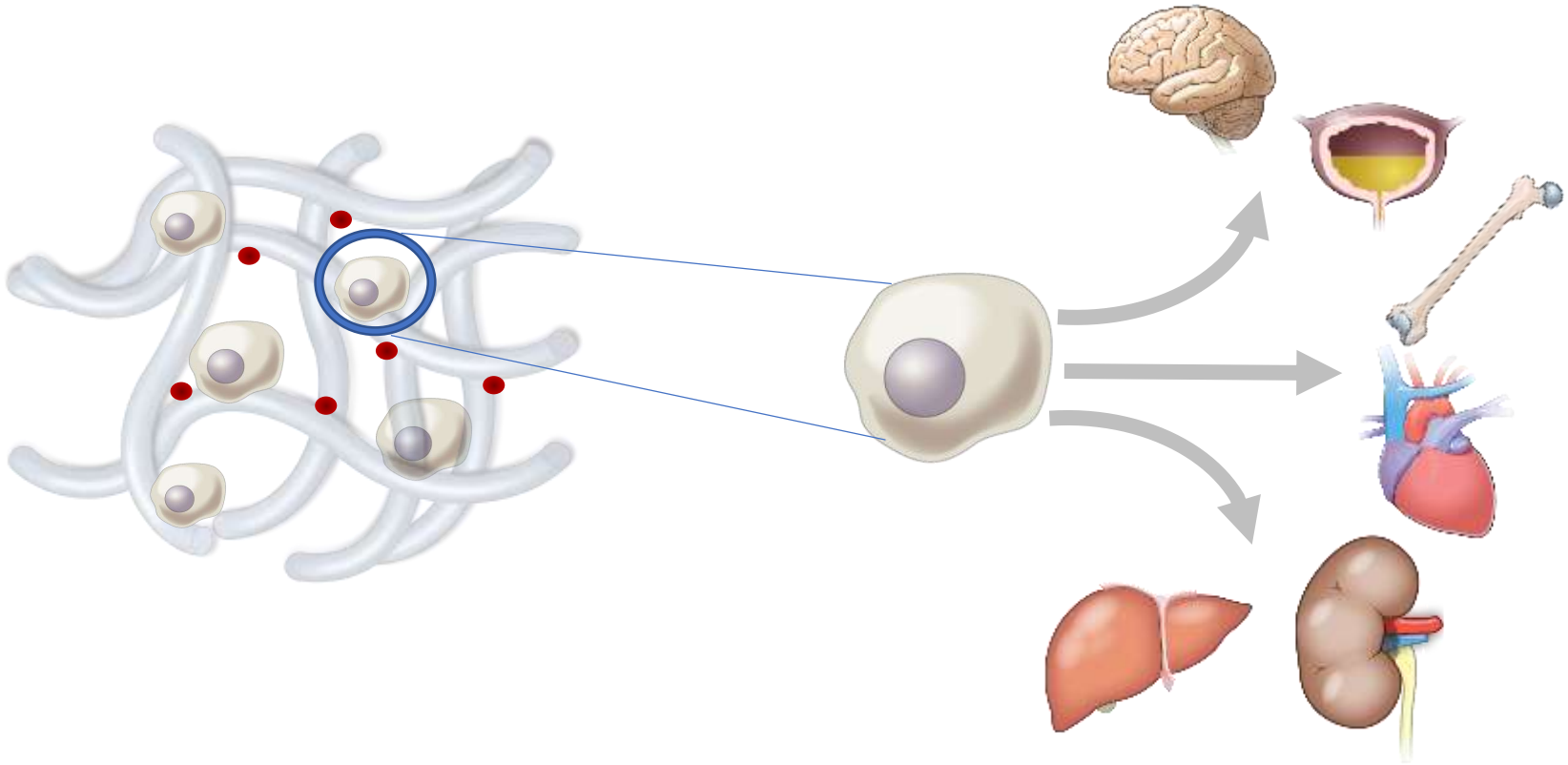
Biomaterials

→ New Tissue

What does clinical translation teach us?

STEM CELLS ENERGIZED REGENERATIVE MEDICINE

But are they a rate limiting factor in repair?

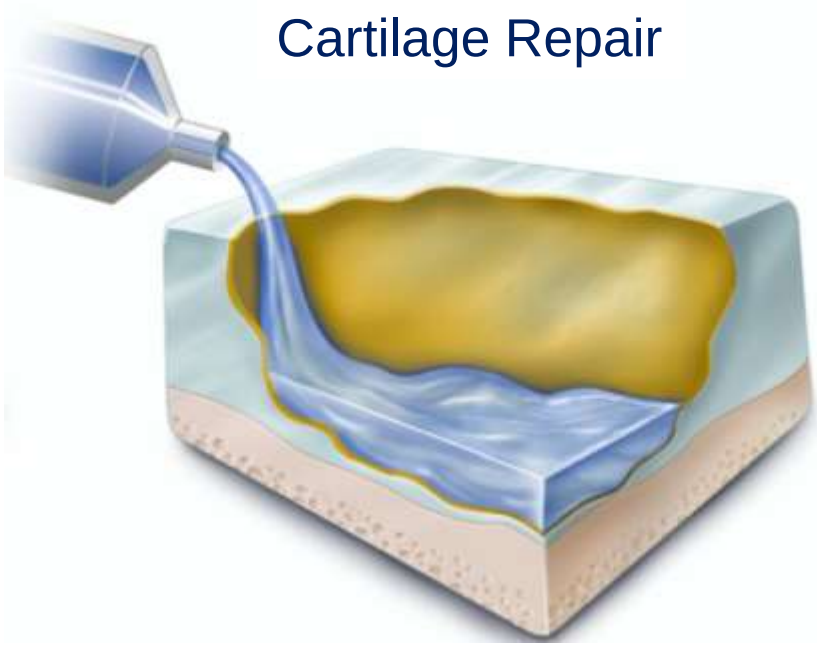


Are stem cells the best target to promote tissue repair?

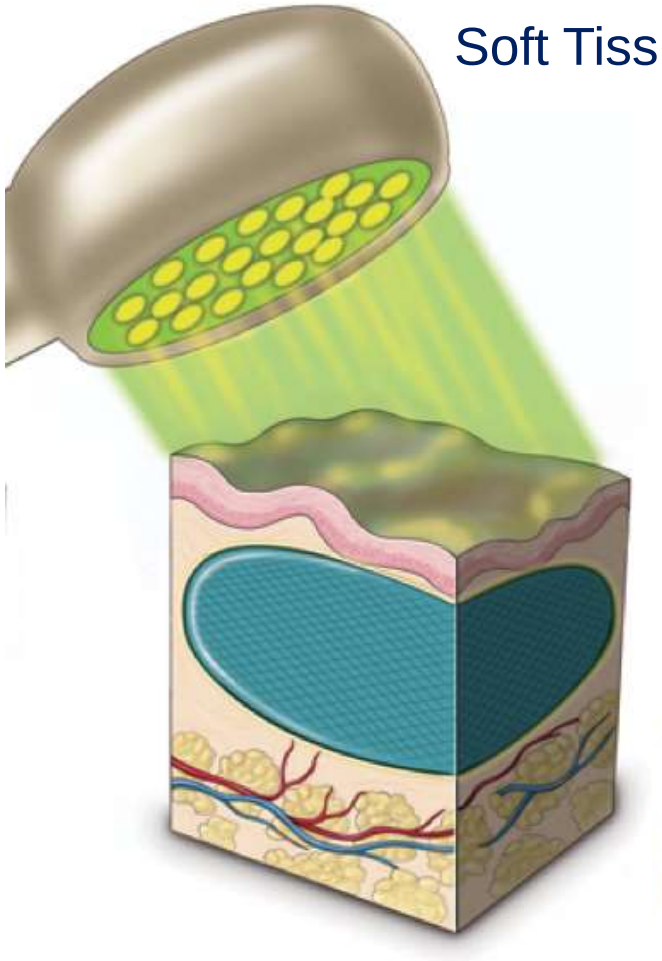
CLINICAL TRANSLATION

Moving to patients helps teach us what is therapeutically relevant

Cartilage Repair



Soft Tissue Filler

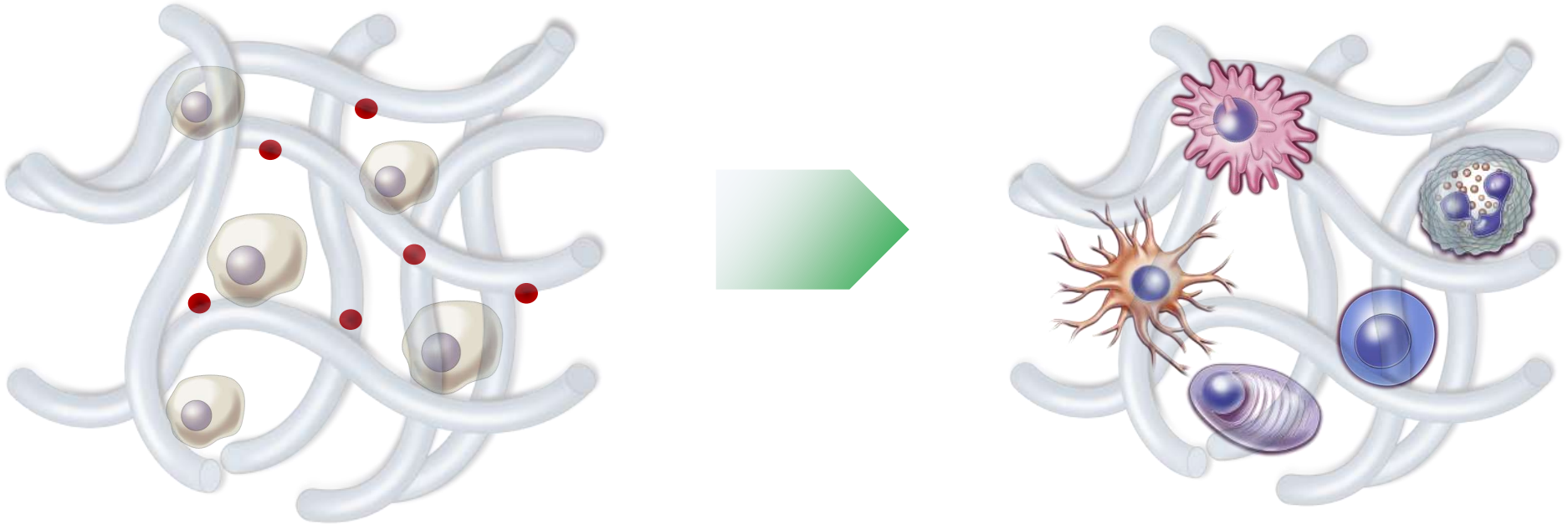


T cells

Redirecting wound healing

Tissue-specific immune response

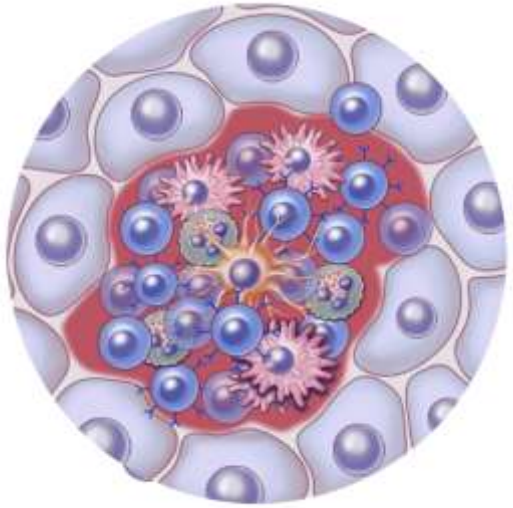
Moving from engineering tissue microenvironments to understanding (and engineering) the tissue immune environment



Local and systemic immunoengineering

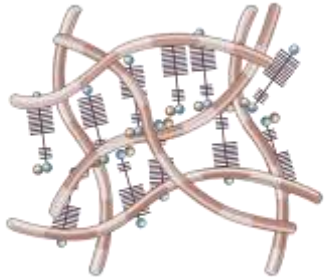
BIOMATERIALS CHANGE THE LOCAL IMMUNE ENVIRONMENT

TRAUMA-IMMUNE RESPONSE



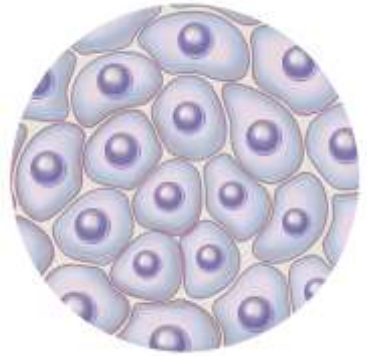
BIOMATERIALS MODIFY IMMUNE RESPONSE

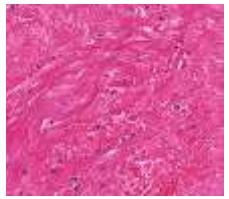
BIOLOGICAL



Pro-regenerative

TISSUE REPAIR

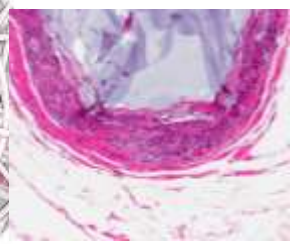




SYNTHETIC

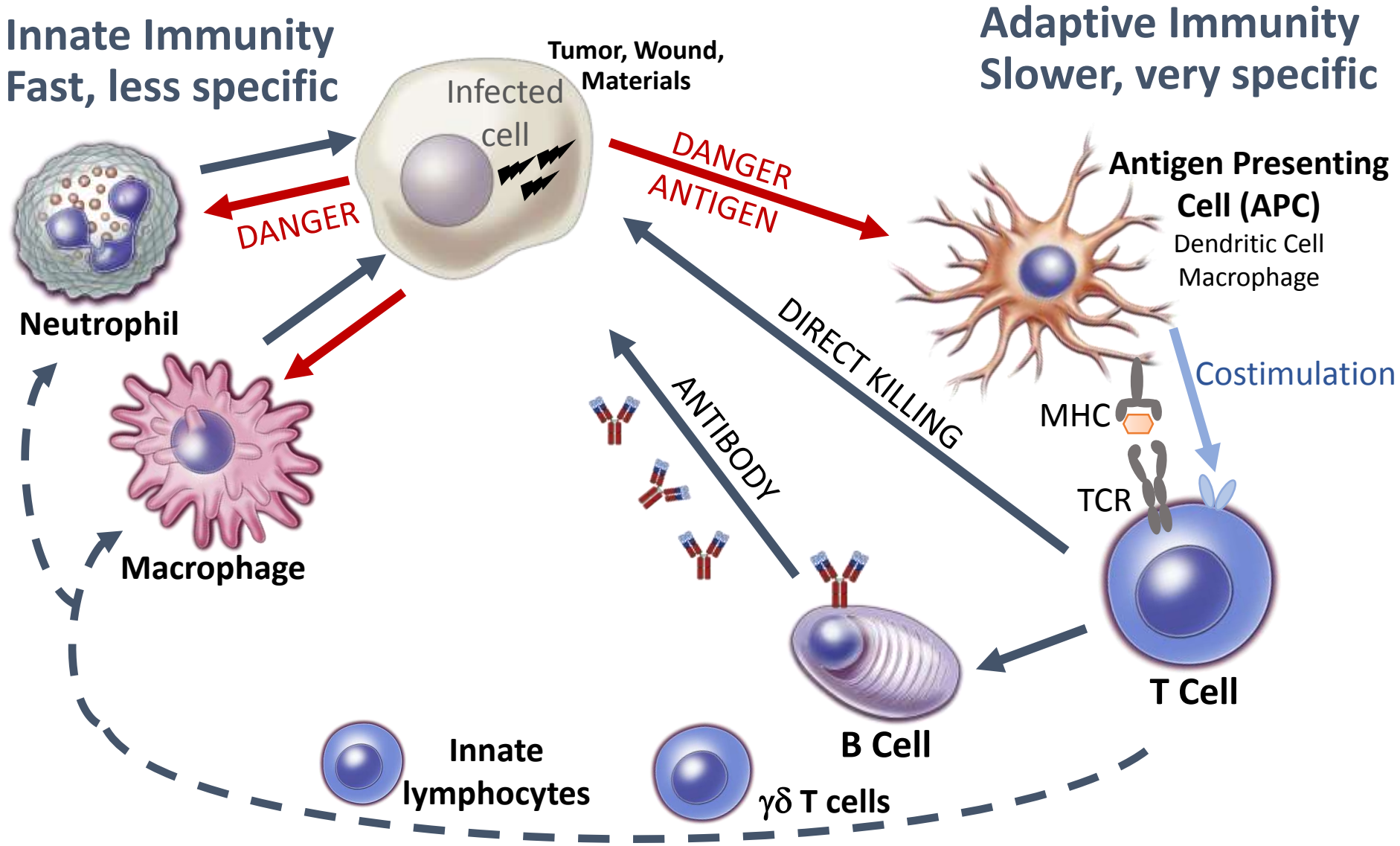
Pro-fibrotic

TISSUE FIBROSIS

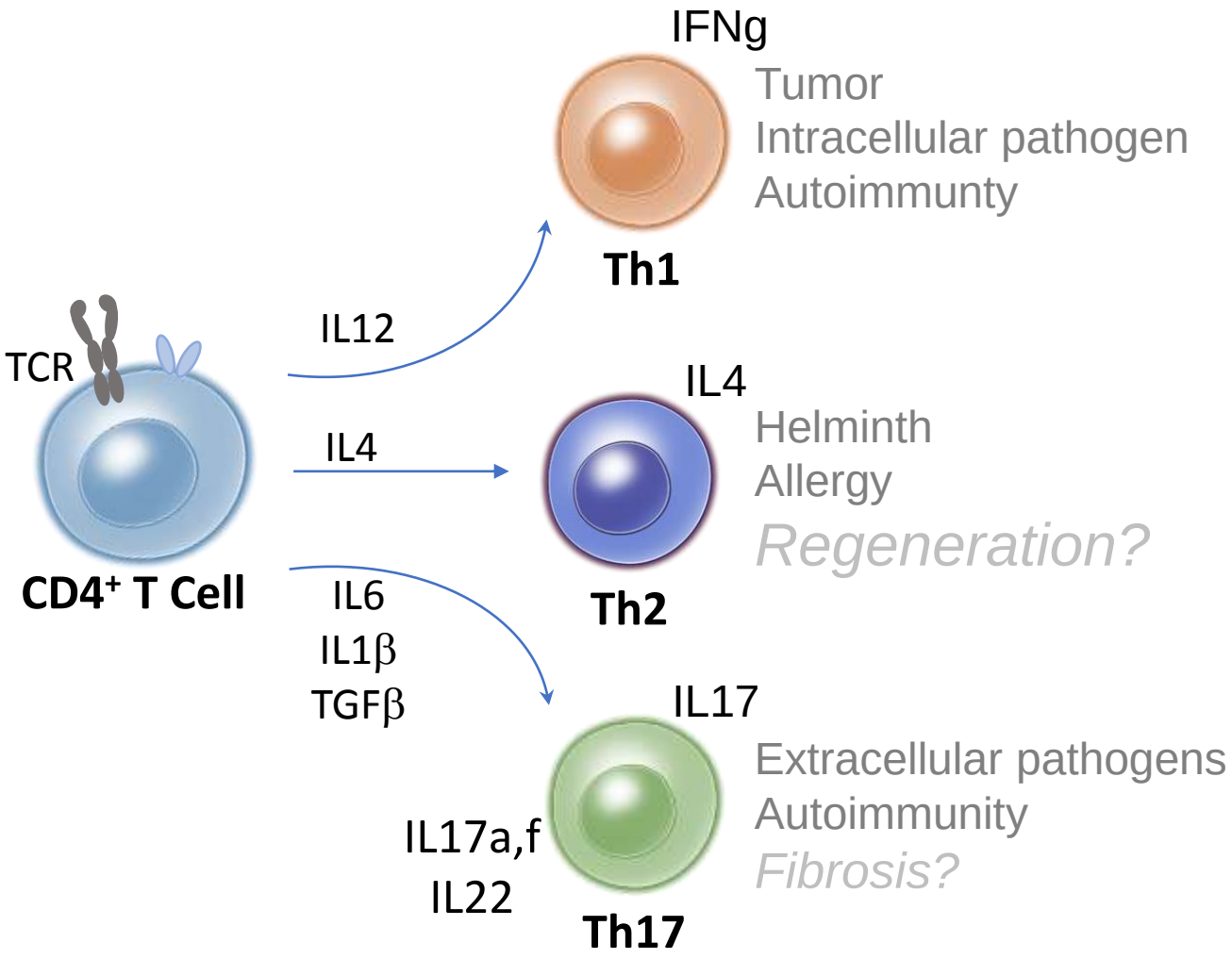


Biomaterials can create a pro-regenerative or pro-fibrotic tissue environment

Innate and Adaptive Immune System are Closely Linked



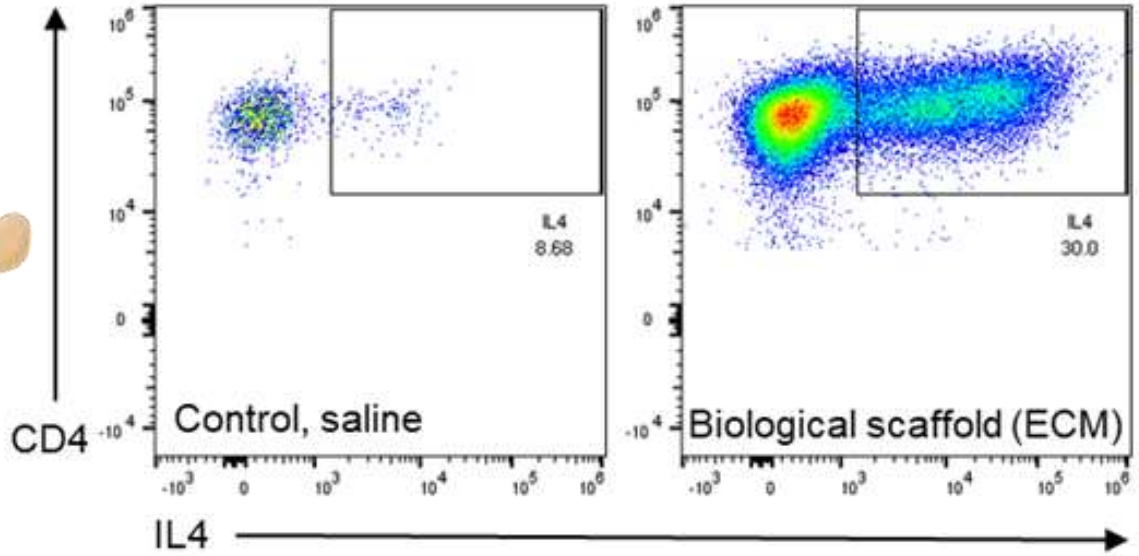
Digging a little deeper….the T cells



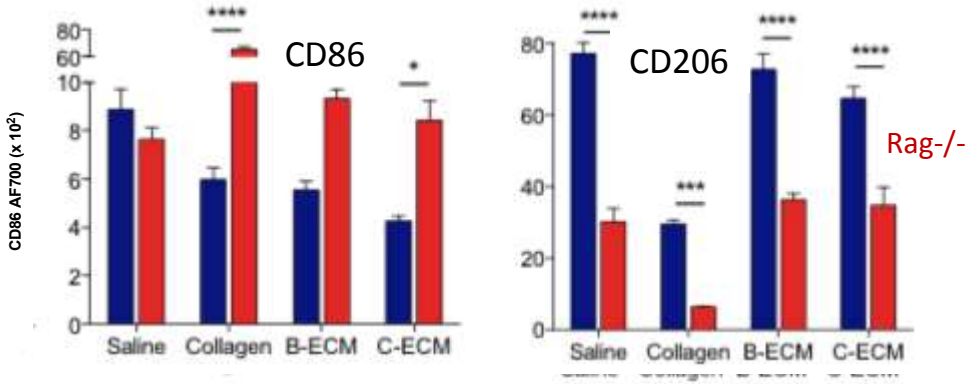
- Systemic impact
- Antigen specificity
- Memory

BIOLOGICAL SCAFFOLDS CREATE A PRO-REGENERATIVE IMMUNE ENVIRONMENT

T cells in the Wound/biomaterial

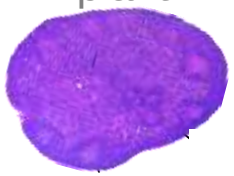


Macs

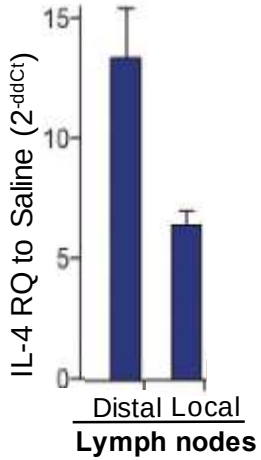


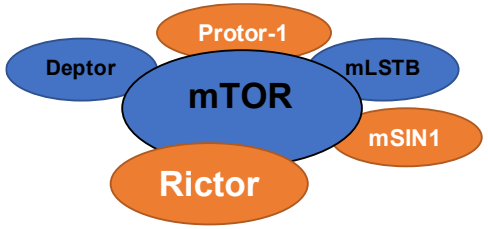
Systemic Changes

Implant



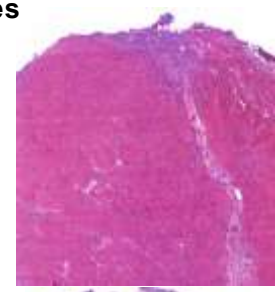
Control

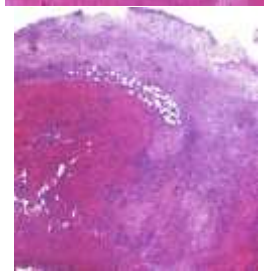




mTORC2 → Th2

Sadtler et al., Science, 2016

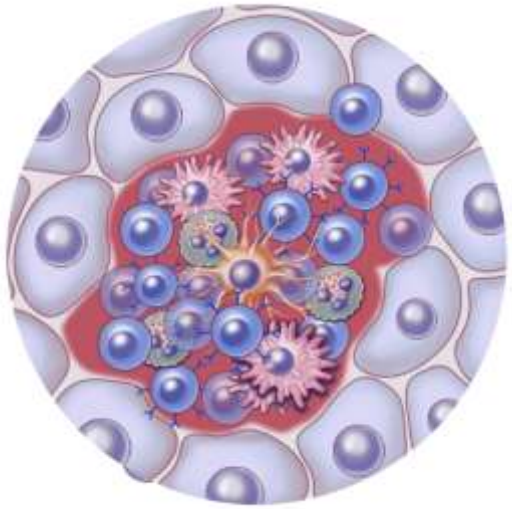




Th2 T cells are required to direct macrophages and create a pro-regenerative environment

A REGENERATIVE IMMUNOTHERAPY APPROACH

The immune system is therapeutically accessible

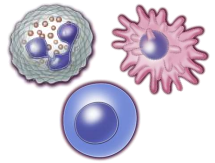


The immune system is the first responder to injury

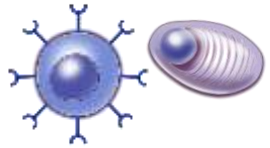
The immune environment determines downstream repair

Engineer immunotherapies to create a pro-regenerative environment

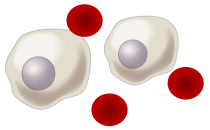
Innate



Adaptive

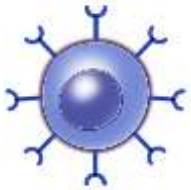


Immune Cells



Stem cells, growth factors, ECM

Tissue Development

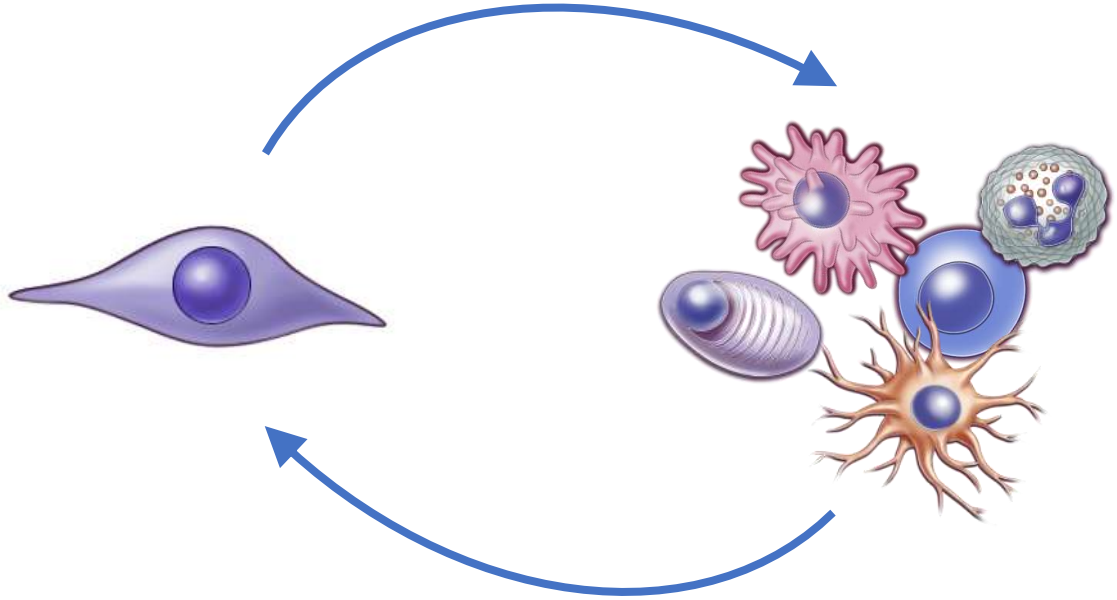


Th2 T cells

T Cells

T cells are the most therapeutically accessible cells in the immune system

How does the immune system connect with tissue stroma?

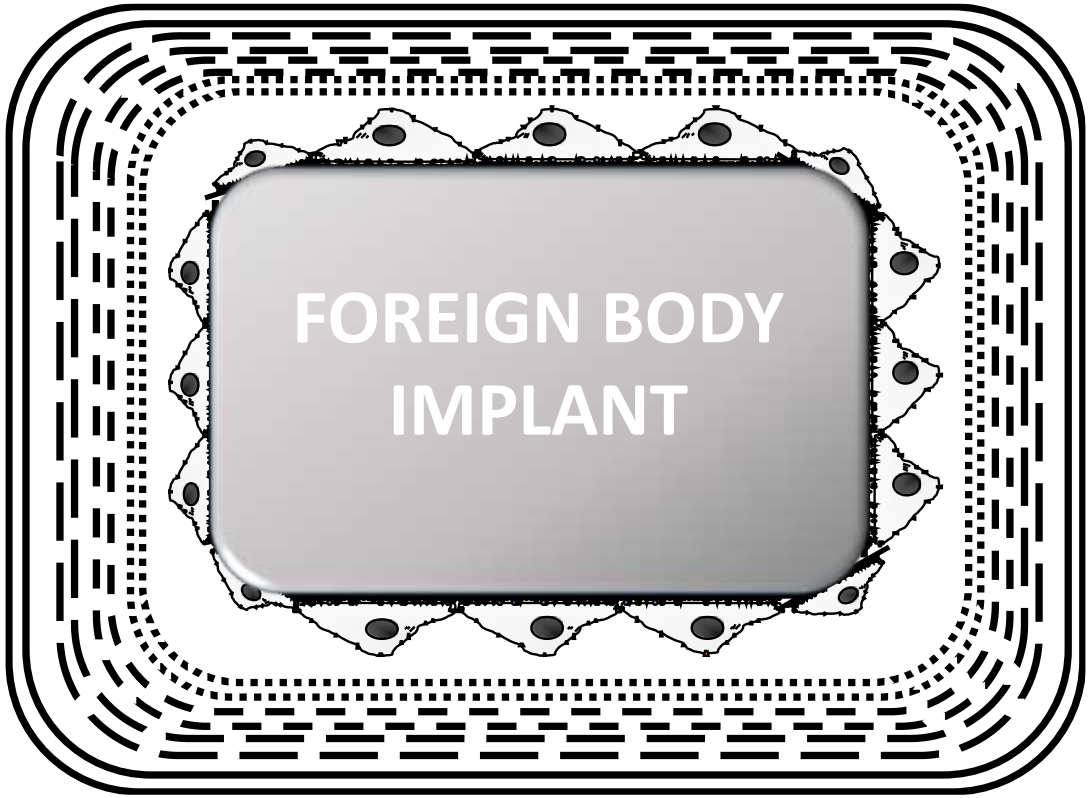


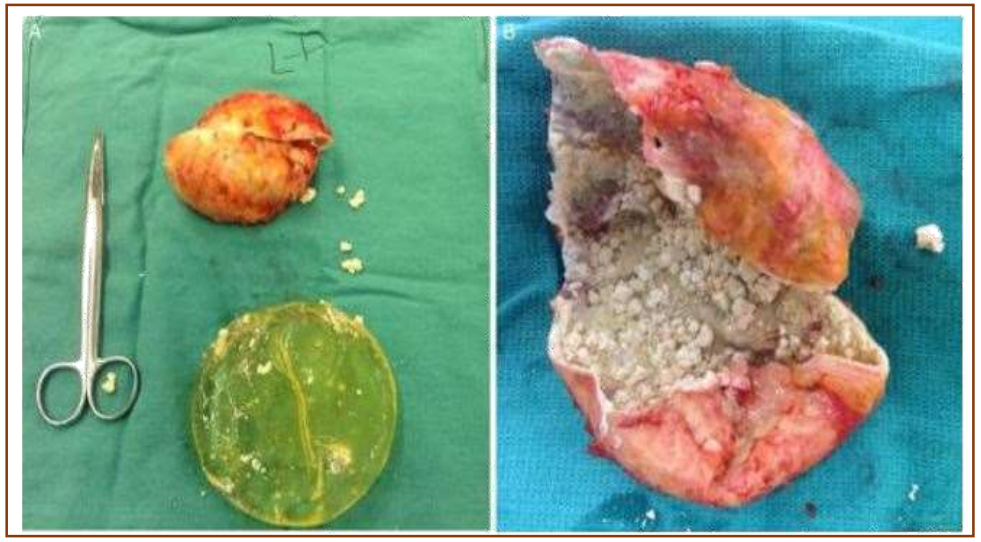
- How does the immune system talk to tissues?

- Are there different fibroblasts?

SYNTHETIC MATERIALS AND THE FOREIGN BODY RESPONSE

Are there common pathways in regeneration and fibrosis?

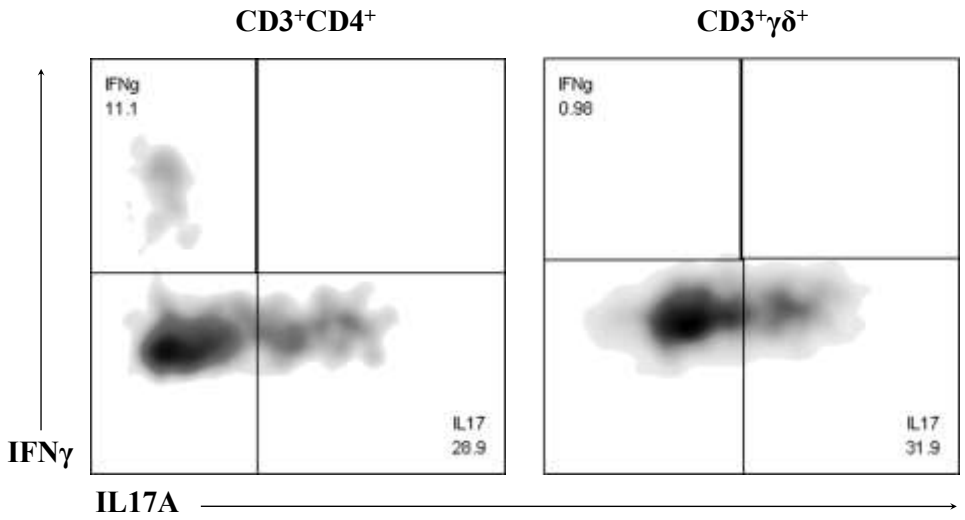




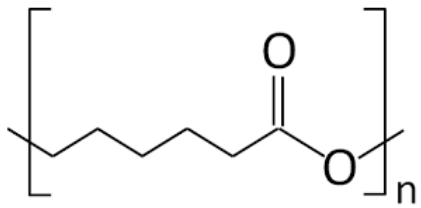
All synthetic materials induce fibrosis/FBR

IL-17 responses and fibrosis induction

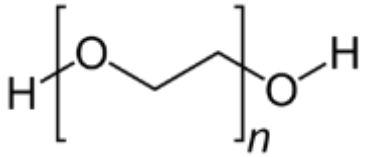
Breast implants/ spacers



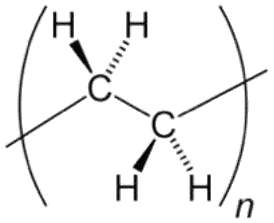
Poly(caprolactone) (PCL)



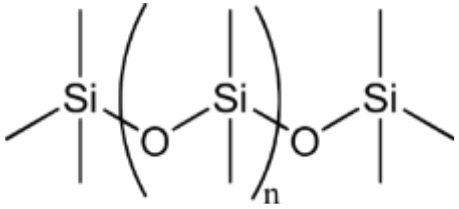
Poly(ethylene glycol) (PEG)



Polyethylene (PE)

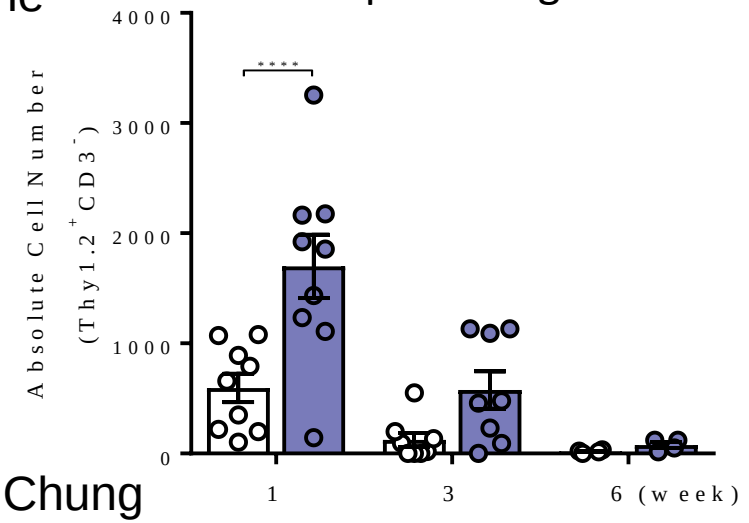


Silicone

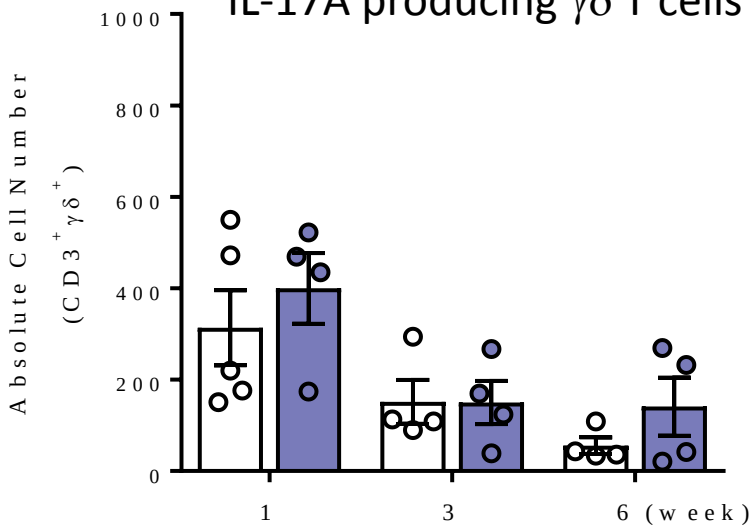


Preclinical murine

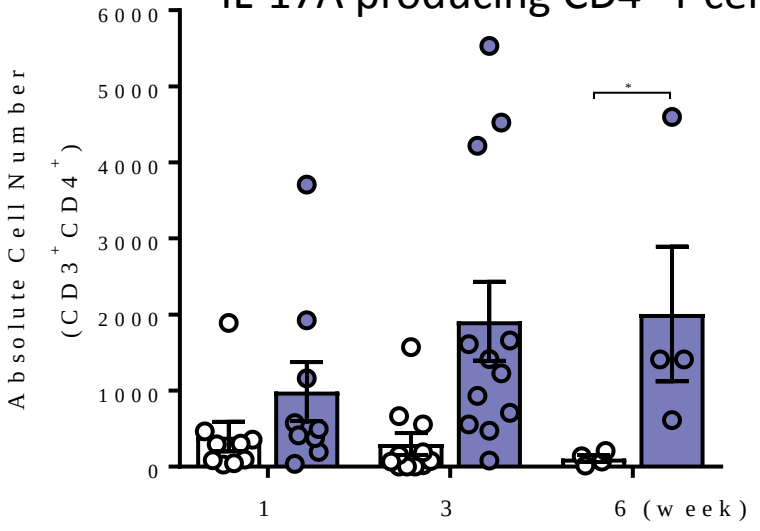
IL-17A producing ILCs



IL-17A producing γδ T cells



IL-17A producing CD4+ T cells



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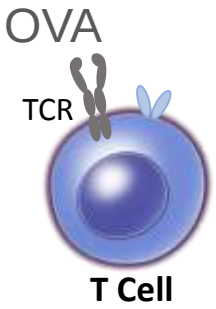
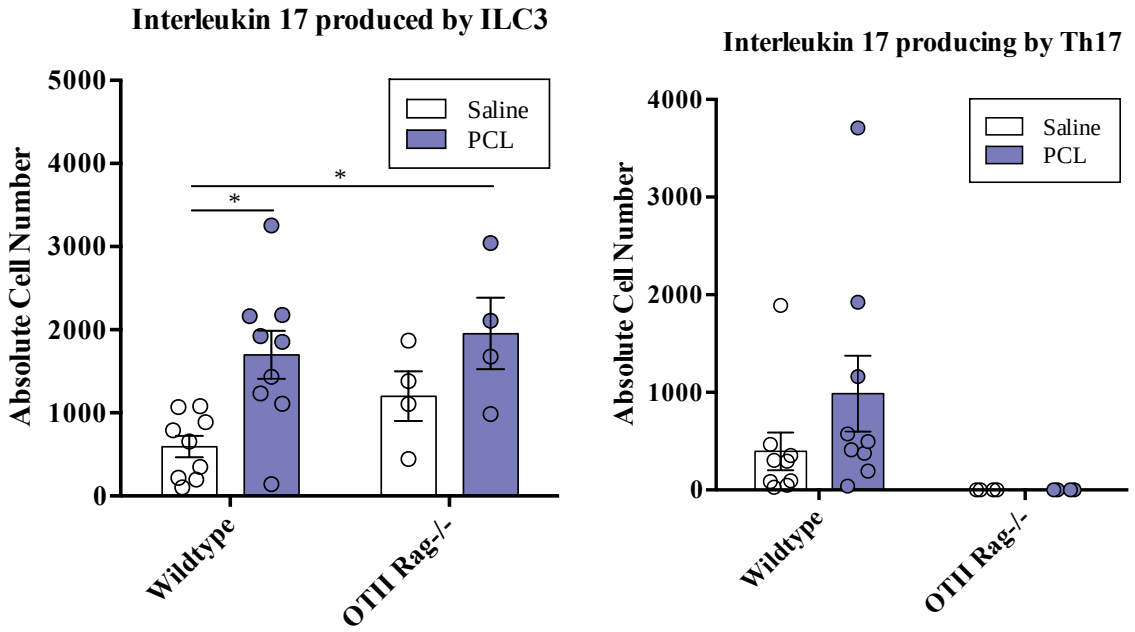
T cell IL-17 is antigen specific

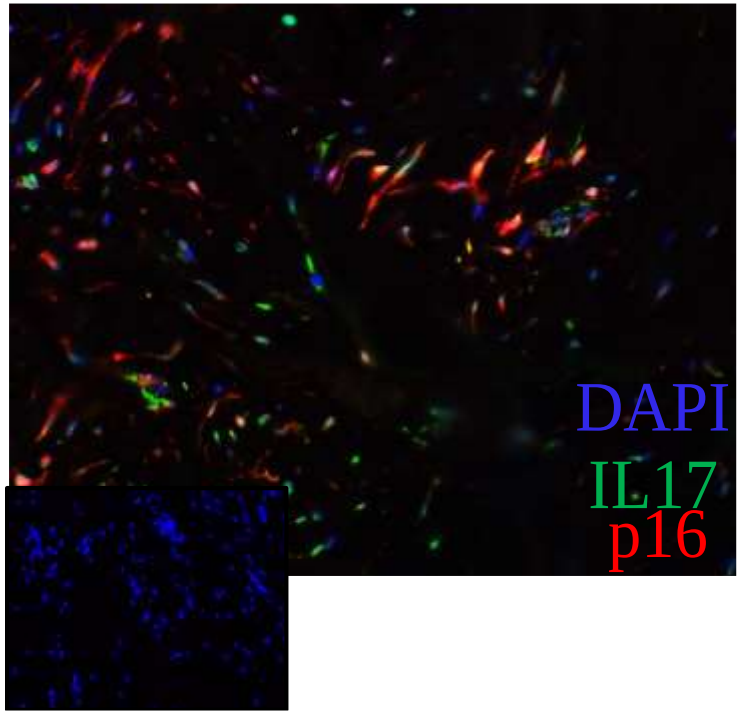
Senescent cells develop!

OT2-Rag-/-





Senescent cells



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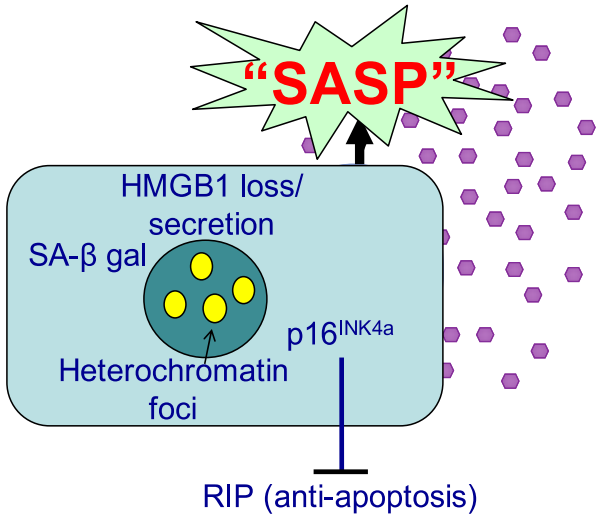
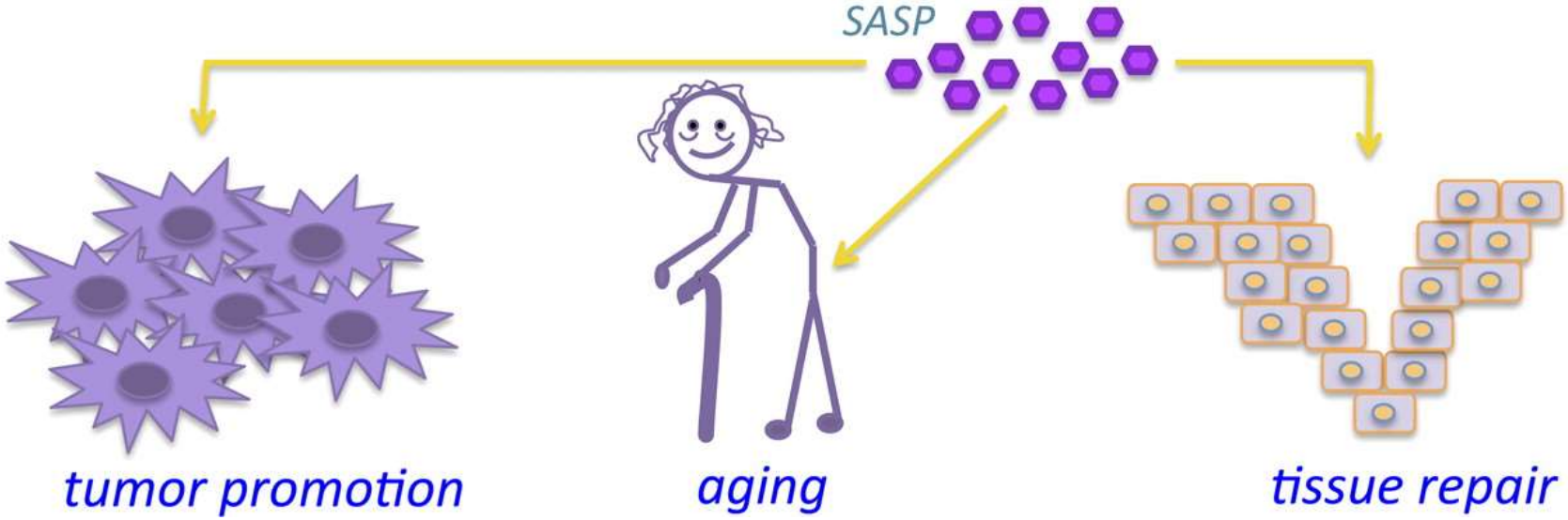
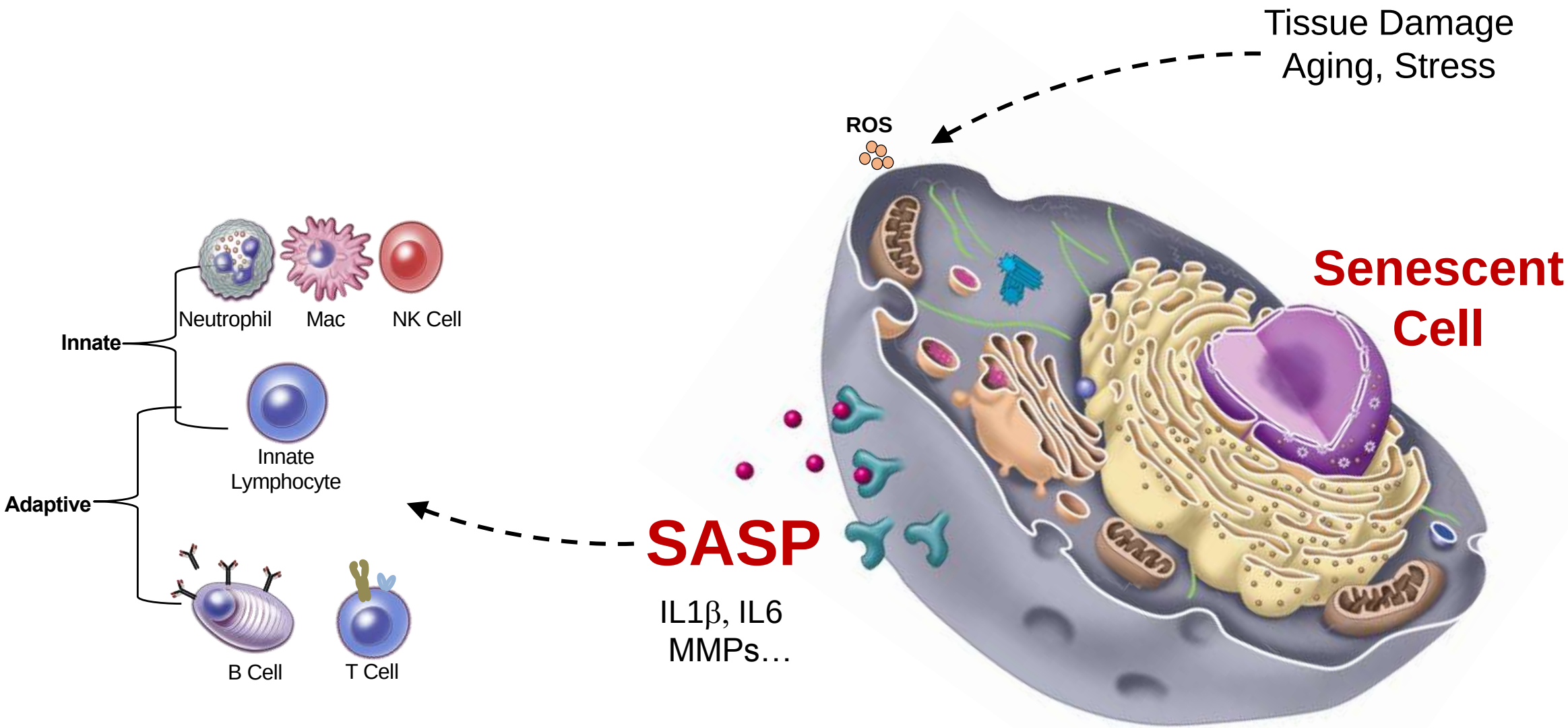
SENESCENT CELLS: A POTENTIAL STROMA-IMMUNE BRIDGE?

SnCs are active through their senescence-associated secretory phenotype (SASP)





SnCs important in repair and implicated in chronic disease


Tissue Damage
Aging, Stress
ROS
Senescent Cell
Innate
Neutrophil
Mac
NK Cell
Innate Lymphocyte
Adaptive
B Cell
T Cell
SASP
IL1β, IL6
MMPs…

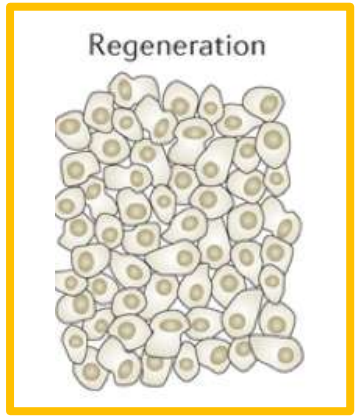
AN IMMUNE MODEL OF TISSUE AND MATERIAL RESPONSES

Introduces new variables and potential need for precision medicine

Muscle

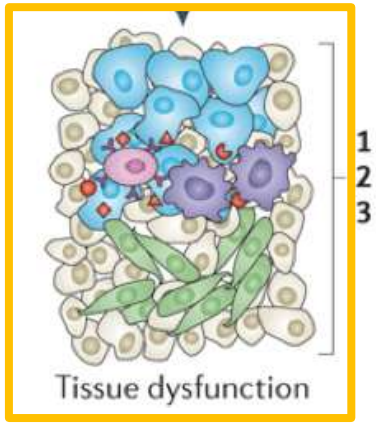
Biological scaffolds

Th2/M2

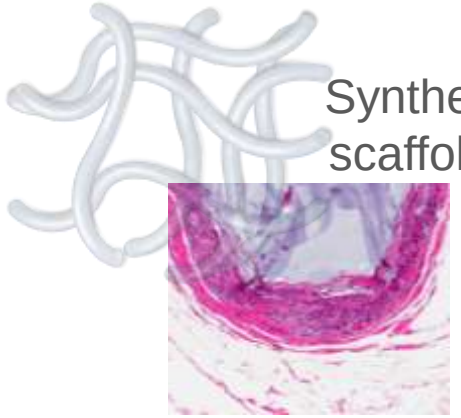


VS

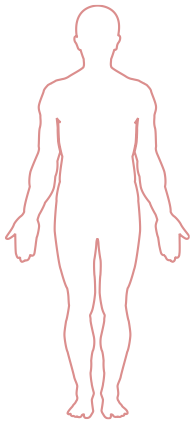
Th17
Senescent cells



Cartilage
Jeon, Nat Med ‘17



Synthetic scaffolds



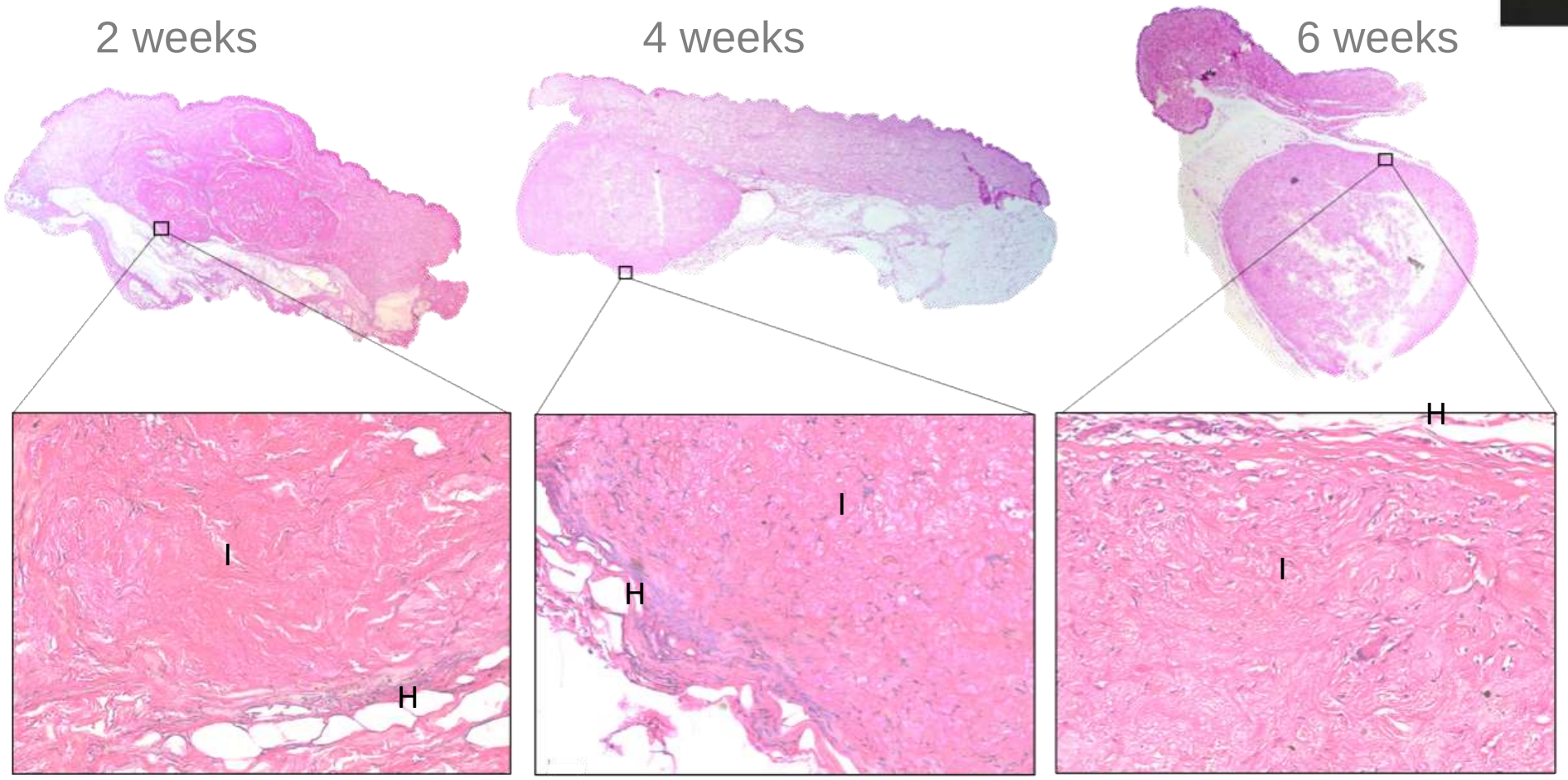
Systemic Factors
Infection
Microbiome
Other injuries
History of exposure
Gender, age…..

New models of tissue and repair introduce systemic factors

Phase I Clinical Trial of an ECM

Applying the new immune knowledge in people

GMP JHU
FDA Biologics

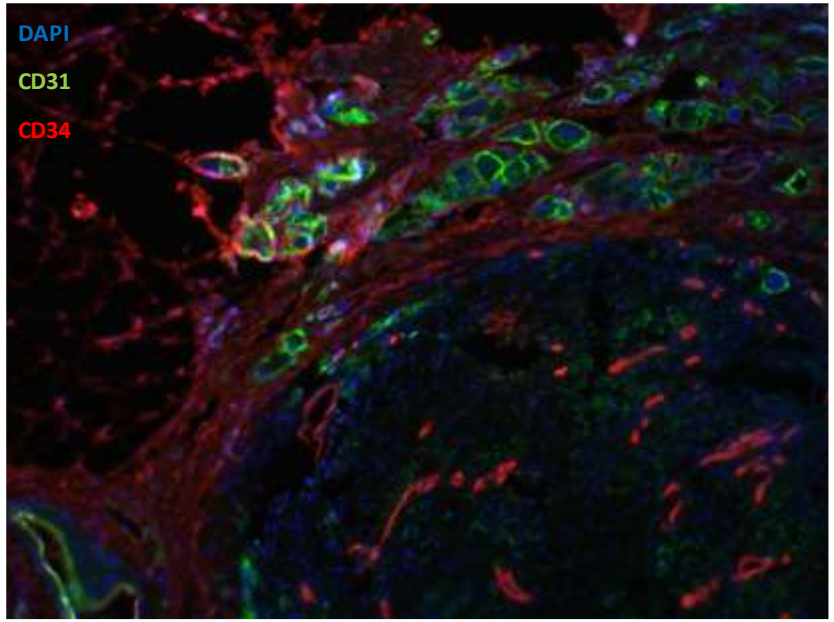


I = Implant H = Host

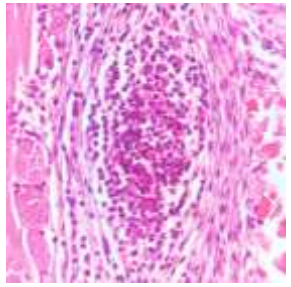
What cells are there and what are they doing?

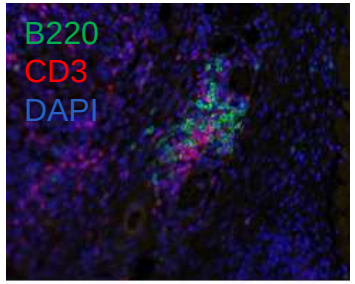
18 weeks post-injection

Vascularization and Stem Cells

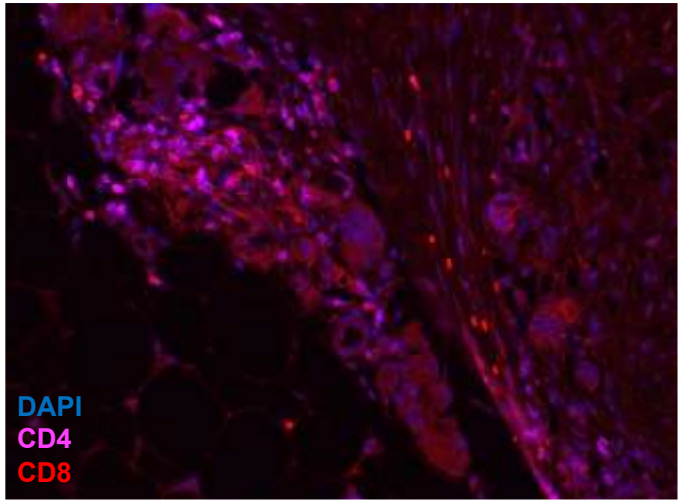


Immune aggregates (Mouse)

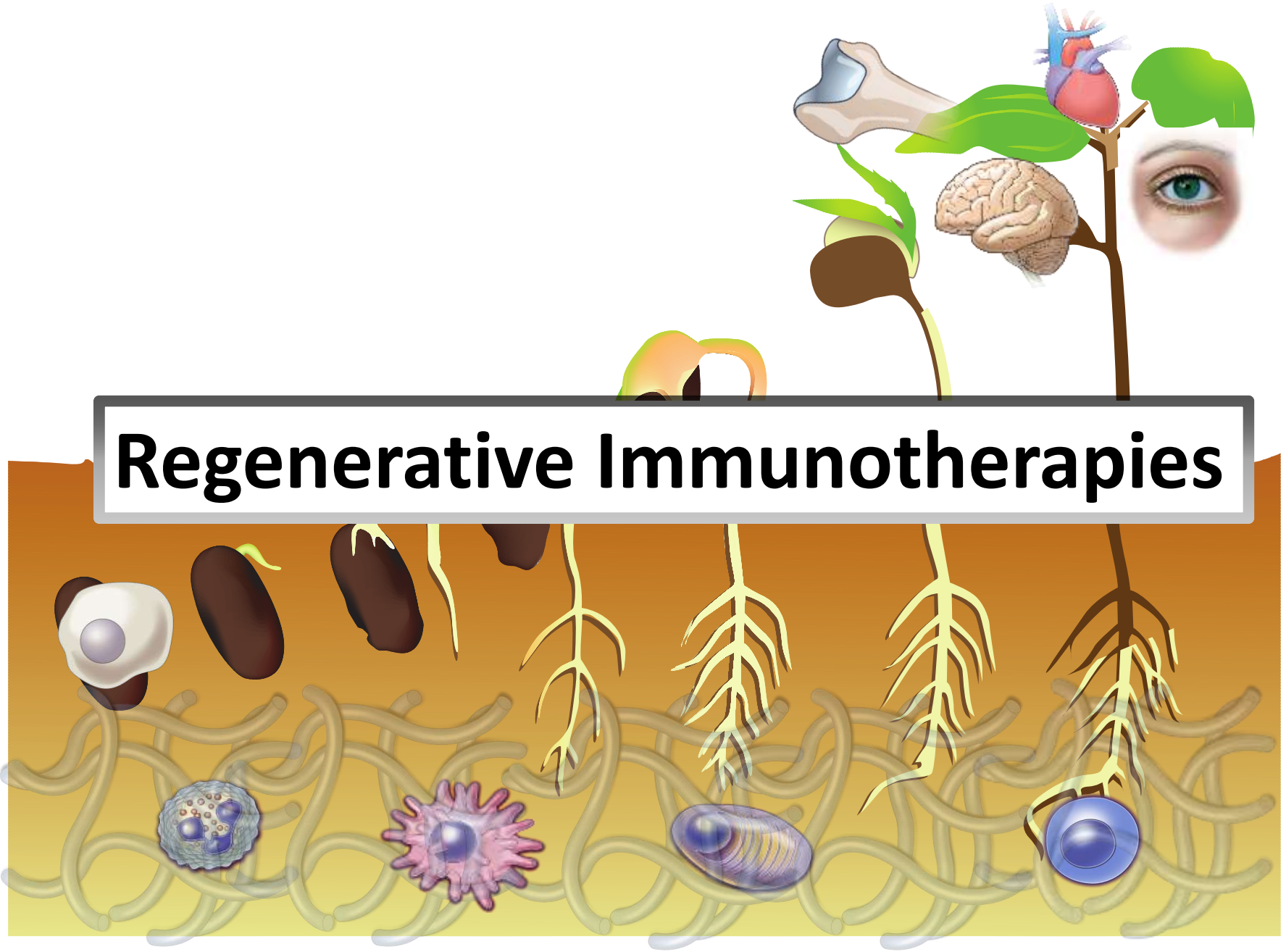




Human



Biological (ECM) scaffolds are biologically (immunologically) active!


Regenerative Immunotherapies

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Hongni Fan
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ACell
Healing through Regenerative Medicine

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Bloomberg~Kimmel Institute for Cancer Immunotherapy

SUPPORTED BY
RPB
Research to Prevent Blindness

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