JOHNS HOPKINS UNIVERSITY

TTEC TRANSLATIONAL TISSUE ENGINEERING CENTER

Manufacturing complex biologics for regenerative immunology

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December 1, 2022

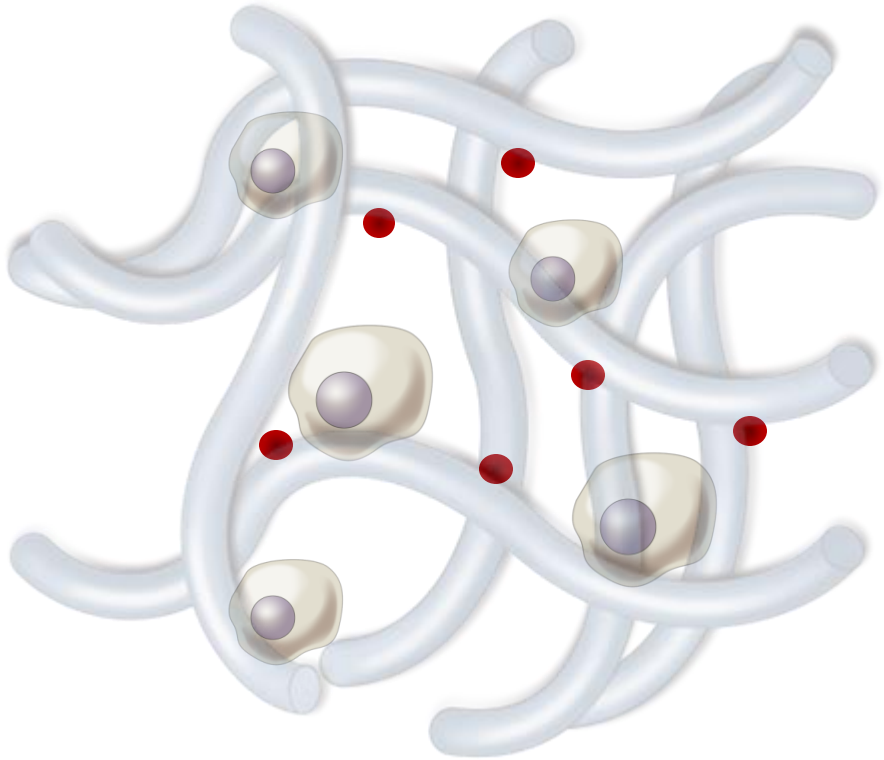
@JHElisseeff

TISSUE ENGINEERING AS A STRATEGY FOR REPAIR

Biomaterial scaffolds + biological signals + cells

Global organ donation:
136K, >7% yearly growth

Osteoarthritis:
Single most common cause of disability >60, ~10-15% of population

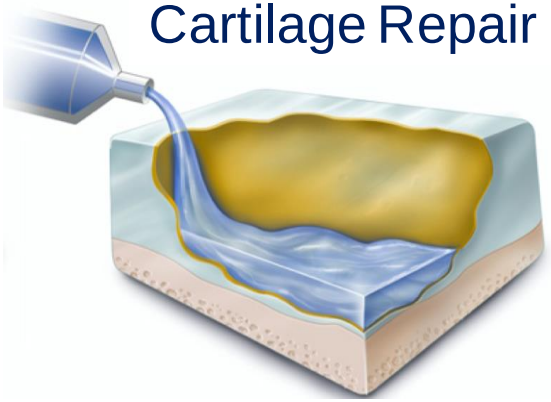


Clinical translation slow in tissue engineering

CLINICAL TRANSLATION INFORMS NEW RESEARCH DIRECTION

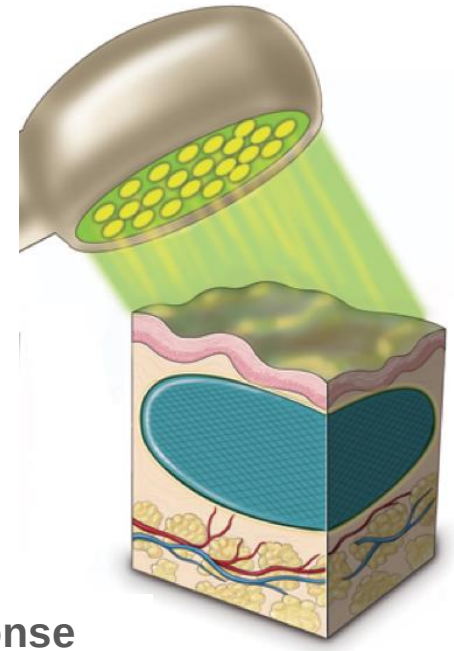
Understand the biomaterial immune response and engineer for repair

Cartilage Repair

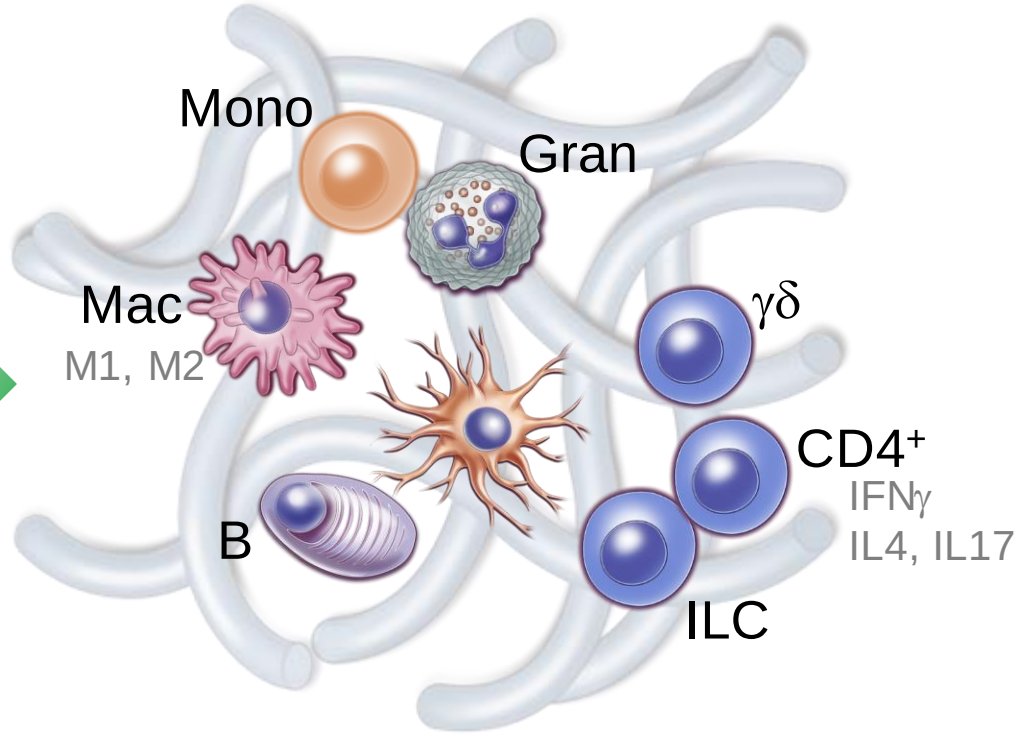


Redirecting wound healing

Soft Tissue Filler



Tissue specific immune response

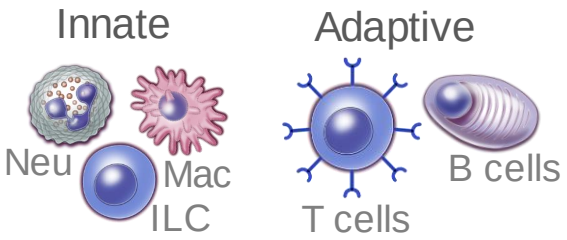


Lessons in translation: Regenerative immunotherapies for tissue repair

REGENERATIVE IMMUNOLOGY

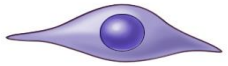
Marrying regenerative medicine, immunology and tissue engineering

The immune system is the first responder to injury



Map the immune response to injury (and biomaterials)

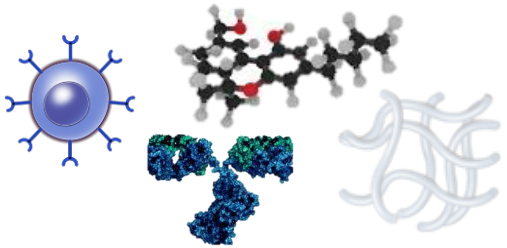
The immune environment determines downstream tissue repair



Senescence
Stem cells

Define immune impact on tissue development

Engineer immunotherapies to create a pro-regenerative environment

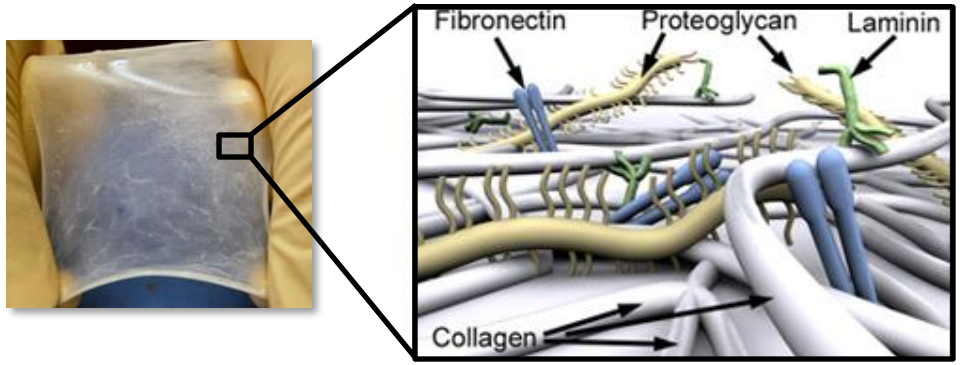


Design and apply Regenerative Immunotherapies

The immune system is therapeutically accessible → the right target for regenerative medicine

BIOLOGICAL SCAFFOLDS IN THE CLINIC

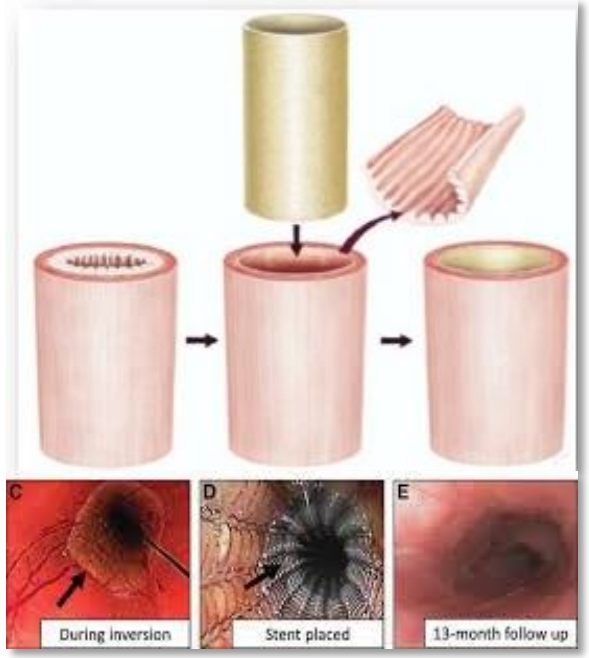
Minimally processed extracellular matrix (ECM)



Breast

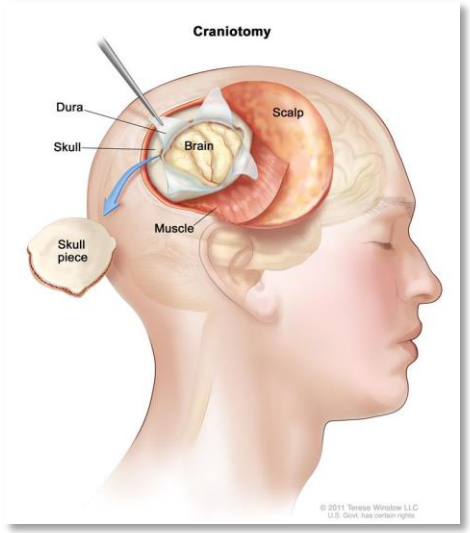
AlloDerm™
Permacol™
www.aestheticplasticsurgerypc.com

Esophagus



Surgisis®
Badylak SF et al. Tiss Eng Part A. 2015.

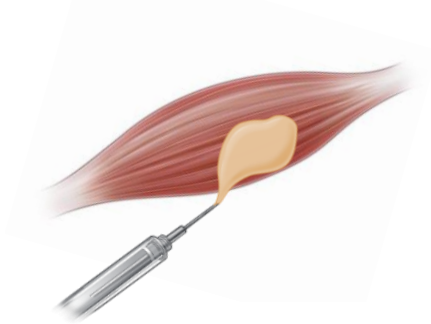
Dura



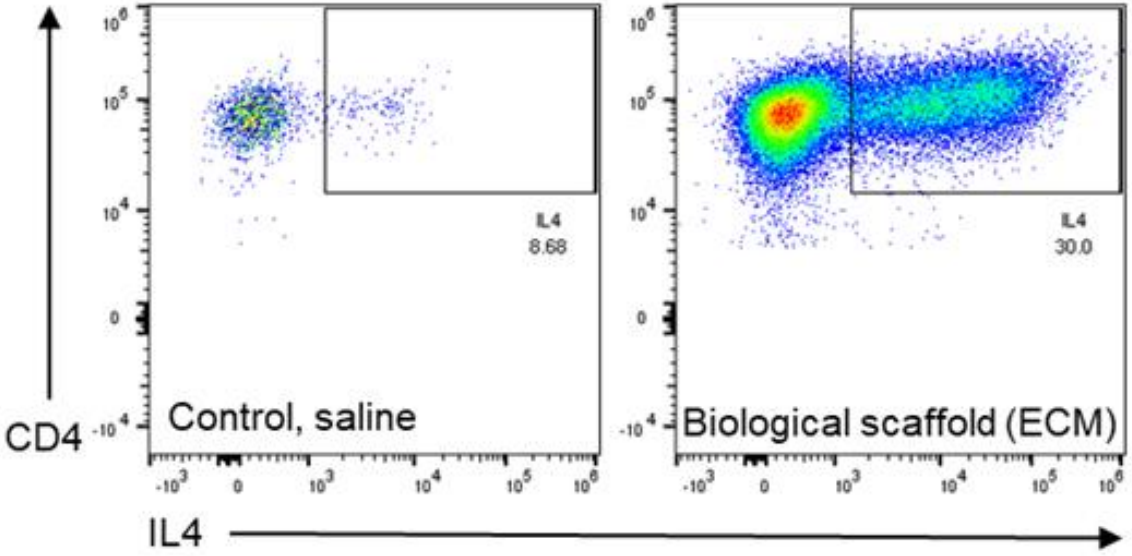
Biodesign® Dural Graft
Durepair™ Regeneration Matrix

ECM materials contain DAMPs and intracellular proteins

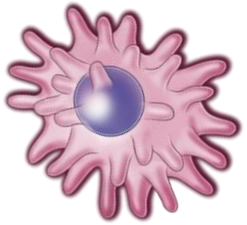
MUSCLE AND BIOLOGICAL SCAFFOLDS: PRO-REGENERATIVE IMMUNE PROFILE



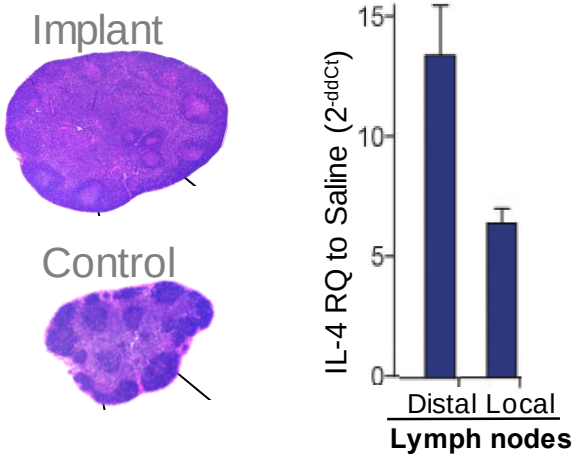
T cells in the Wound/biomaterial



T cells direct macrophage behavior



Lymph node changes



SYSTEMIC IMPACT

Sadtler et al., *Science*, 2016

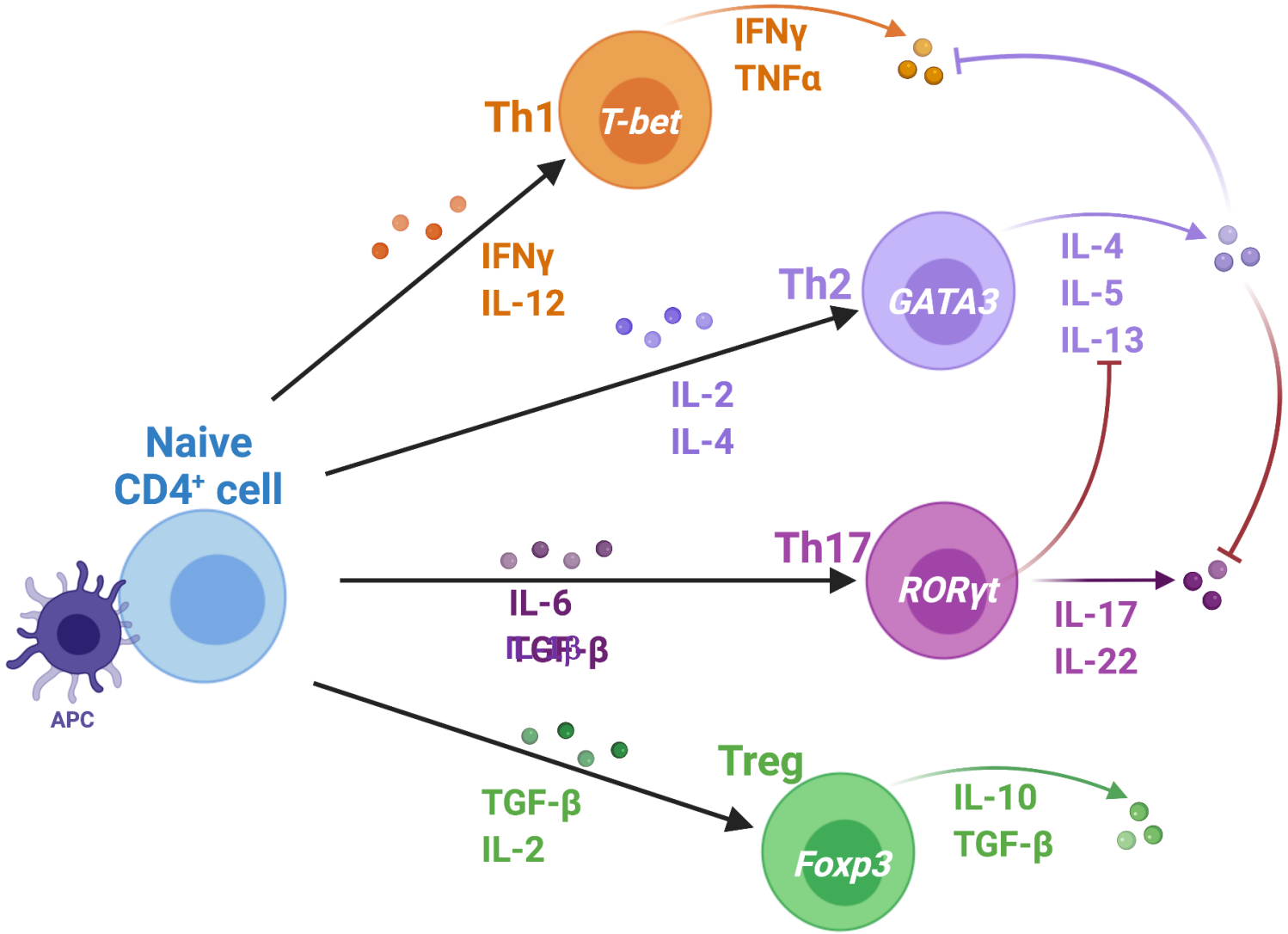
Biomaterials ENHANCE the T_H2 response and create a pro-regenerative environment in muscle

ECM: composition and biologic activity consistency

- Physical properties
  - Color, water, DSC, other
  - Specific components as metric - lipids, collagen?
  - Mechanics/Injectability
- Biological activity
  - Promote appropriate cell infiltration
  - Stimulate new tissue development

ECMs are complex biologics and should be consistently regulated

TYPE 2 IMMUNE RESPONSE: target for regenerative medicine



TYPE 2 IMMUNE STIMULATION

Inspiration from nature → *Schistosomiasis* soluble egg antigen

LETTER

https://doi.org/10.1038/s41586-018-0257-1

Parasitic helminths induce fetal-like reversion in the intestinal stem cell niche

Ysbrand M. Nusse[1,2,6], Adam K. Savage[3,6], Pauline Marangoni[2], Axel K. M. Rosendahl-Huber[2], Tyler A. Landman[2], Frederic J. de Sauvage[4], Richard M. Locksley[3]* & Ophir D. Klein[2,5]*

Th2 Cytokines Are Associated with Persistent Hepatic Fibrosis in Human *Schistosoma japonicum* Infection FREE

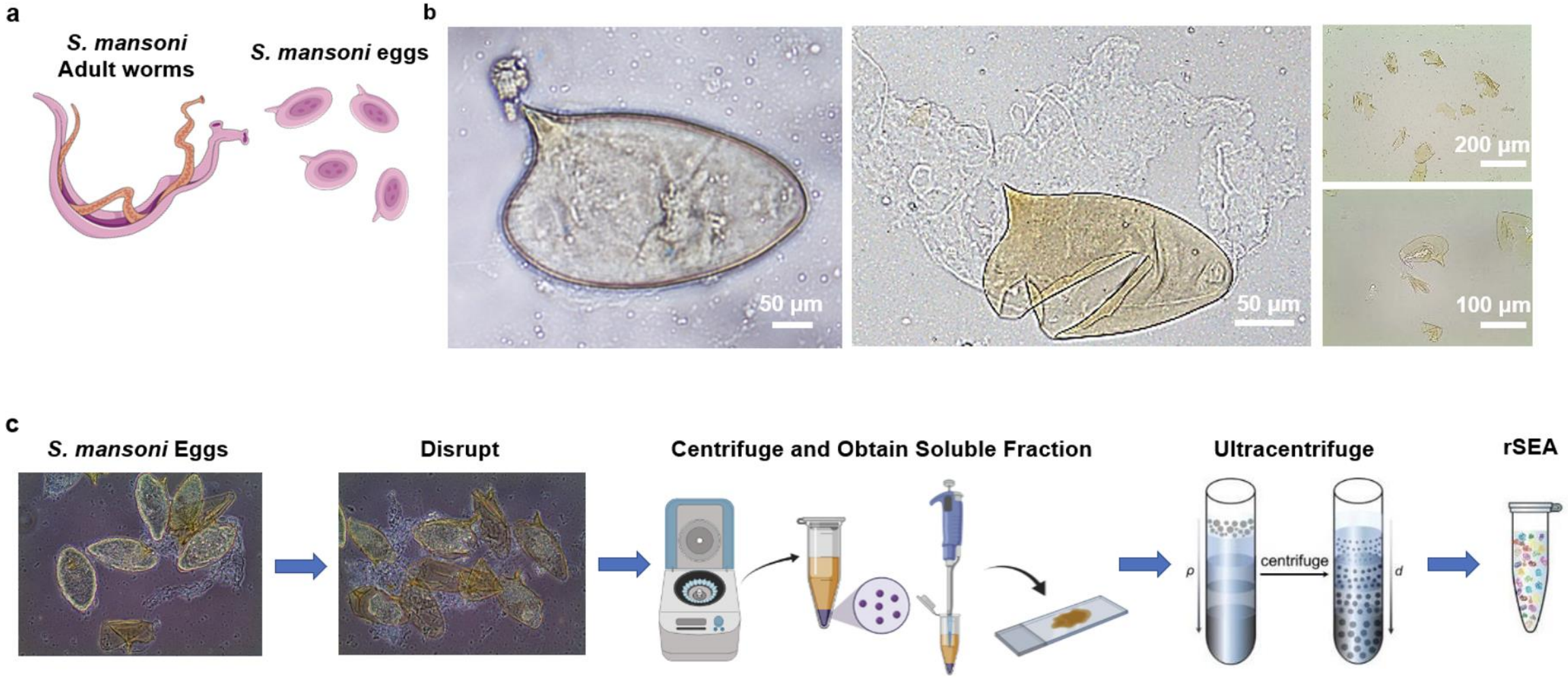
H. M. Coutinho ✉, L. P. Acosta, H. W. Wu, S. T. McGarvey, L. Su, G. C. Langdon, M. A. Jiz, B. Jarilla, R. M. Olveda, J. F. Friedman ... Show more

The Journal of Infectious Diseases, Volume 195, Issue 2, 15 January 2007, Pages 288–295, https://doi.org/10.1086/510313

Published: 15 January 2007 **Article history** ▾

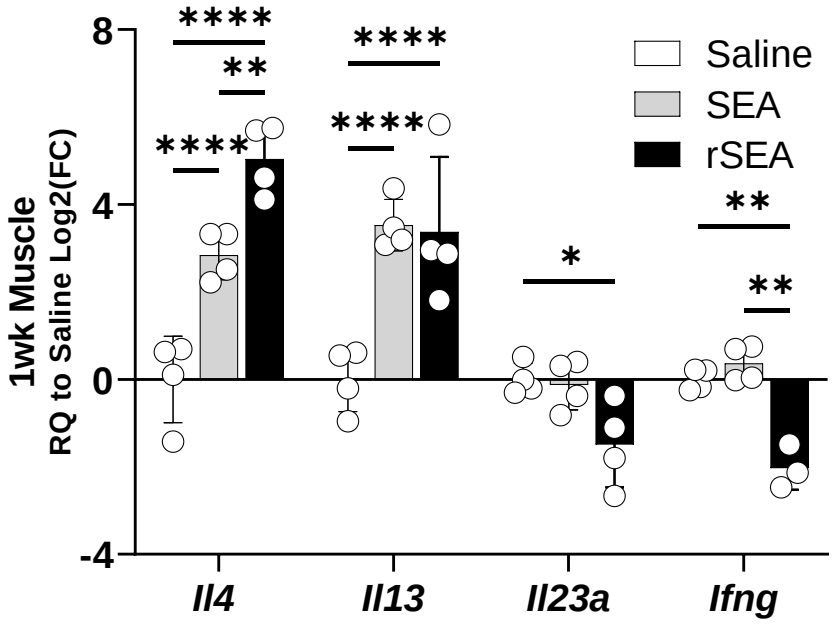
Maestas et al, Biorvx, 2022

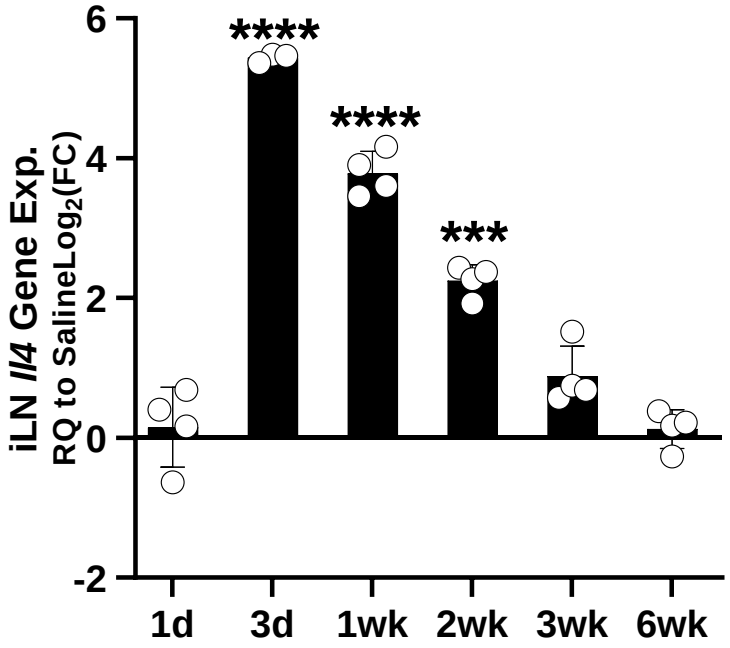
SEA: FORMULATING FOR REPAIR AND REGENERATION



Maestas et al, Biorvx, 2022

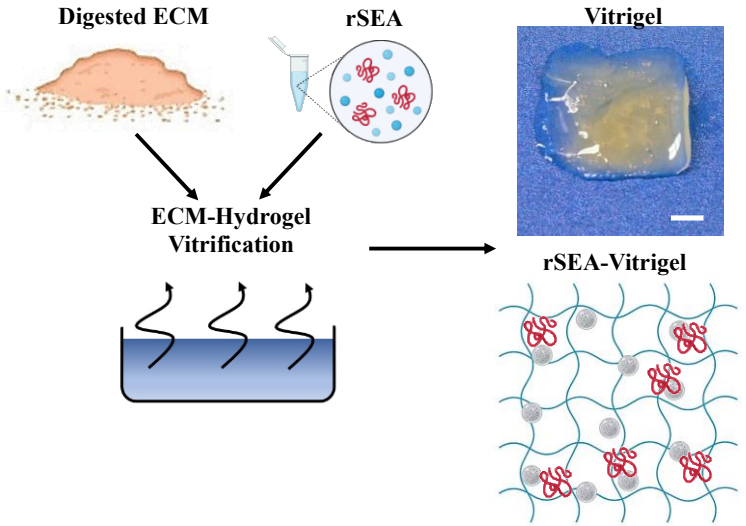
rSEA PROMOTES EXTENDED TYPE 2 IMMUNE RESPONSE

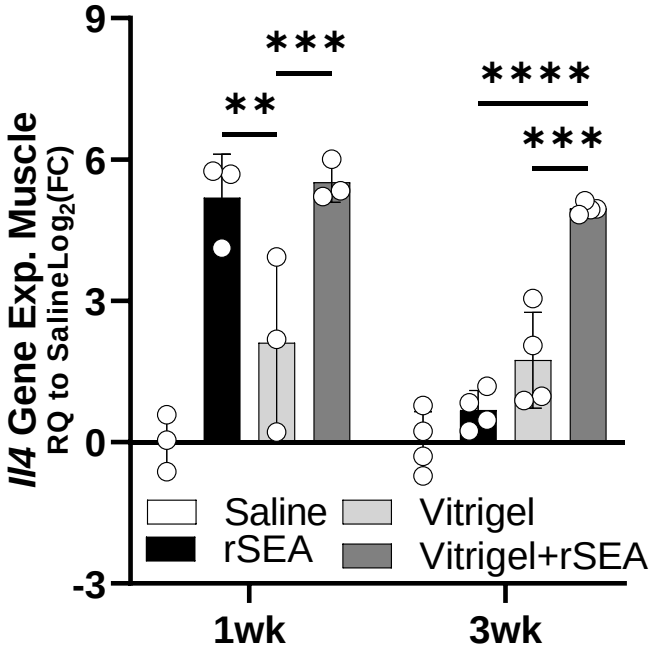


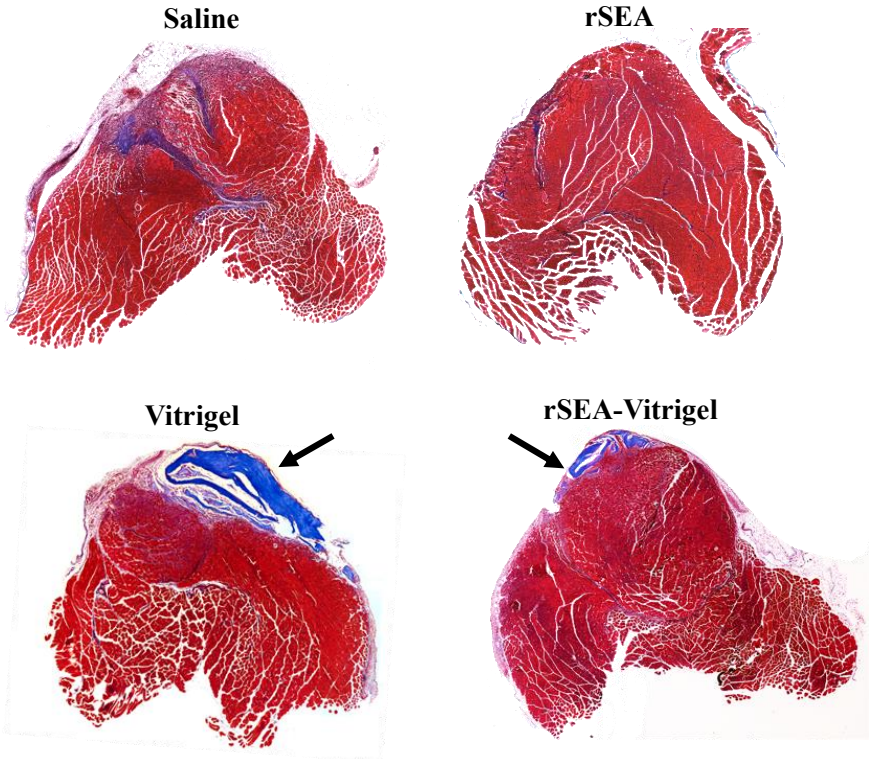


Maestas et al, Biorvx, 2022

rSEA PROMOTES EXTENDED TYPE 2 IMMUNE RESPONSE



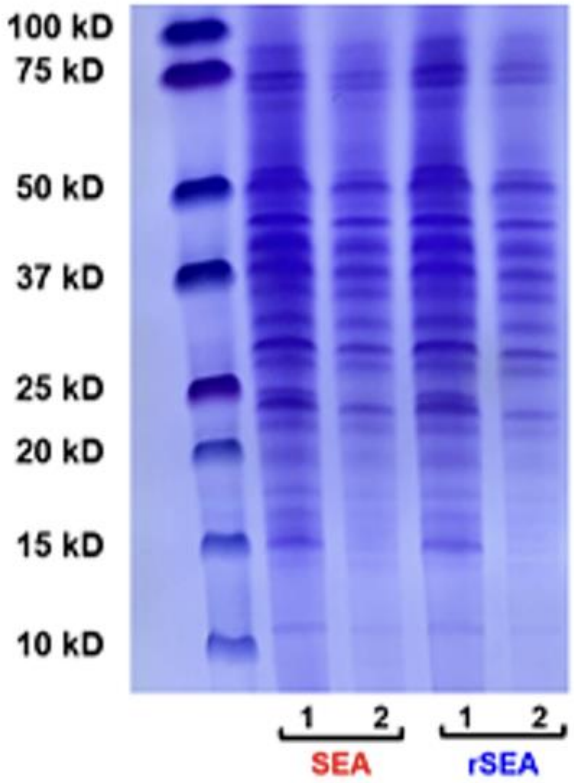




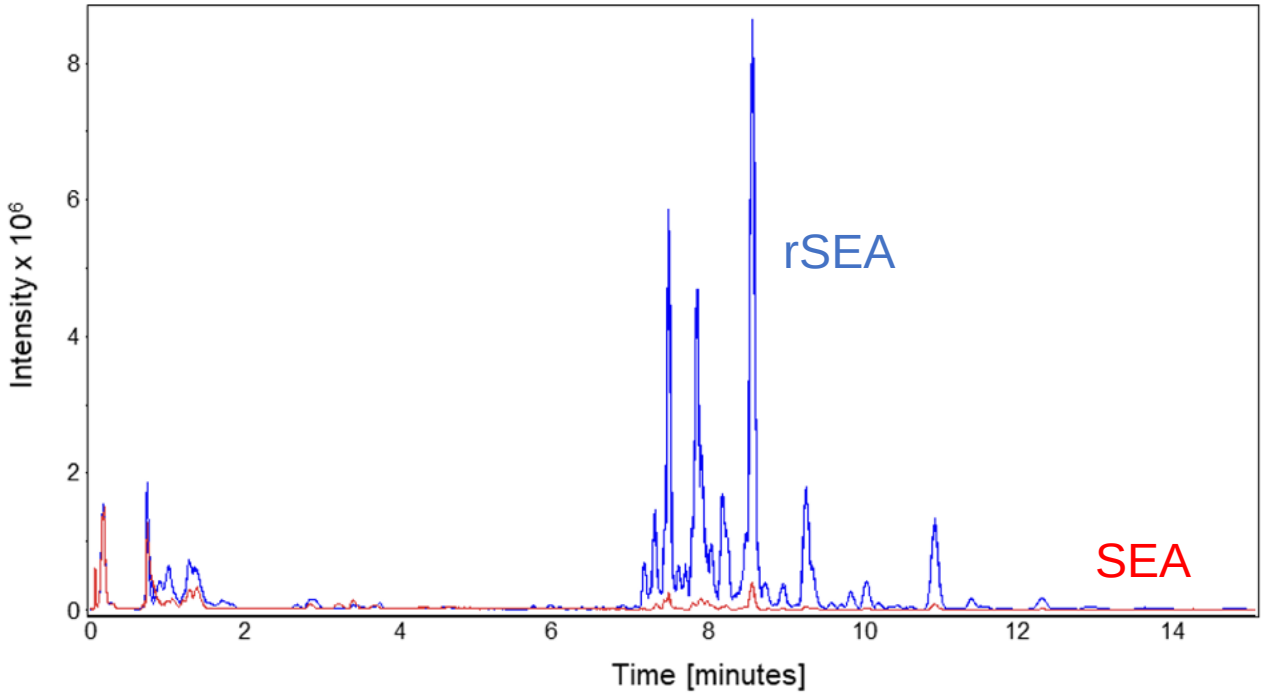
Maestas et al, Biorvx, 2022

rSEA: A COMPLEX MIXTURE

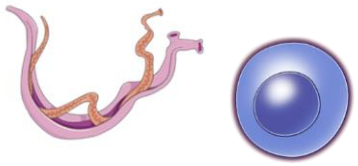
Proteins

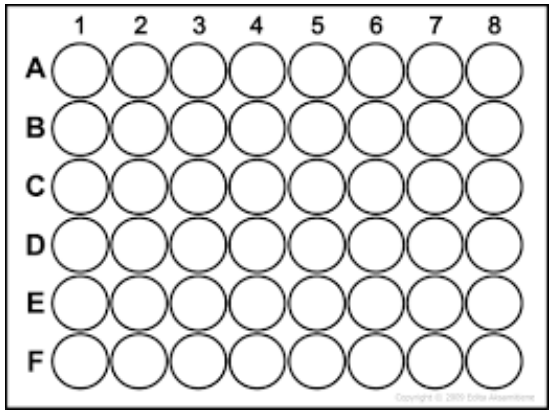


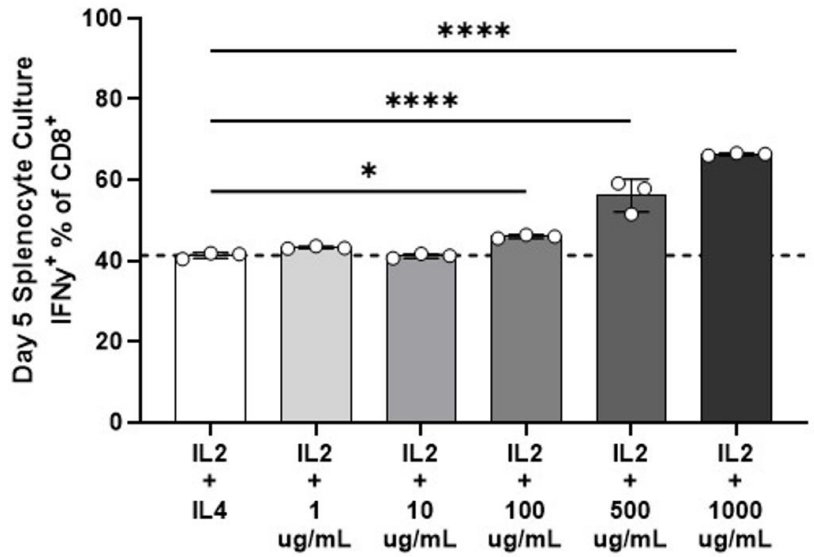
Lipids

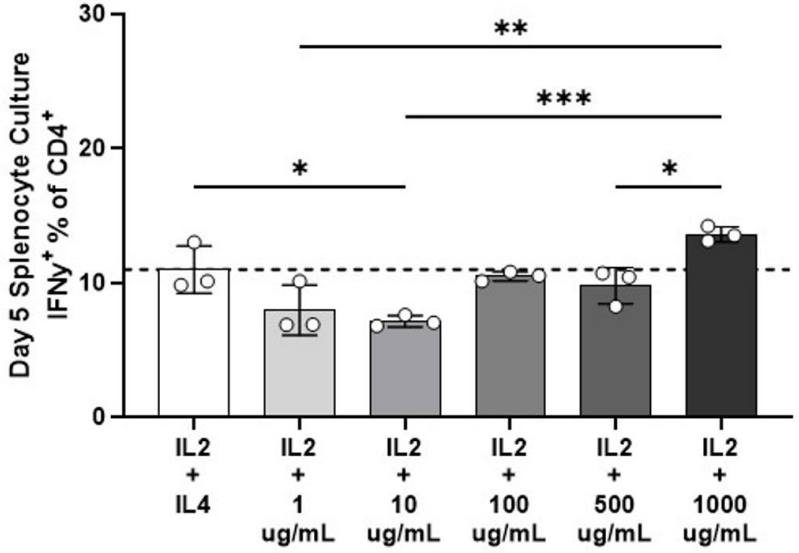


Validating biological activity: developing relevant screens



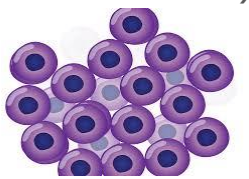




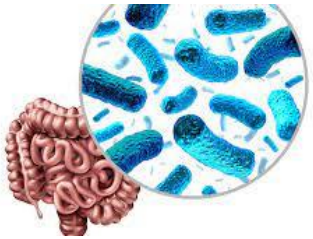


From lessons in translation to Lost in translation…

Cancer
(comorbidities)



Aging

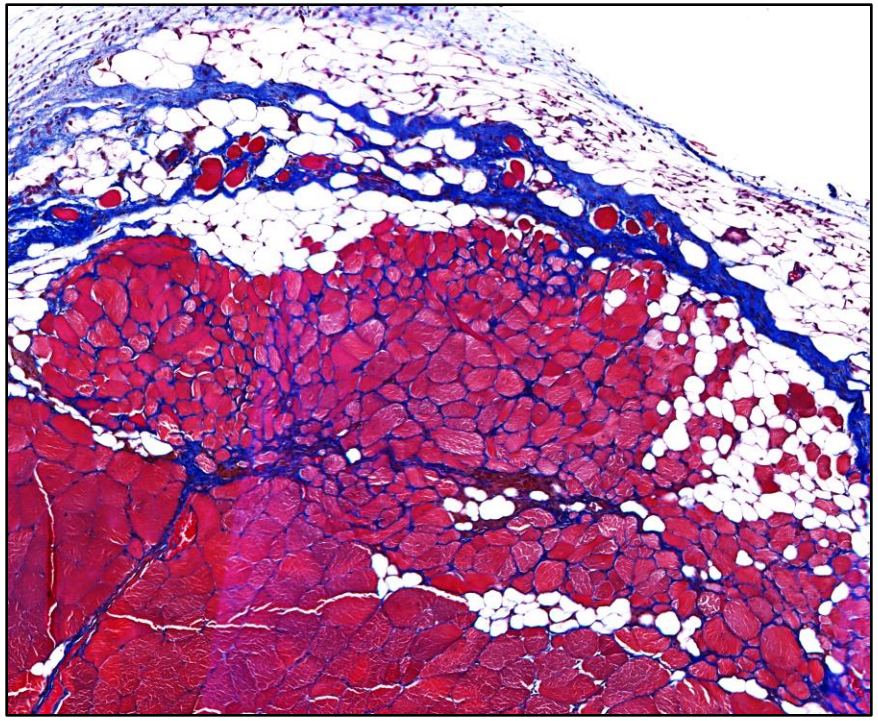


Microbiome

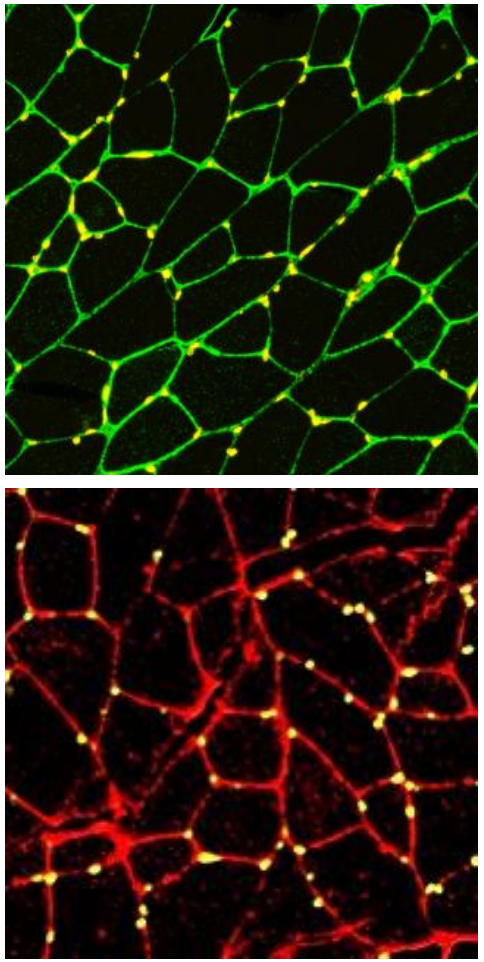
Infection

REGENERATIVE BIOMATERIAL RESPONSE IN AGING ANIMALS?

Increased adipogenesis and fibrosis in 20 month old mice



Reduced muscle repair



Dystrophin / DAPI / Laminin

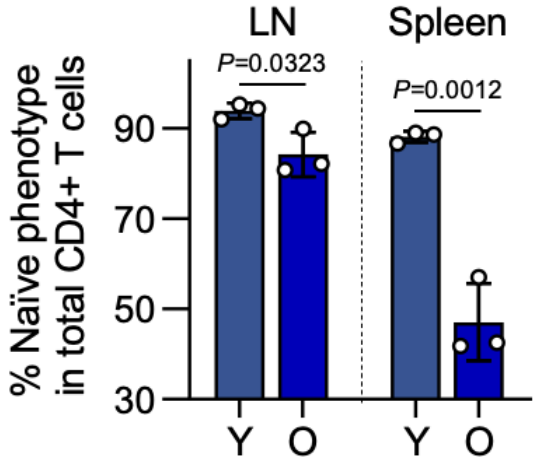
Han, Biorvx, 2021

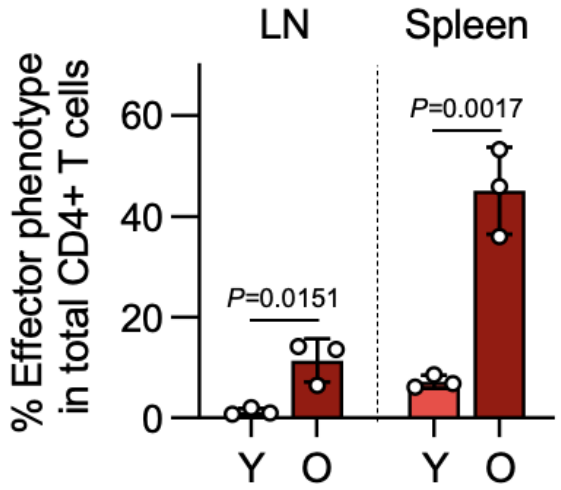
Aging

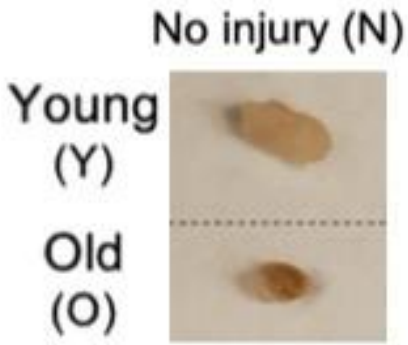
Need for combination therapies

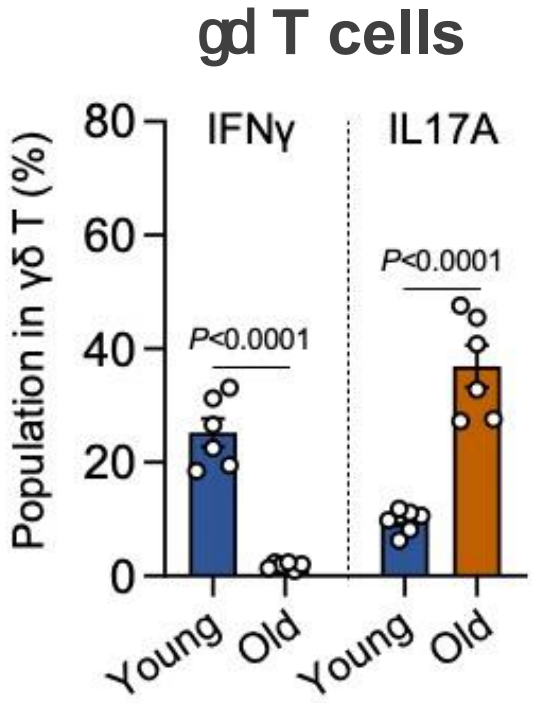
Han et al, Biorvx, 2022

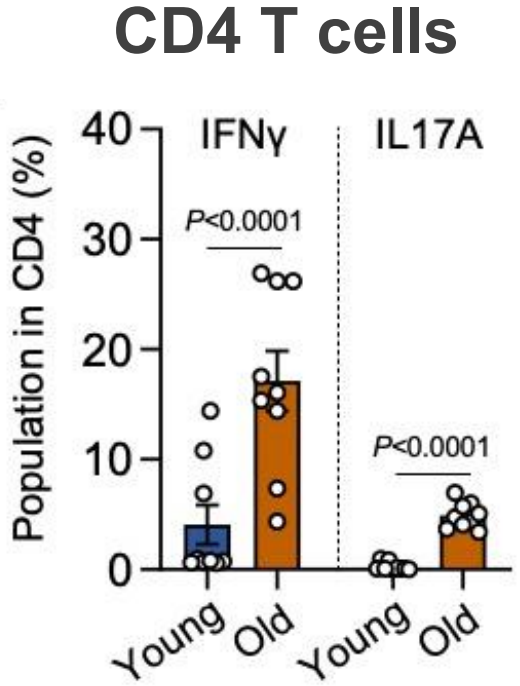
ADAPTIVE IMMUNE CHANGES WITH AGING





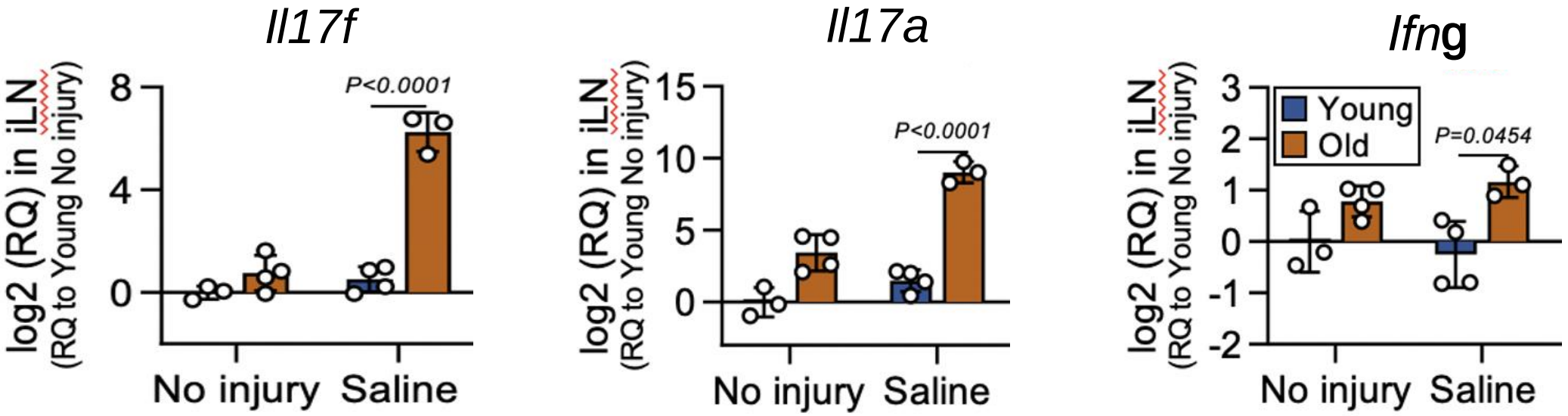




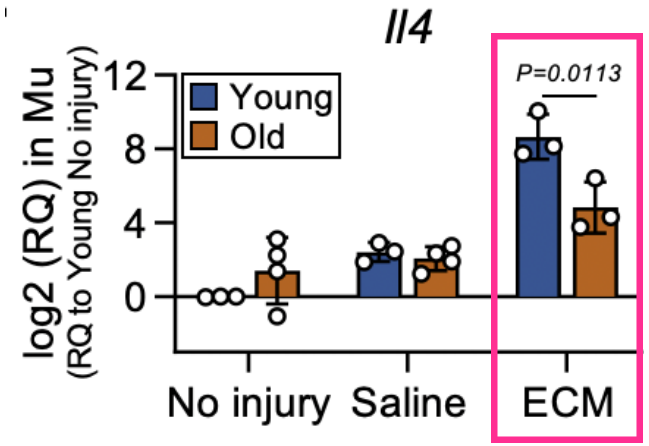


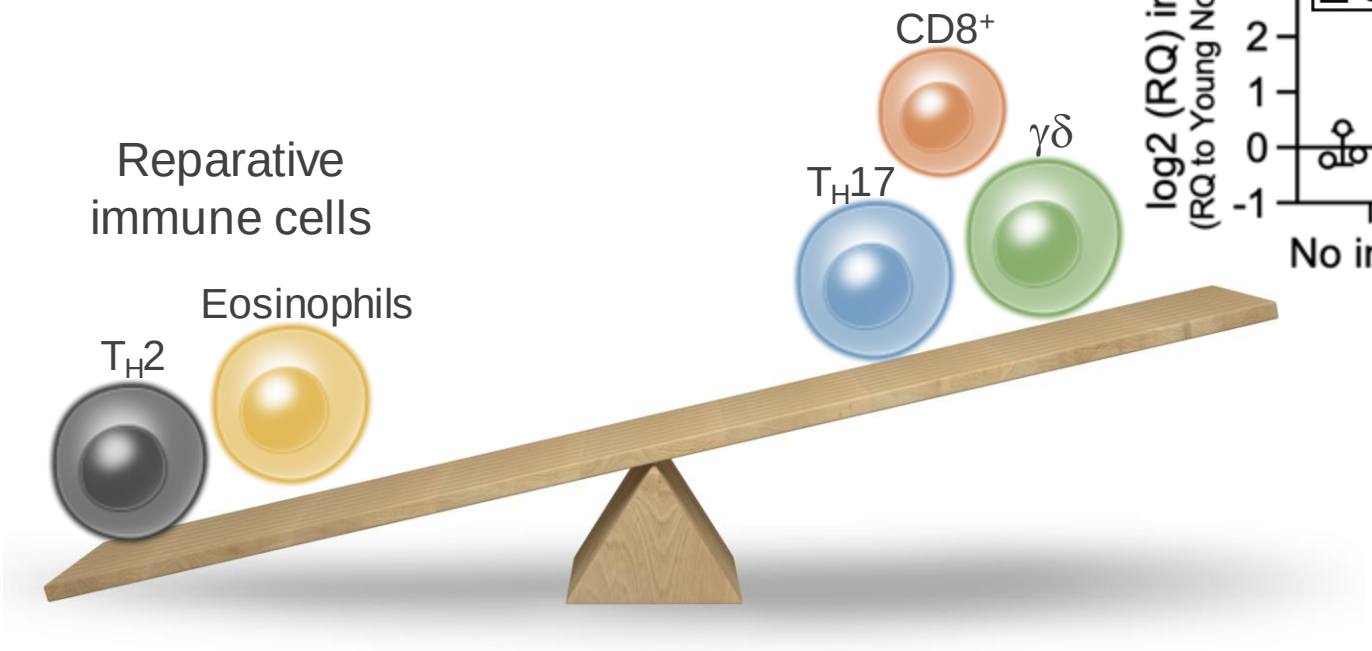
Han, Biorvx, 2021

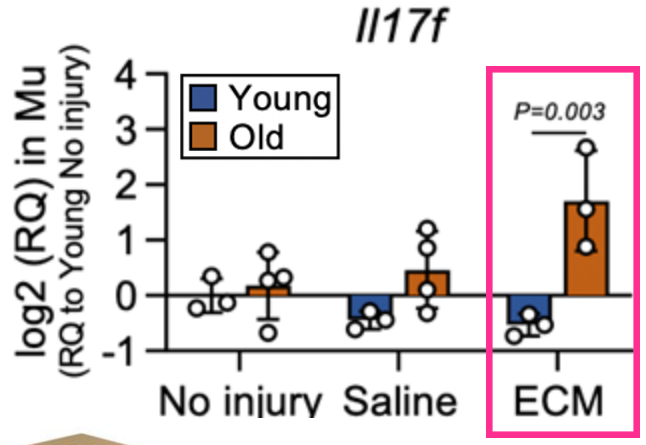
INJURY UNCOVERS AGING DIFFERENCES IN SECONDARY IMMUNE STRUCTURES



IMMUNE CHANGES IN AGING MUSCLE INJURY



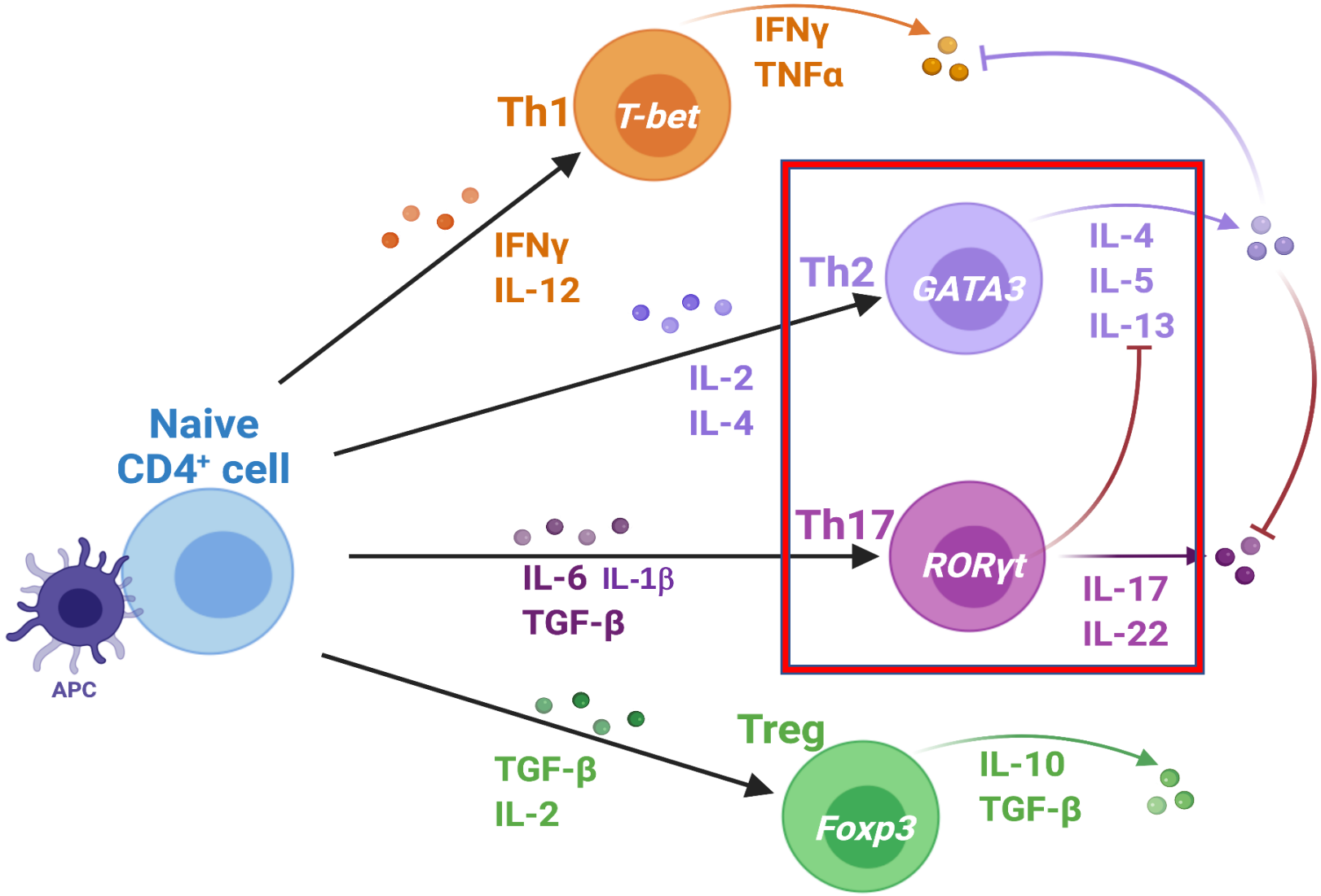




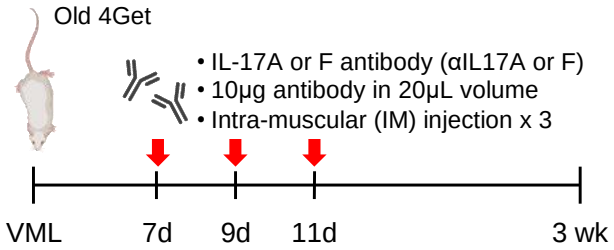
Han, Biorvx, 2021

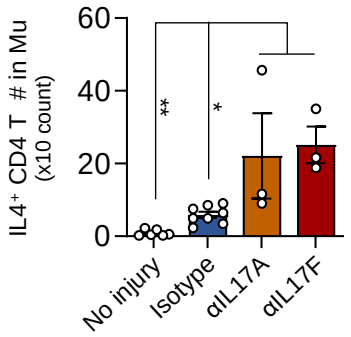
Regenerative immune cells decrease and inflammatory cells increase with age

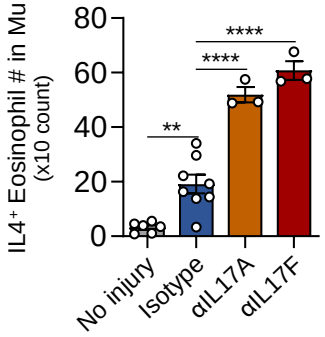
IL17 negative regulation of IL4

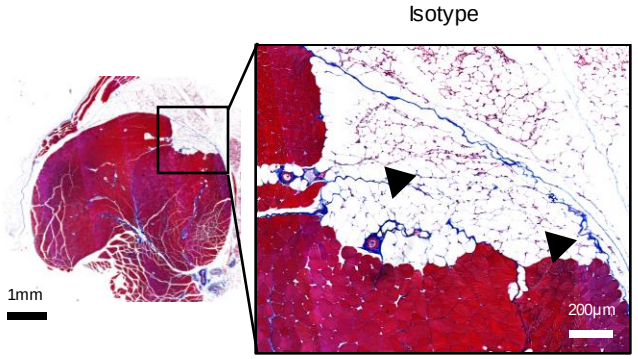


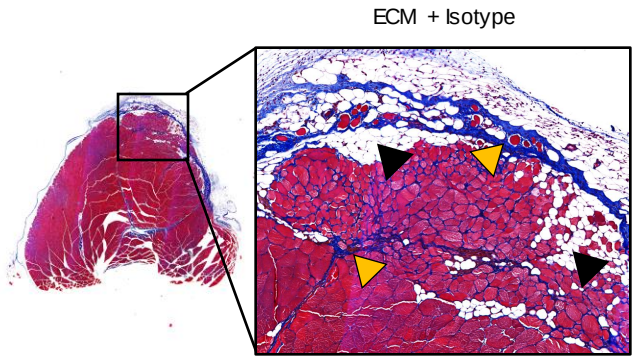
COMBINATION THERAPY RESTORES TISSUE REPAIR

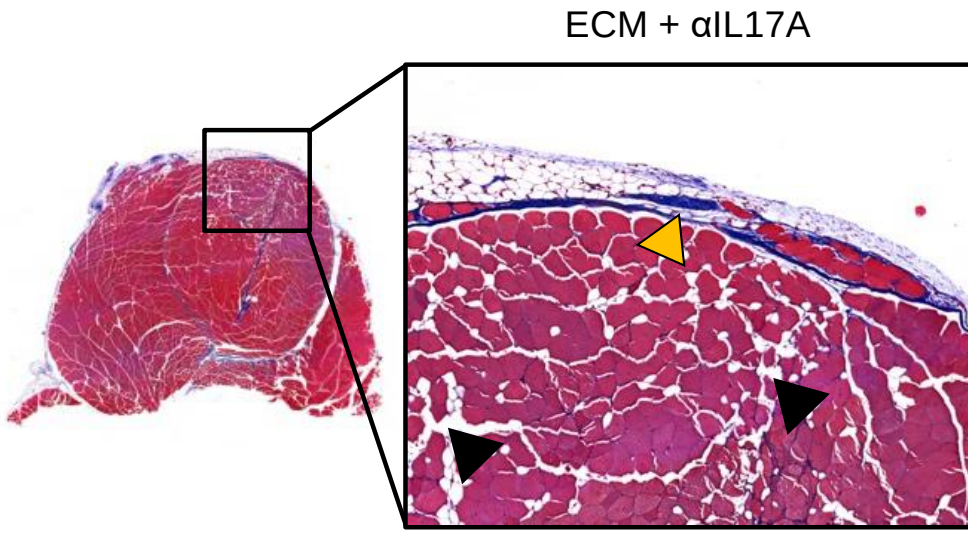












Manufacturing complex biologics

- Needed for targeting the multiple contributors to repair
  - Multiple mechanisms of action
- Consistent regulation needed
- Physical, compositional and biological release assays
- Combination products for aging and personalized medicine

Acknowledgements

Current Lab members

Chris Cherry
David Maestas
Anna Ruta
Joscelyn Meijas
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Helen Nguyen
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Katlin Stivers
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Jonathan Powell
Franck Housseau
Sudipto Ganguly
Ada Tam
Janis Taube, Bob Anders

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Darren Baker, Mayo
Jan van Deursen
Doahong Zhou, UF

Clinical
Gedge Rosson, Plastic Surgery
Clifton (Bing) Bingham, Rheum
Damon Cooney, Plastic Surgery
Gerald Brandacher, Plastic Surgery

Recent Lab Alumni
Liam Chung
Heather Jacobs
Kaitlyn Sadtler
Okhee Jeon
Chaekyu Kim
Matthew Wolf, PhD
Sven Sommerfeld, PhD
Jim Andorko
Hong Zhang
Jordan Garcia, MD
Erika Moore

TTEC Administration
Bahar Zarrabi, MBA
Dallas Auer
Pam Goldberg
Eileen Snyder

Computational
Elana Fertig
Patrick Cahan
Chris Cherry

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AGED T CELLS ARE DIFFERENT

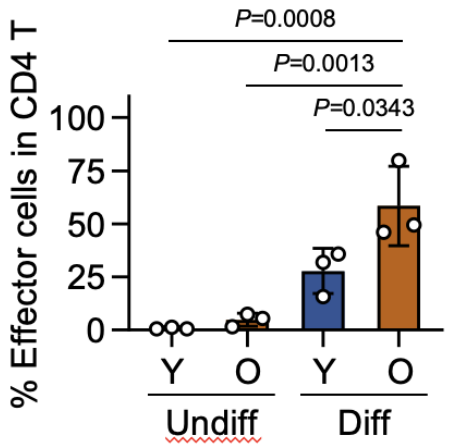
Naïve CD4 splenocyte isolation

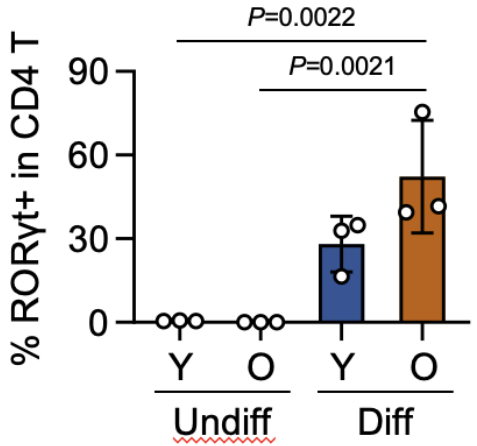
⬇

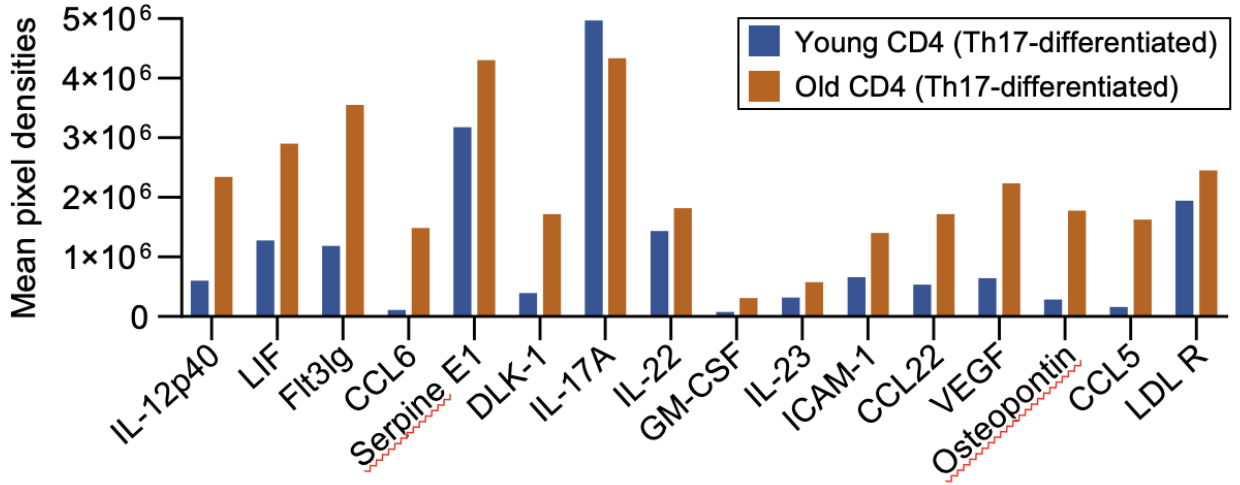
Normal media
(Undifferentiated: Undiff)
or
Th17 differentiation media
(Differentiated: Diff)

⬇

Flow cytometry
&
Proteome profiler assay





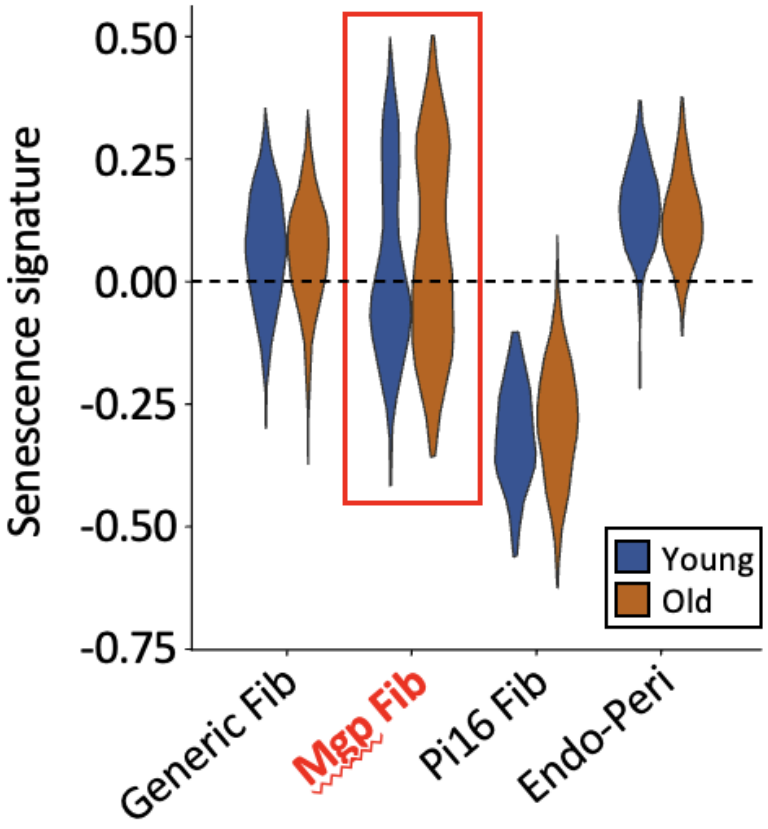


Han, Biorvx, 2021

Aged T cells differentiate more to Th17 and secrete different proteins

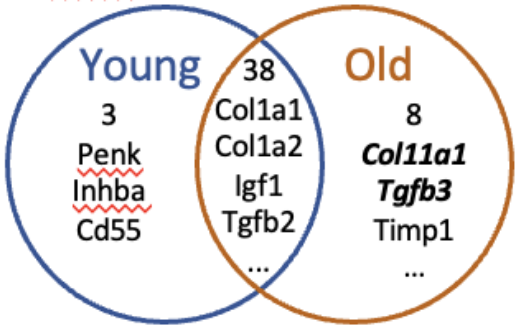
AGED SnCs ARE DIFFERENT IN MUSCLE WOUND

Senescent cells

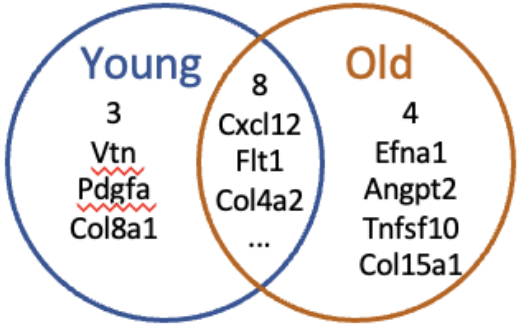


Secreted ligand signature

Mgp fibroblast cluster



Endo-Peri cluster



Jin Han

Young and old senescent cells are a little different!