MANCHESTER 1824

The University of Manchester

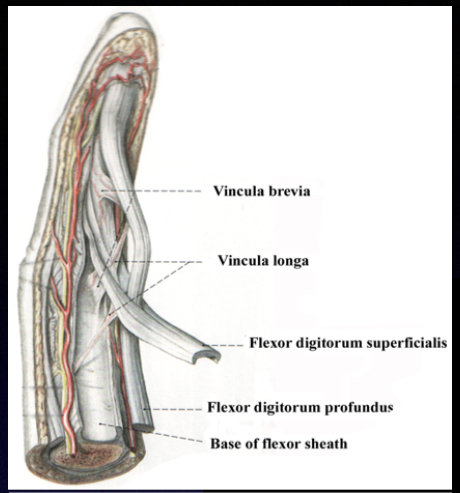
11th Southampton Course for Therapists and Surgeons

Pathophysiology of Stiffness

Speaker: Mr Jason Wong

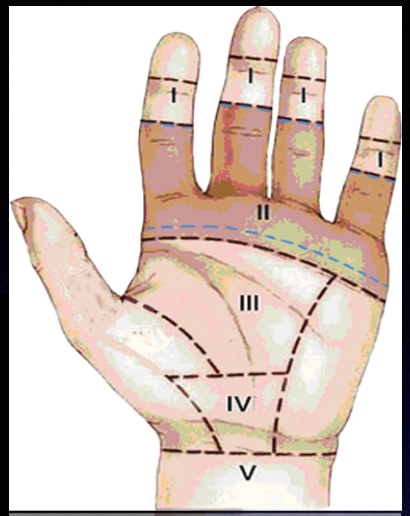
Academic Consultant in Plastic Surgery

Plastic Surgery Research Group, Blond McIndoe Laboratories, University of Manchester, UK

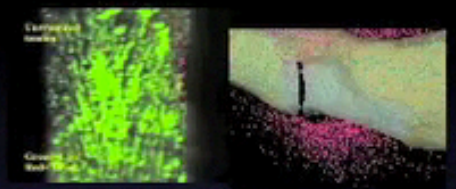


My interests

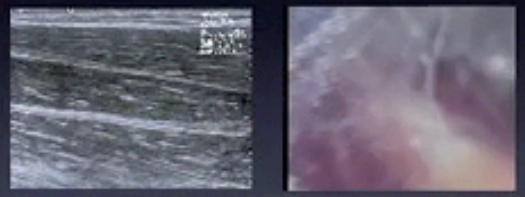
Using the hand as a model...



Tissue injury



Tissue dynamics



Tissue healing

My interests

Tissue Engineering

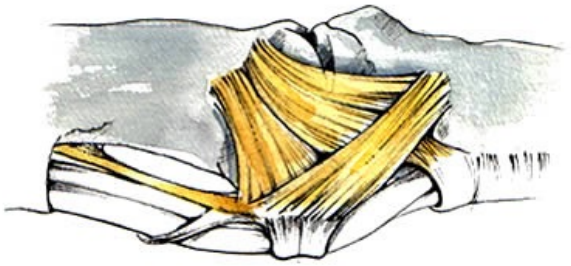
Tissue Regeneration

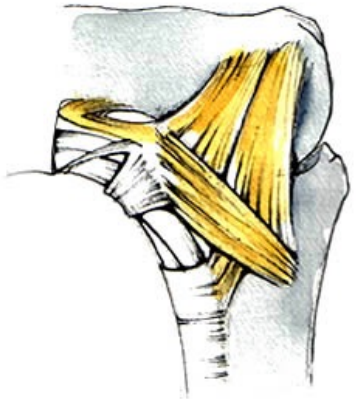
Definitions

Stiffness is the rigidity of an object — the extent to which it resists deformation in response to an applied force.

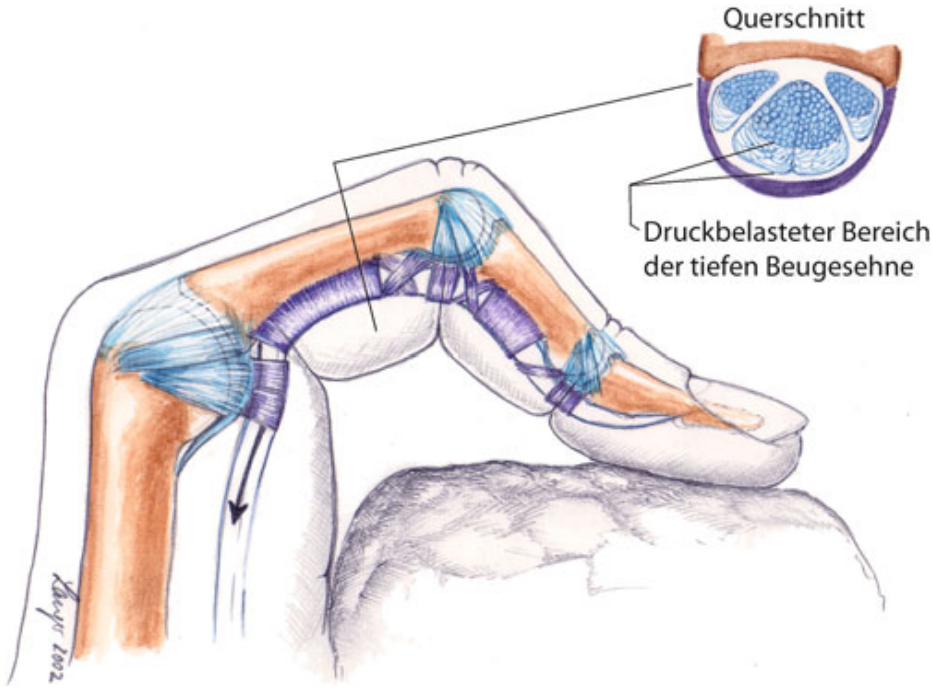
The complementary concept is **flexibility** or pliability: the more flexible an object is, the less stiff it is.

Joint problem





Tendon problem



Skin problem

Images by Sammut/ Langer

Joint stiffness may be either the symptom of pain on moving a joint, the symptom of loss of range of motion or the physical sign of reduced range of motion.

- **Pain on movement** is commonly caused by osteoarthritis, often in quite minor degrees, and other forms of arthritis. It may also be caused by injury or overuse and rarely by more complex causes of pain such as infection or neoplasm. The range of motion may be normal or limited by pain. "Morning stiffness" pain which eases up after the joint has been used, is characteristic of rheumatoid arthritis.[1]

- **Loss of motion** (symptom): the patient notices that the joint (or many joints) do not move as far as they used to or need to. Loss of motion is a feature of more advanced stages of arthritis including osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Stiffness in upper limb

- Tendons/ ligaments
- Skin
- Joints
- Fascia
- Muscle
- Neurological

Rheumatoid arthritis

Infection

Surgery

Trauma

Gout

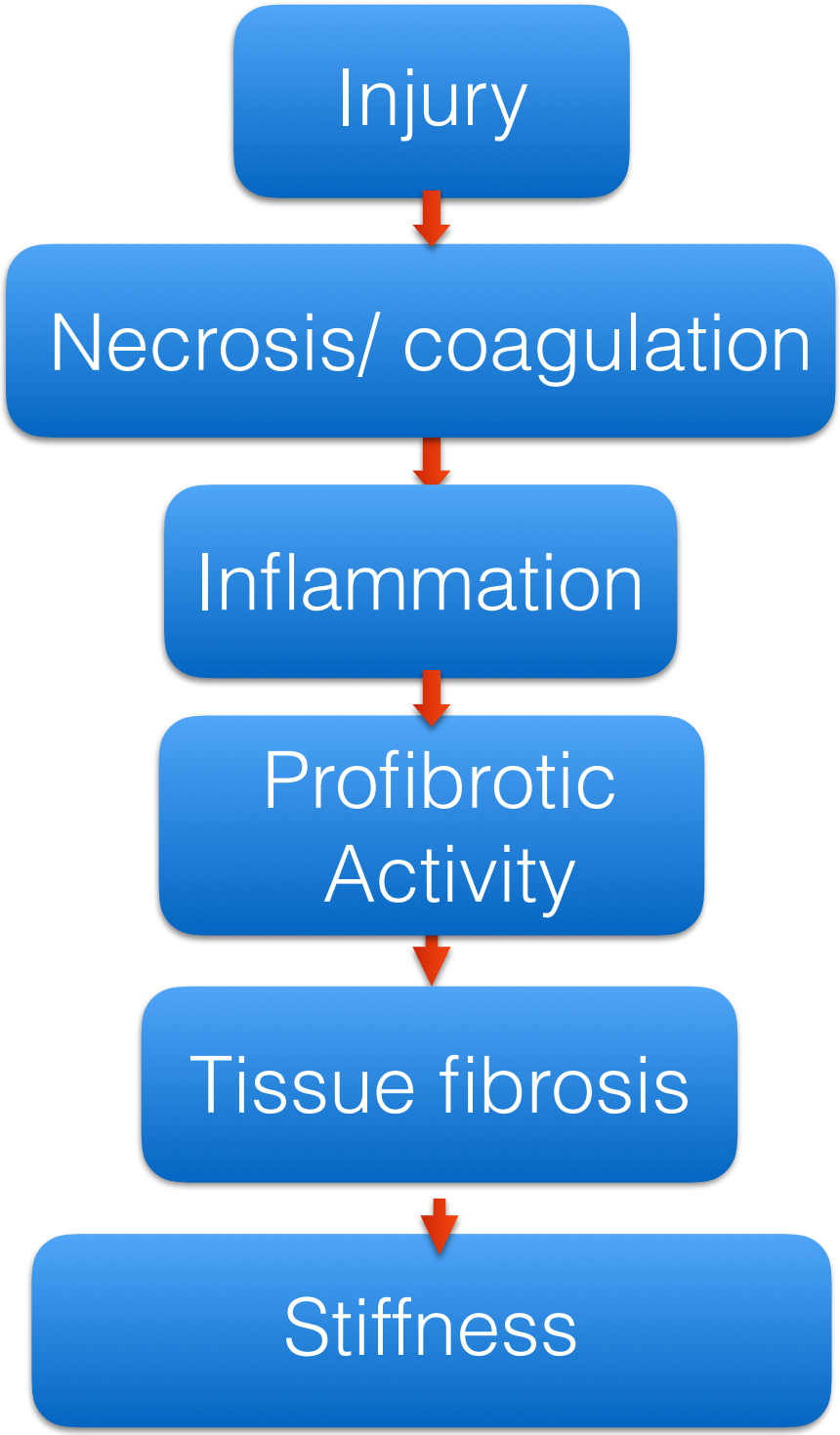
Psoriaratic arthritis

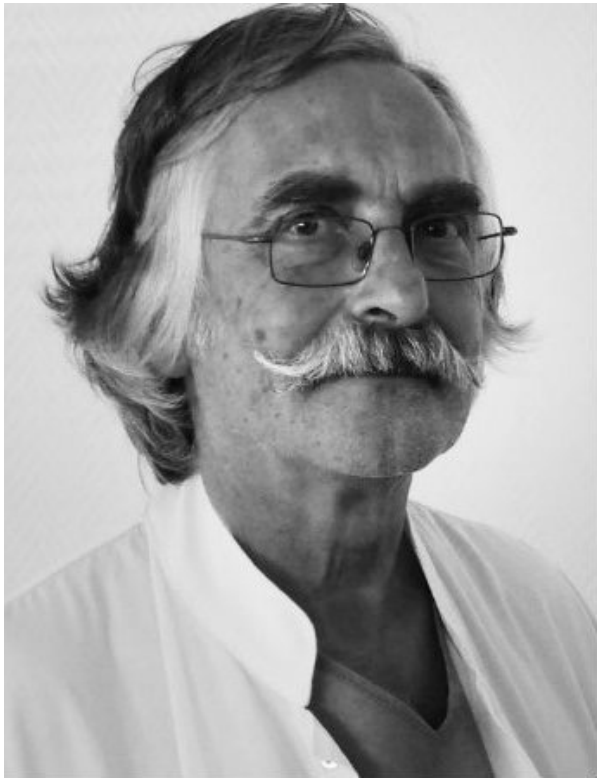
Compartment Syndrome

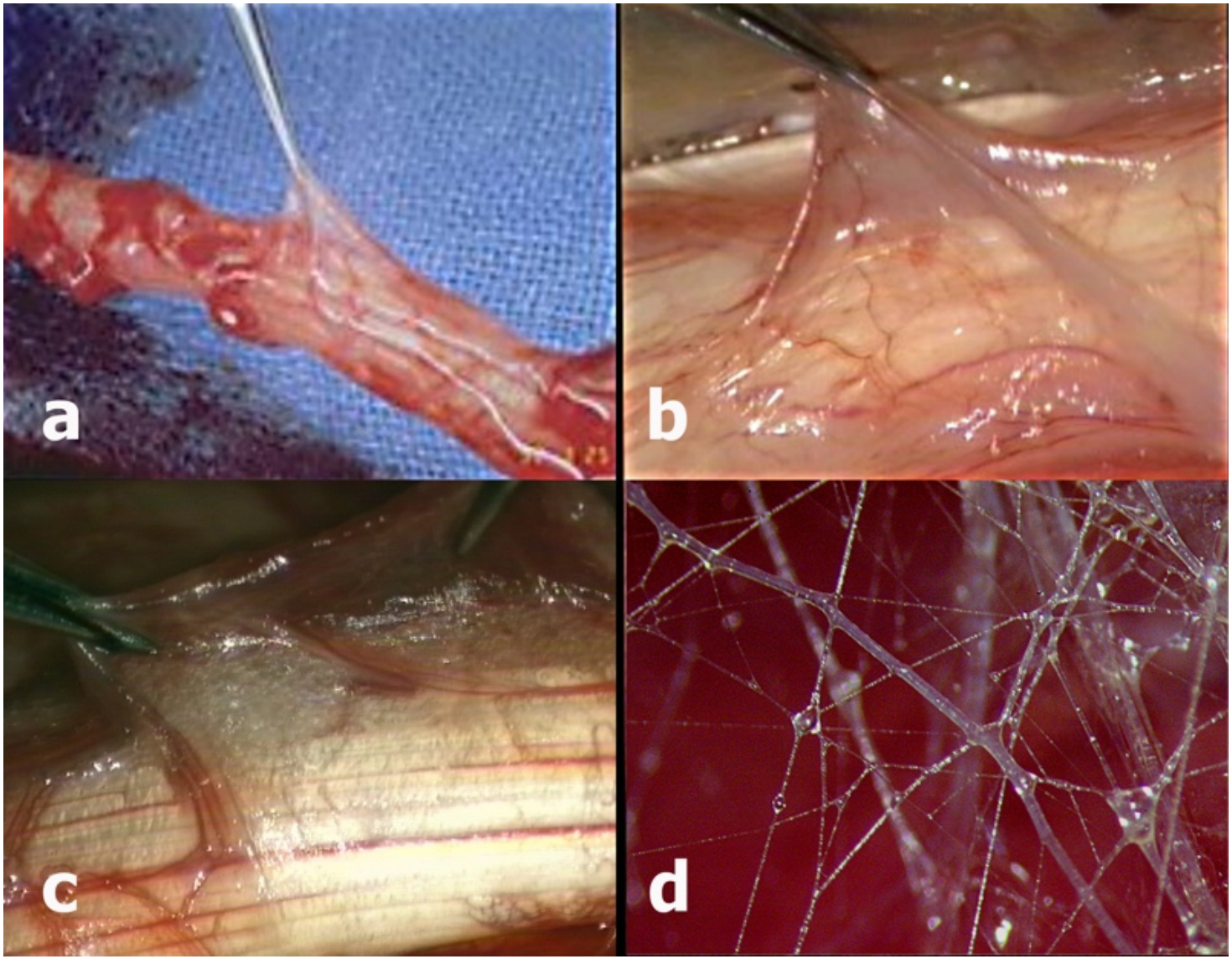
Scleroderma

Osteoarthritis

What is the unifying pathogenesis?


Injury
Necrosis/ coagulation
Inflammation
Profibrotic Activity
Tissue fibrosis
Stiffness





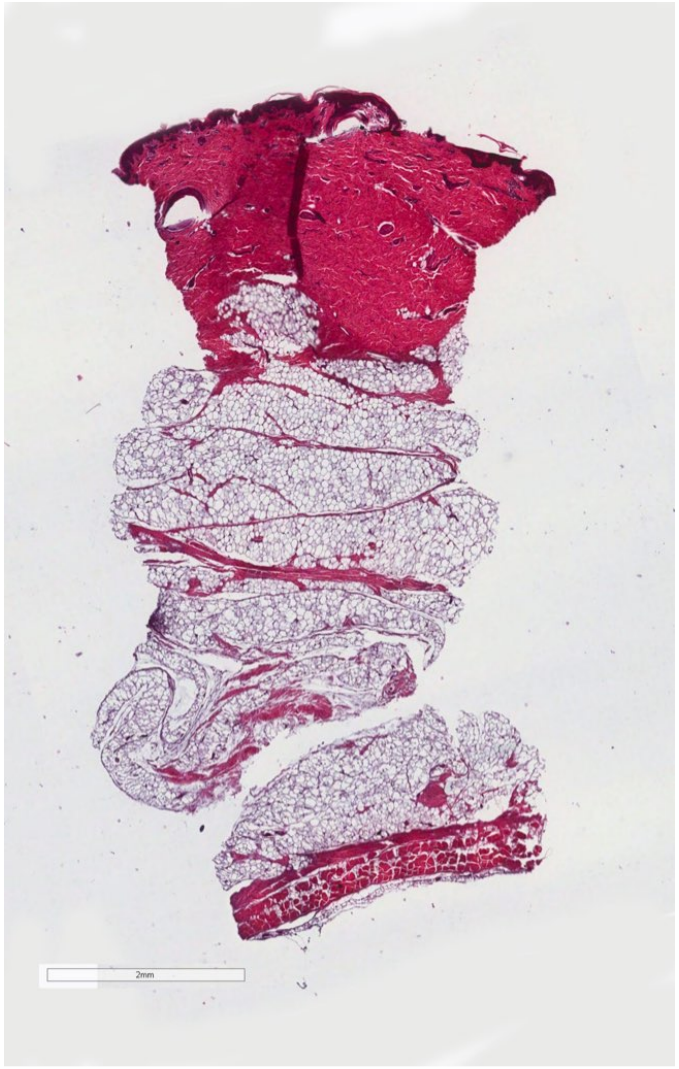
Guimberteau et al 2010

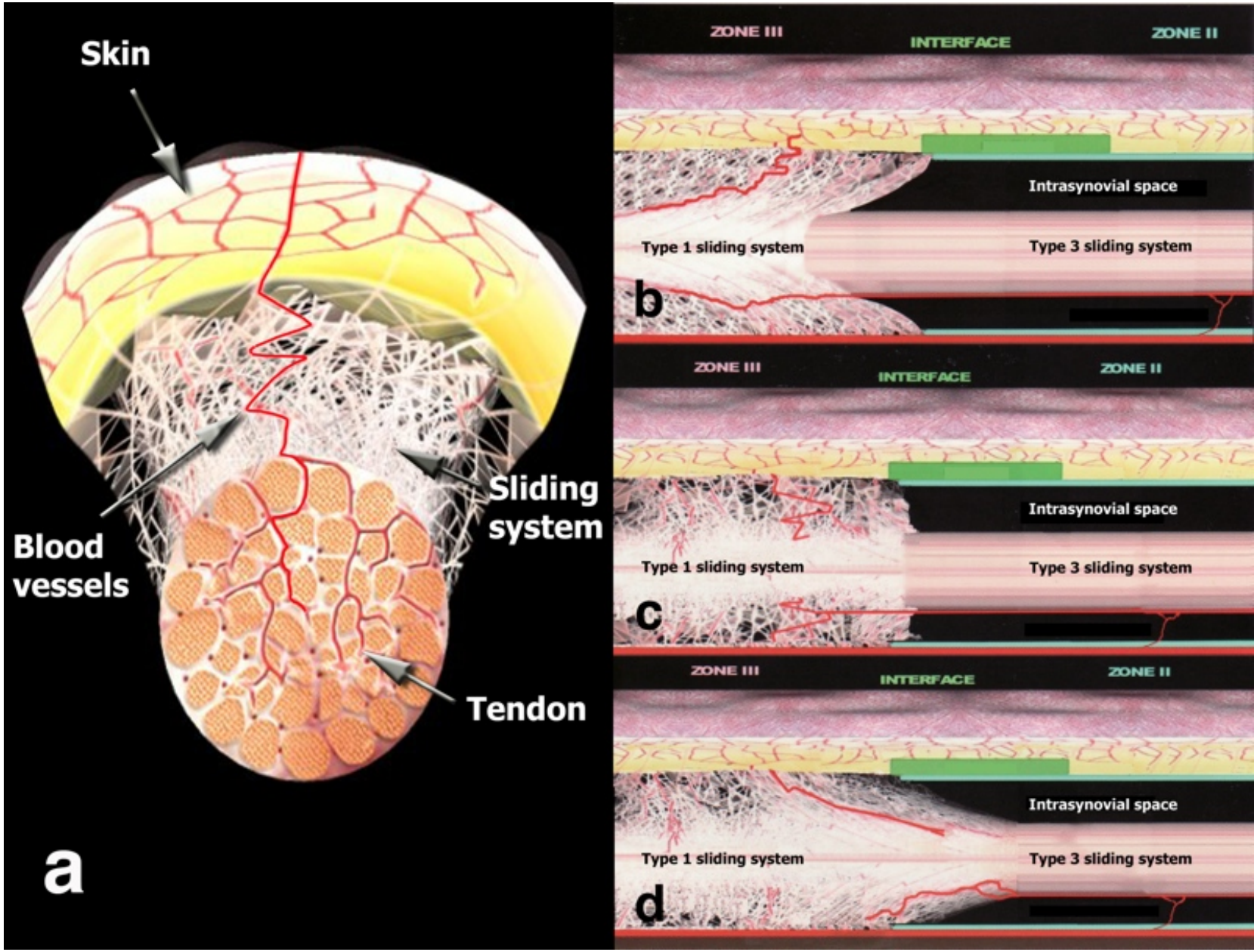
The neglected tissue

Microvacuolar system

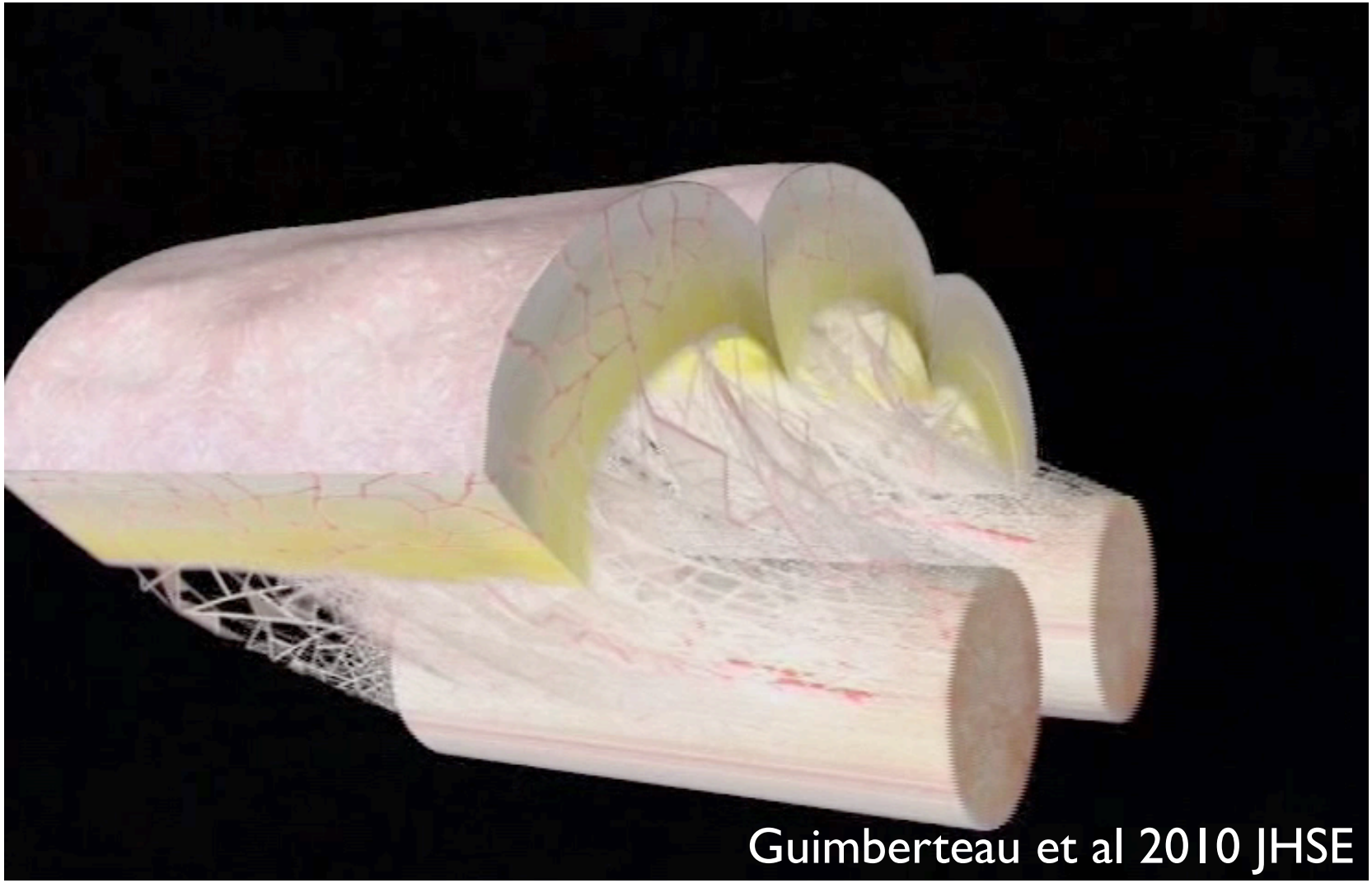
- AKA Areolar tissue, superficial fascia, reticular tissue, loose connective tissue

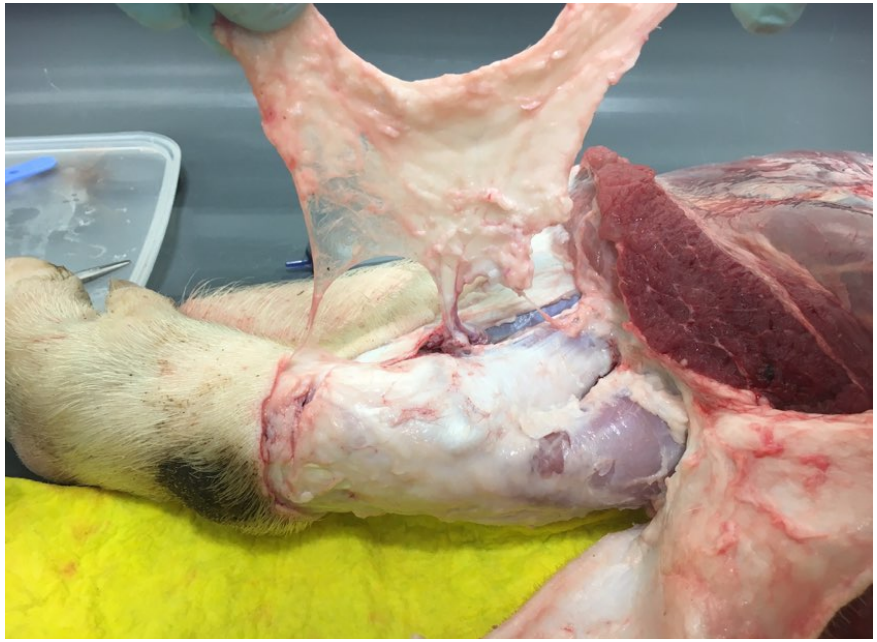
- Microvacuolar system surrounds all moving structures within the body providing **dynamic structural support and glide**

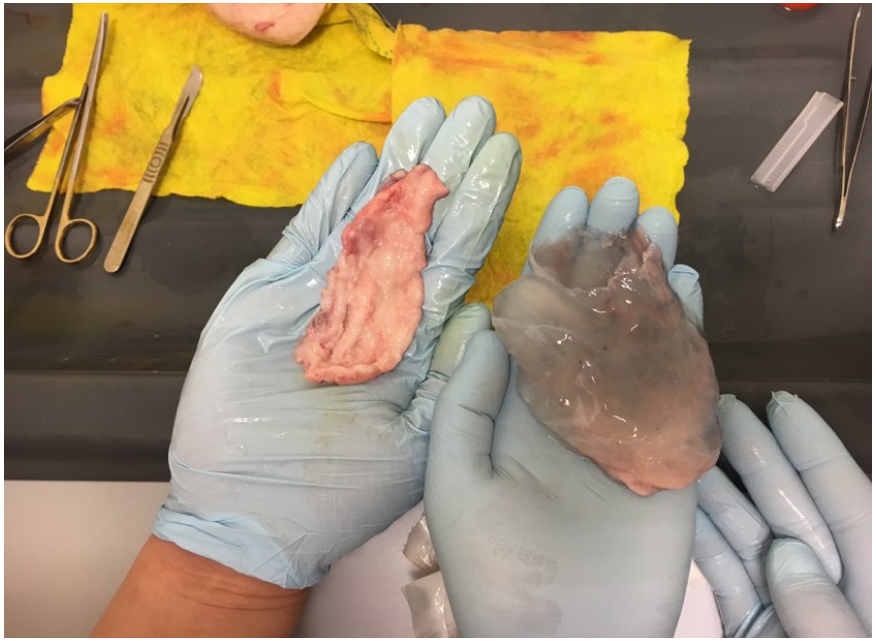




Guimberteau et al 2010 JHSE


Guimberteau et al 2010 JHSE

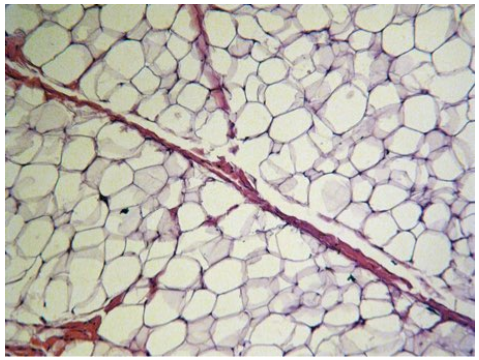




Highly hydrophilic
High GAG content

Triggers for fibrosis

- Injury- Trauma, Surgical, Thermal
- Infection
- Immunological causes
- Ischaemia/ infarction/ Reperfusion
- Drugs

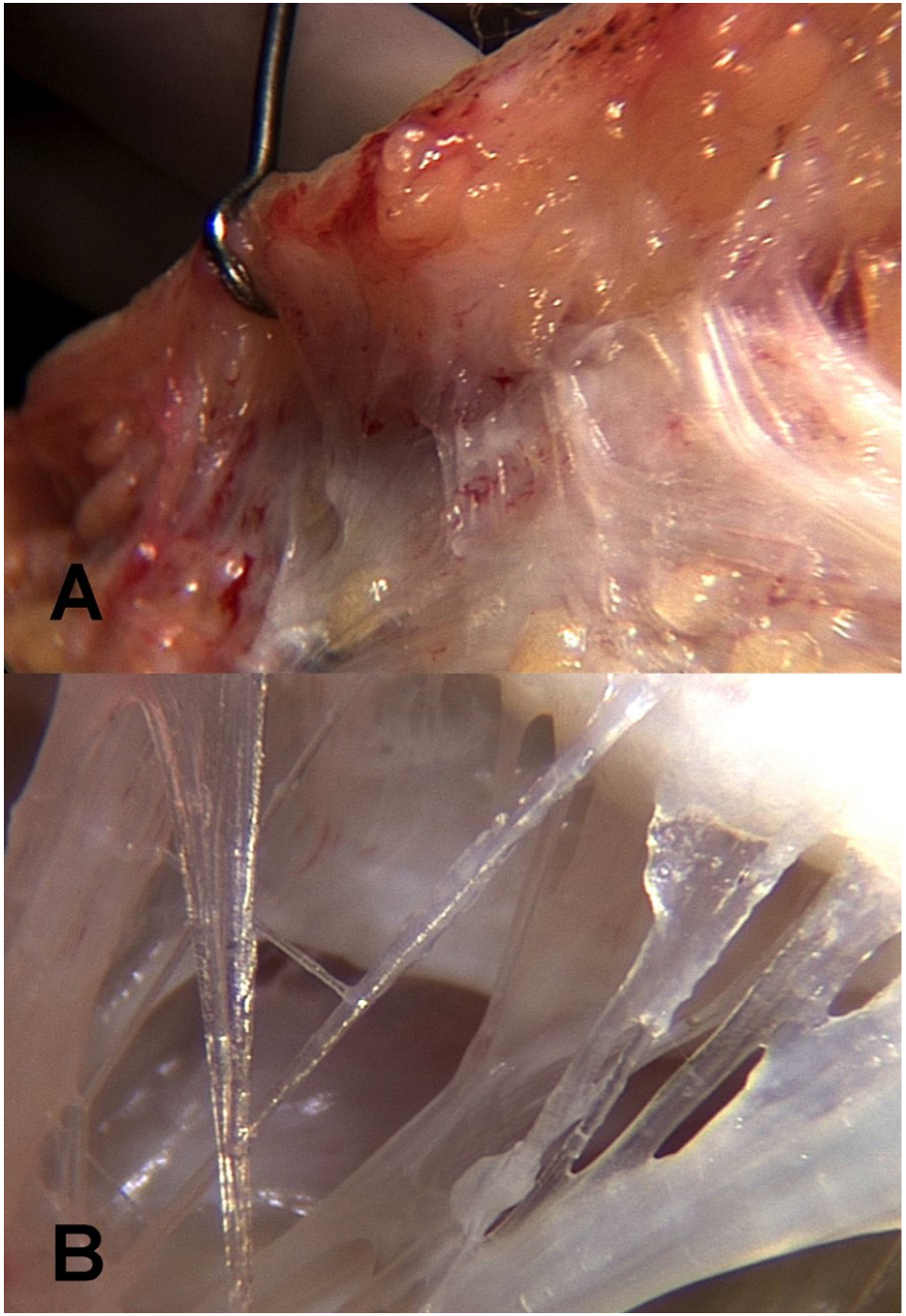


Fibrosis

- The microvacuolar tissue is **highly susceptible to damage during inflammation** from the increased vascular permeability, but also its **sponge-like** composition

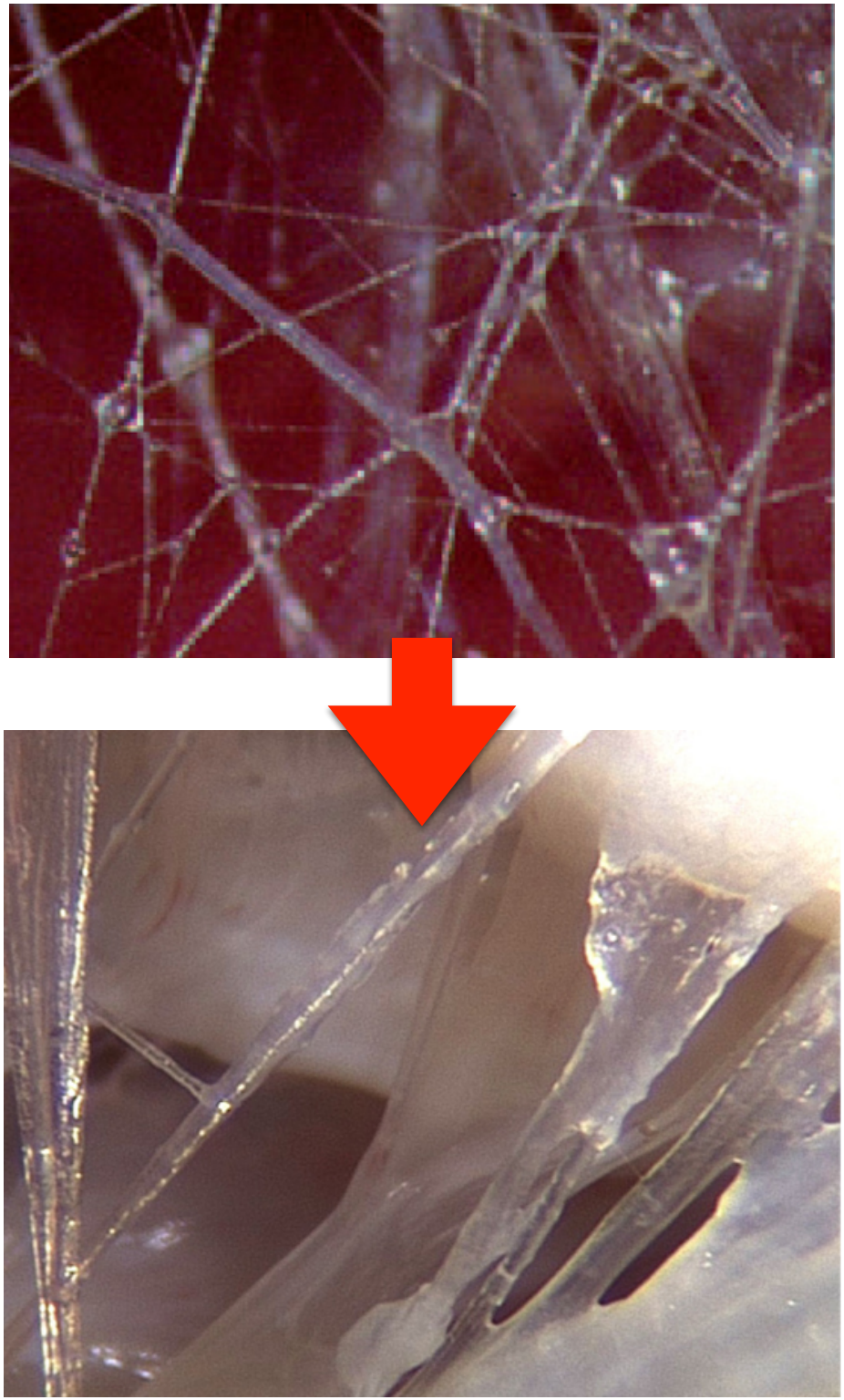
- The tissue acts as an active reservoir for interstitial fluid and becomes waterlogged

- Oedema and overall injury to the microvacuolar tissue causes **scarring**, fibrosis and adhesions and the tissue becomes **inelastic, swollen** and more vulnerable to further trauma



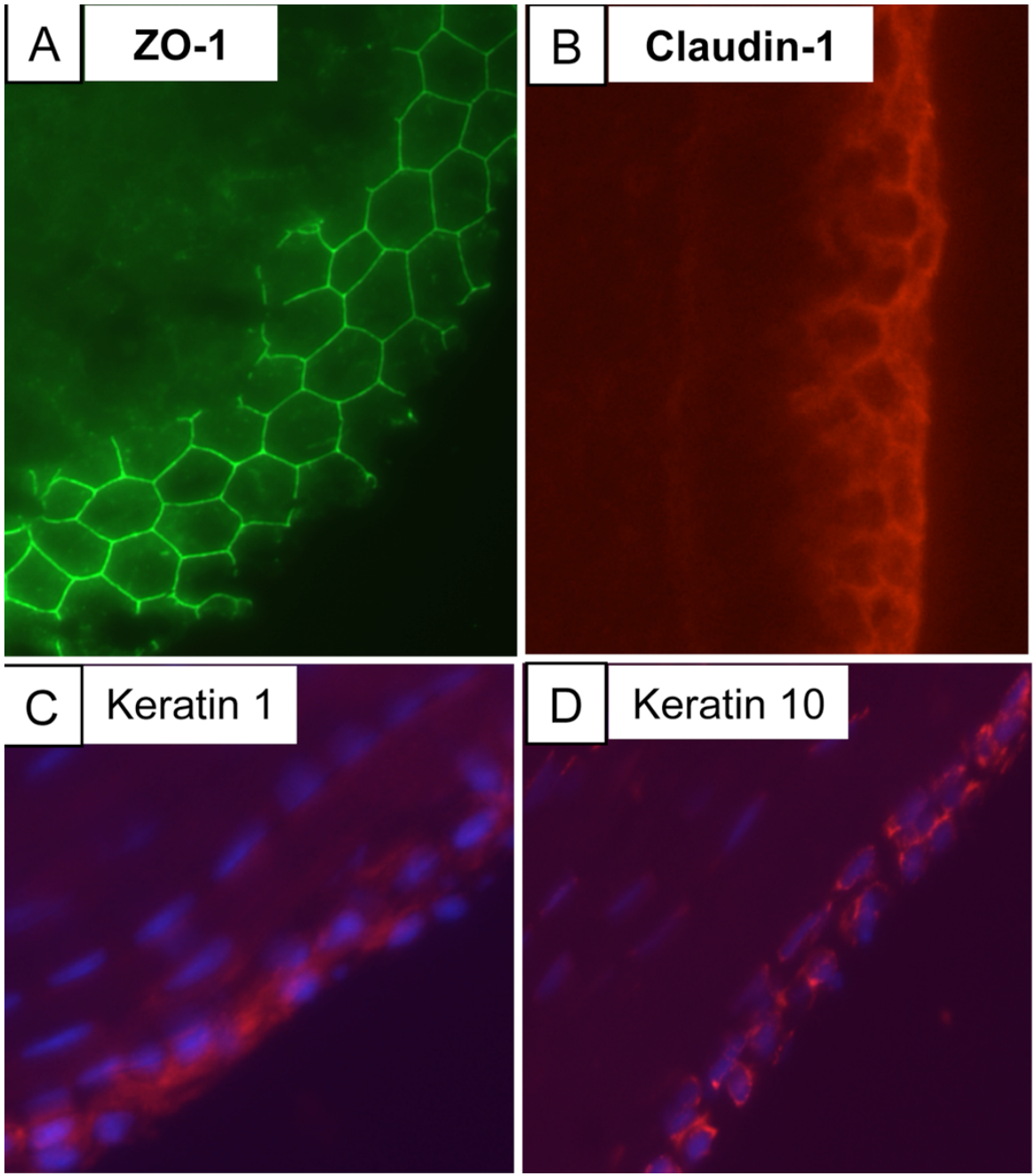
When the microvacuolar becomes fibrosed

- Gliding planes become scarred
- Stiff fibrotic tissue surrounding everything that moves

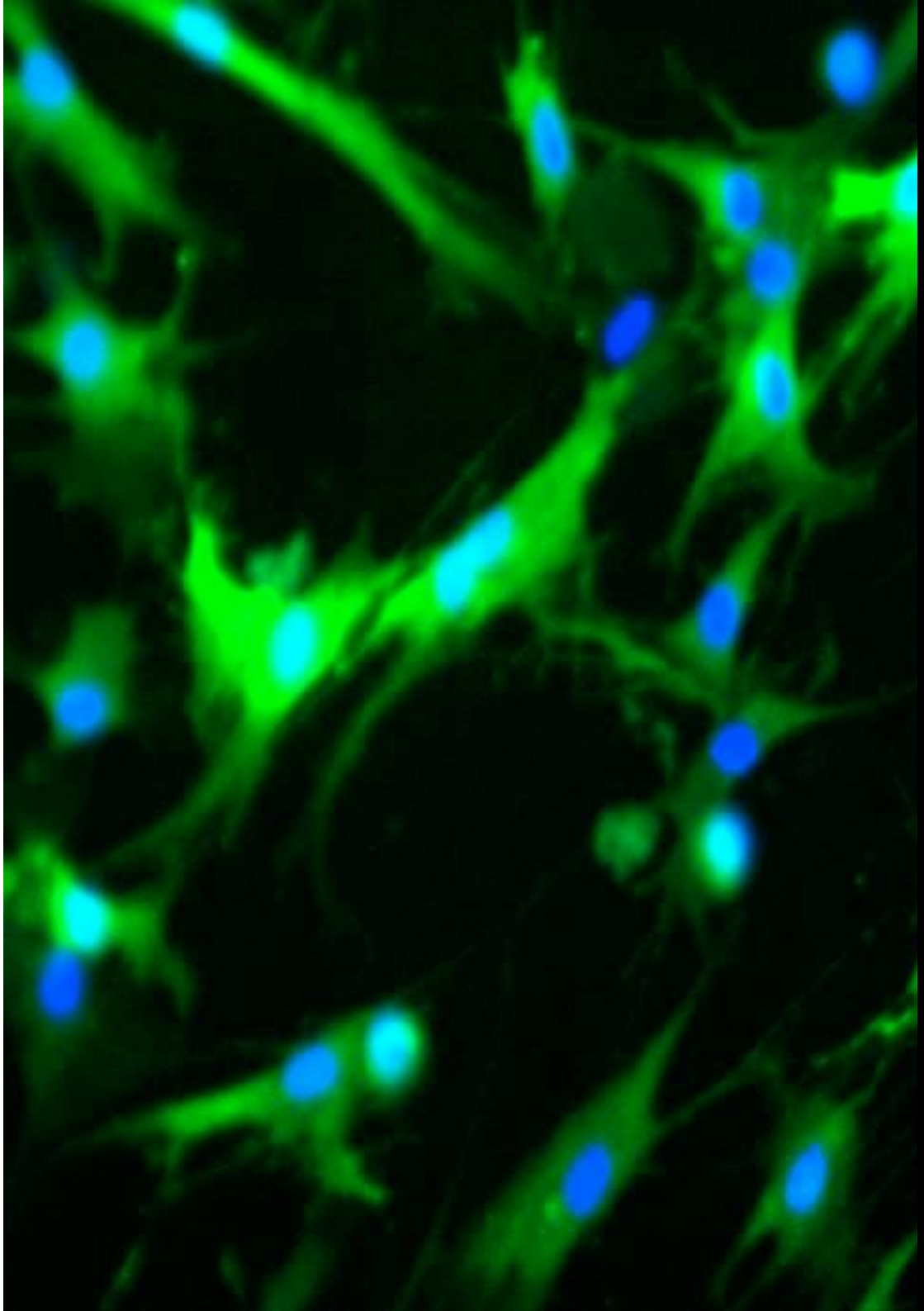


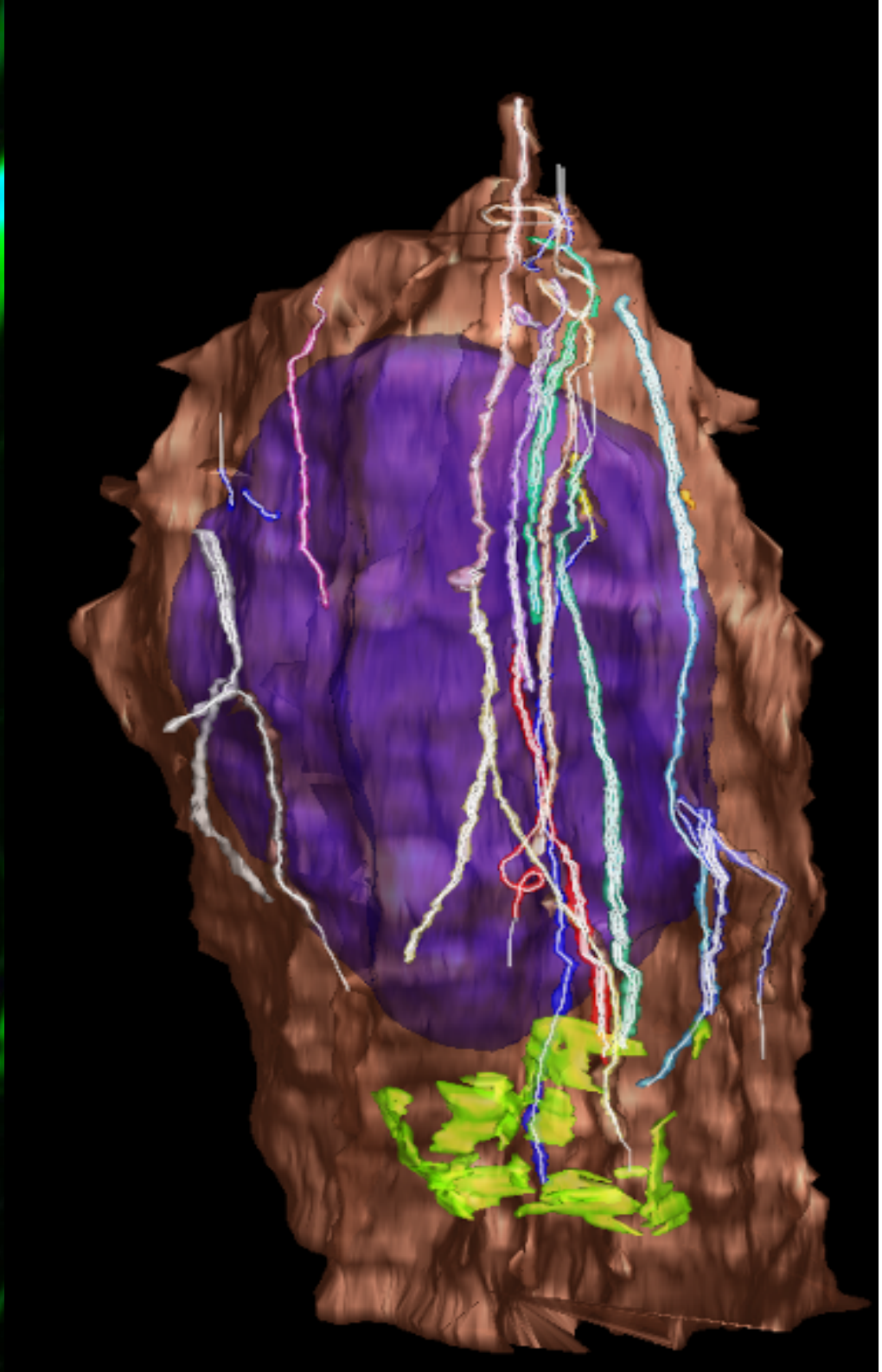
Key ingredients to fibrosis

All tissues have a skin



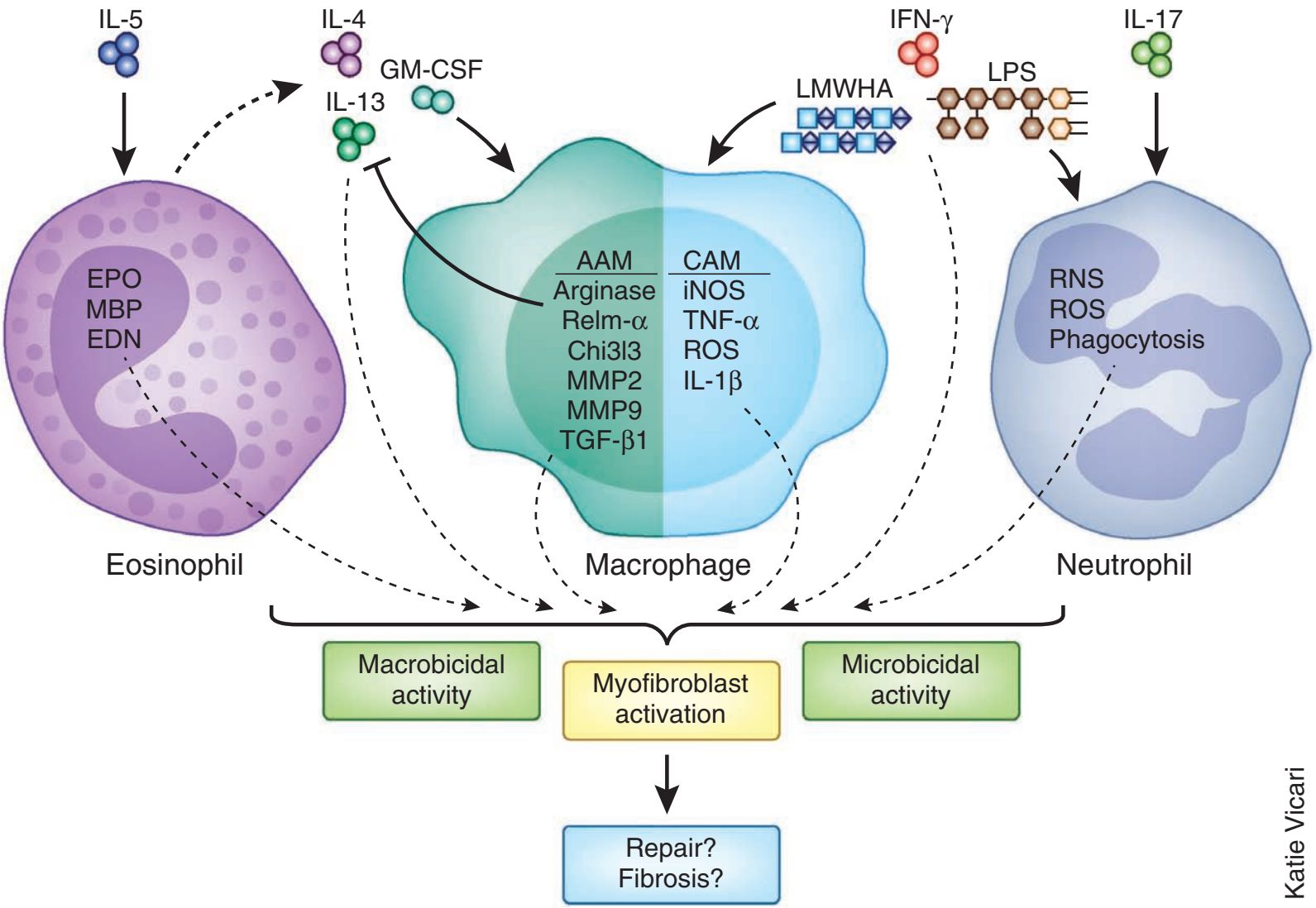
Taylor 2011 Matrix Bio





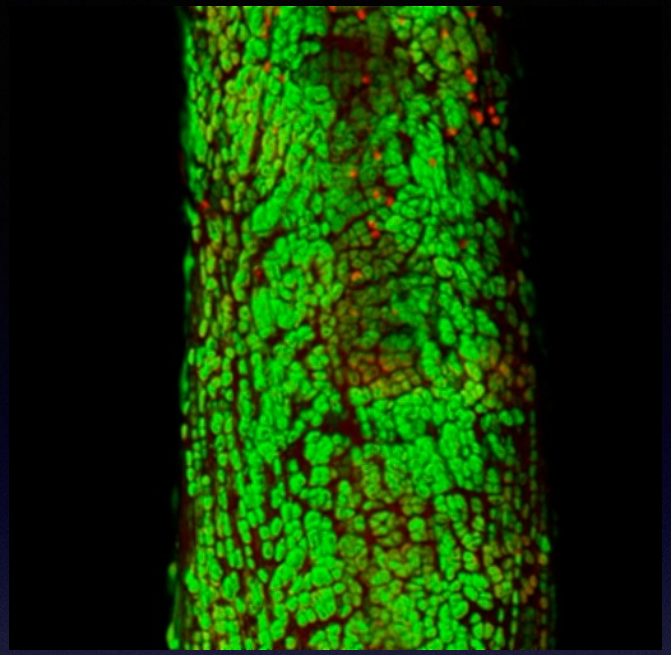

Gunter Von Hagen

Inflammatory cells

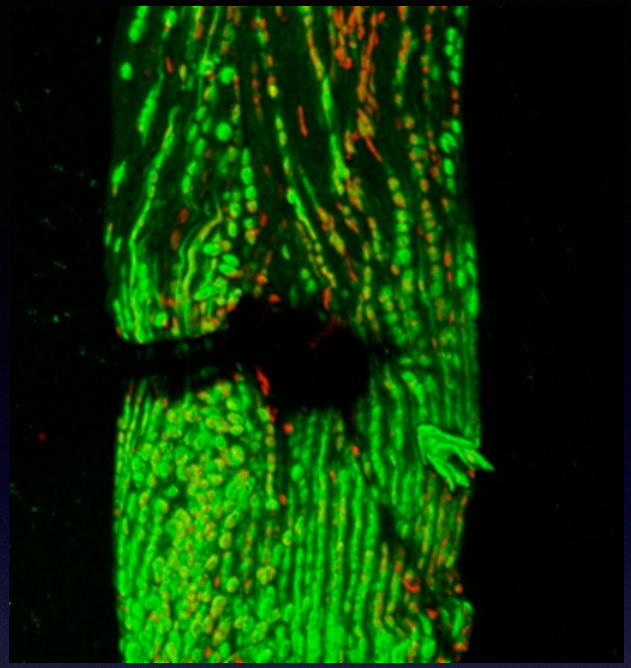


Wynn and Ramalingham 2012 Nature

Injury Response

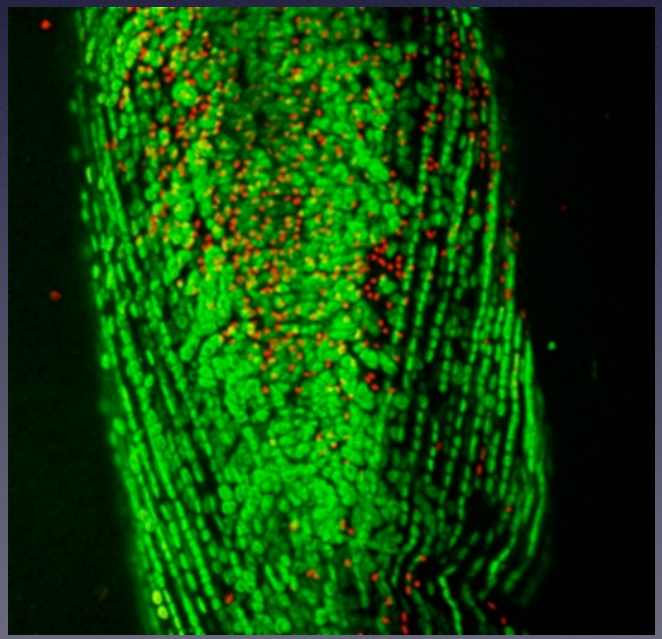


Normal

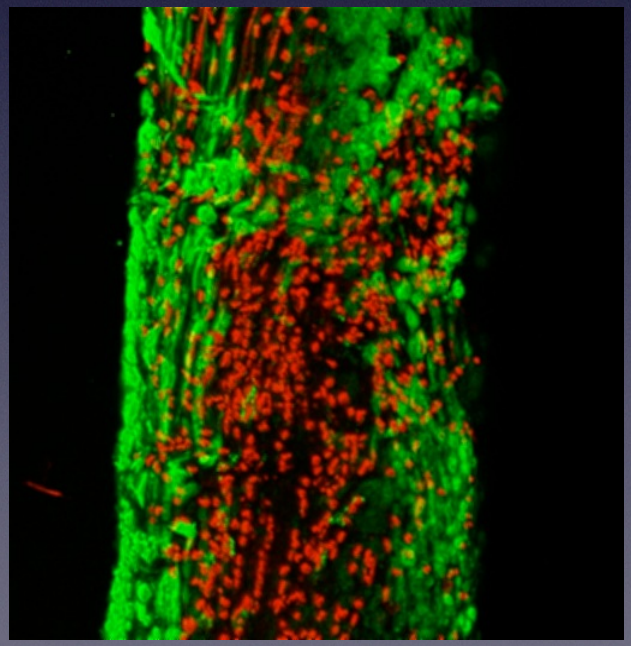


Sutured

Live Dead Staining
Green =Living
Red =Dead

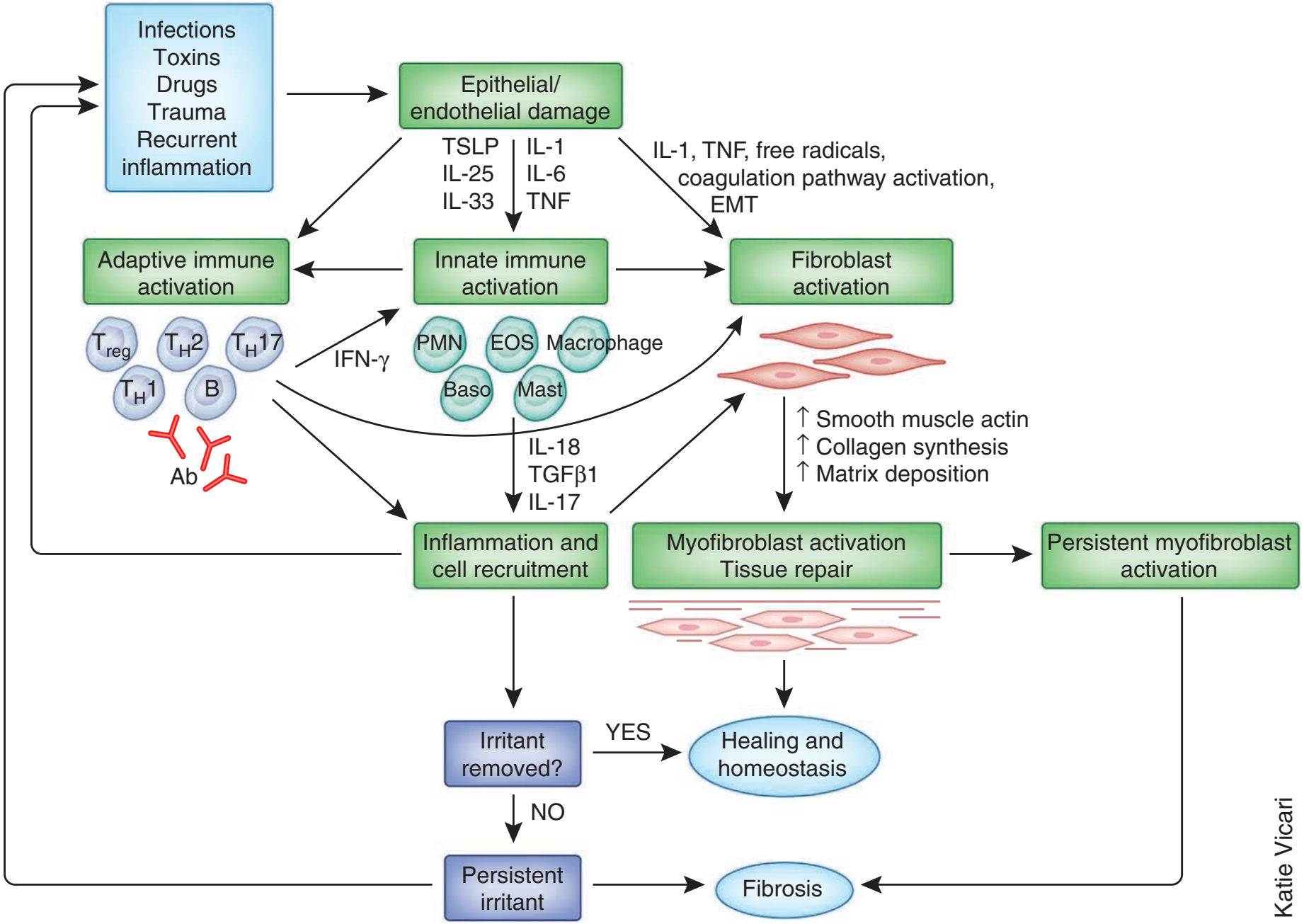


Abrasion

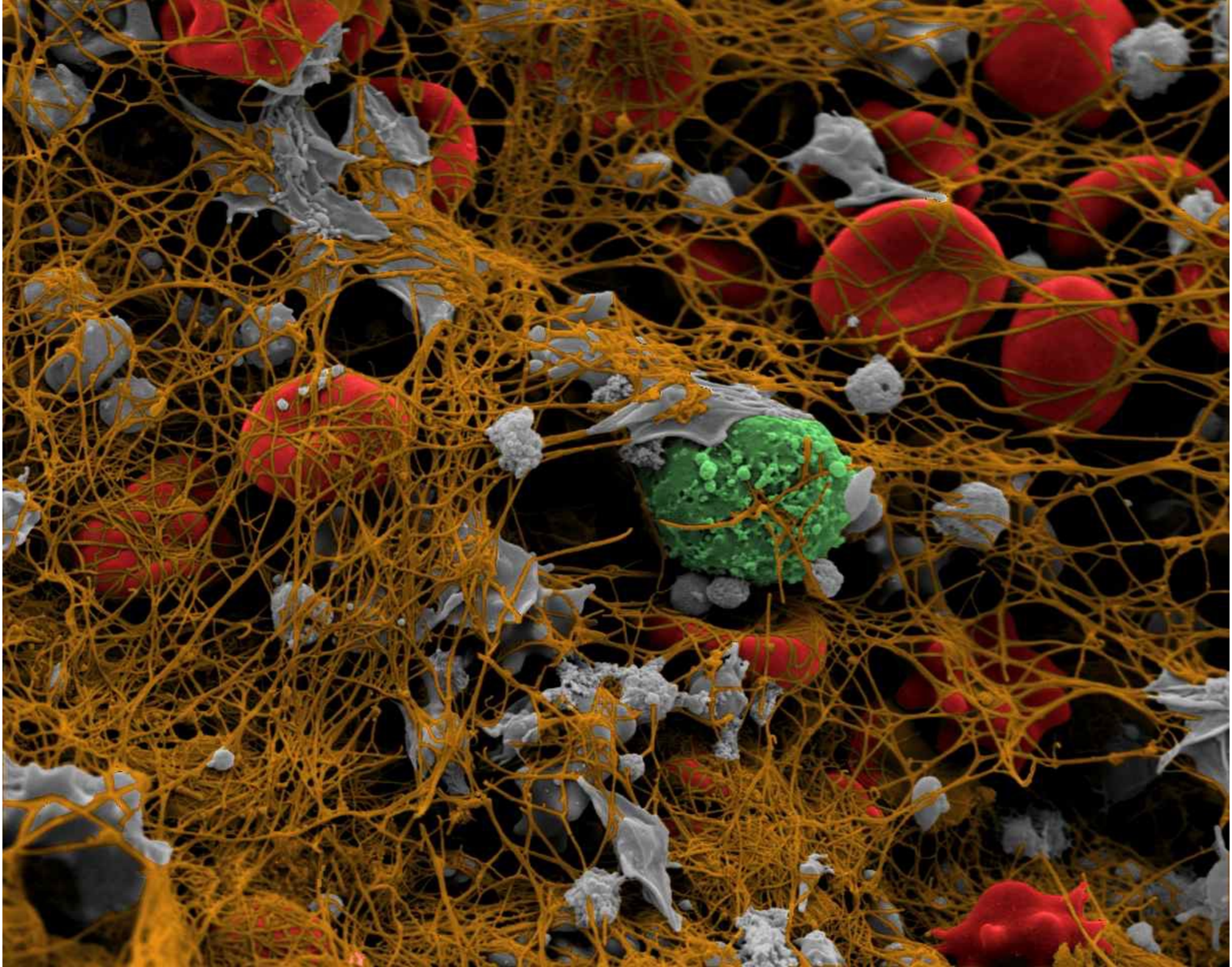


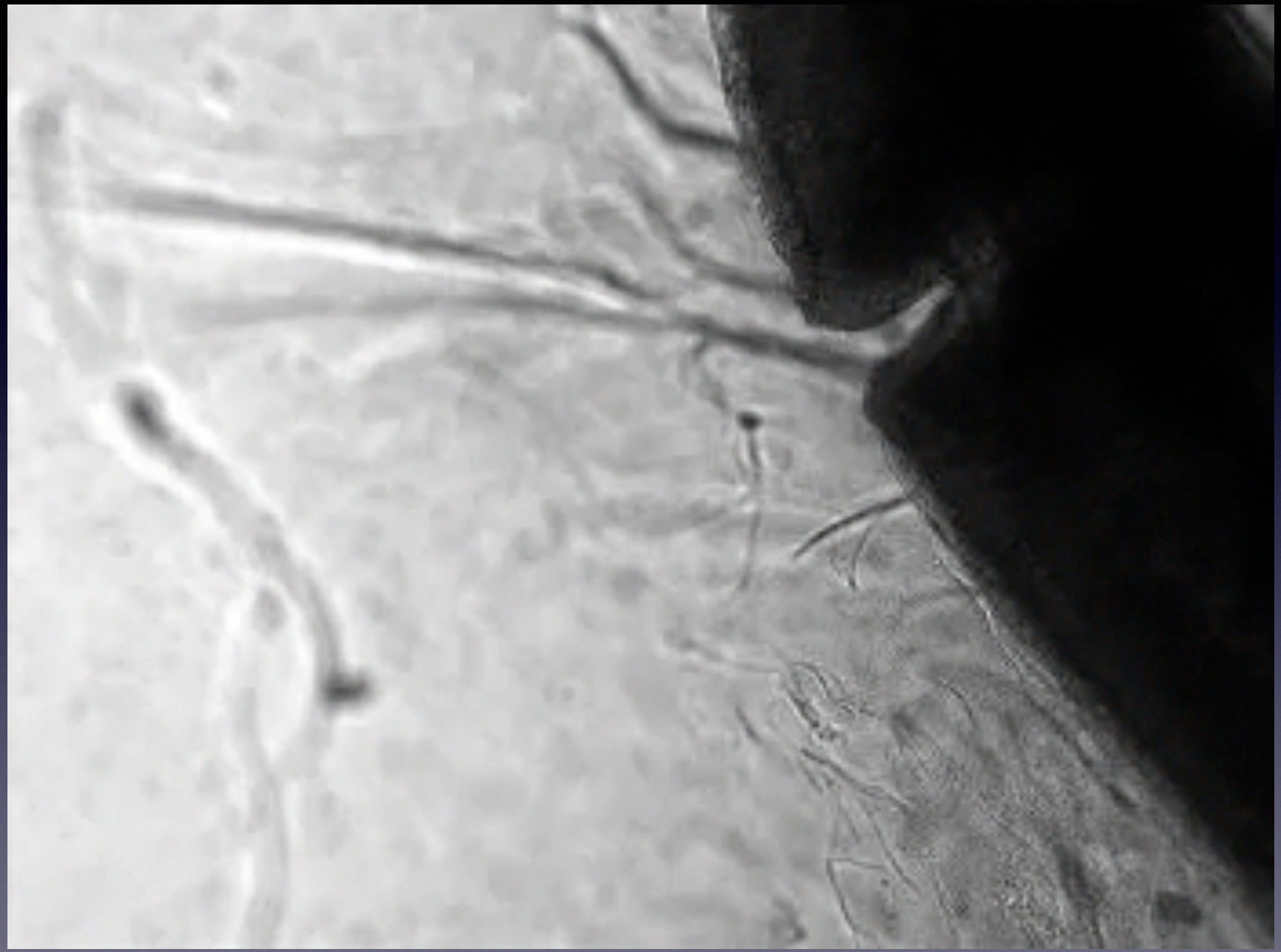
Avulsed

Wong et al 2010 Matrix Bio



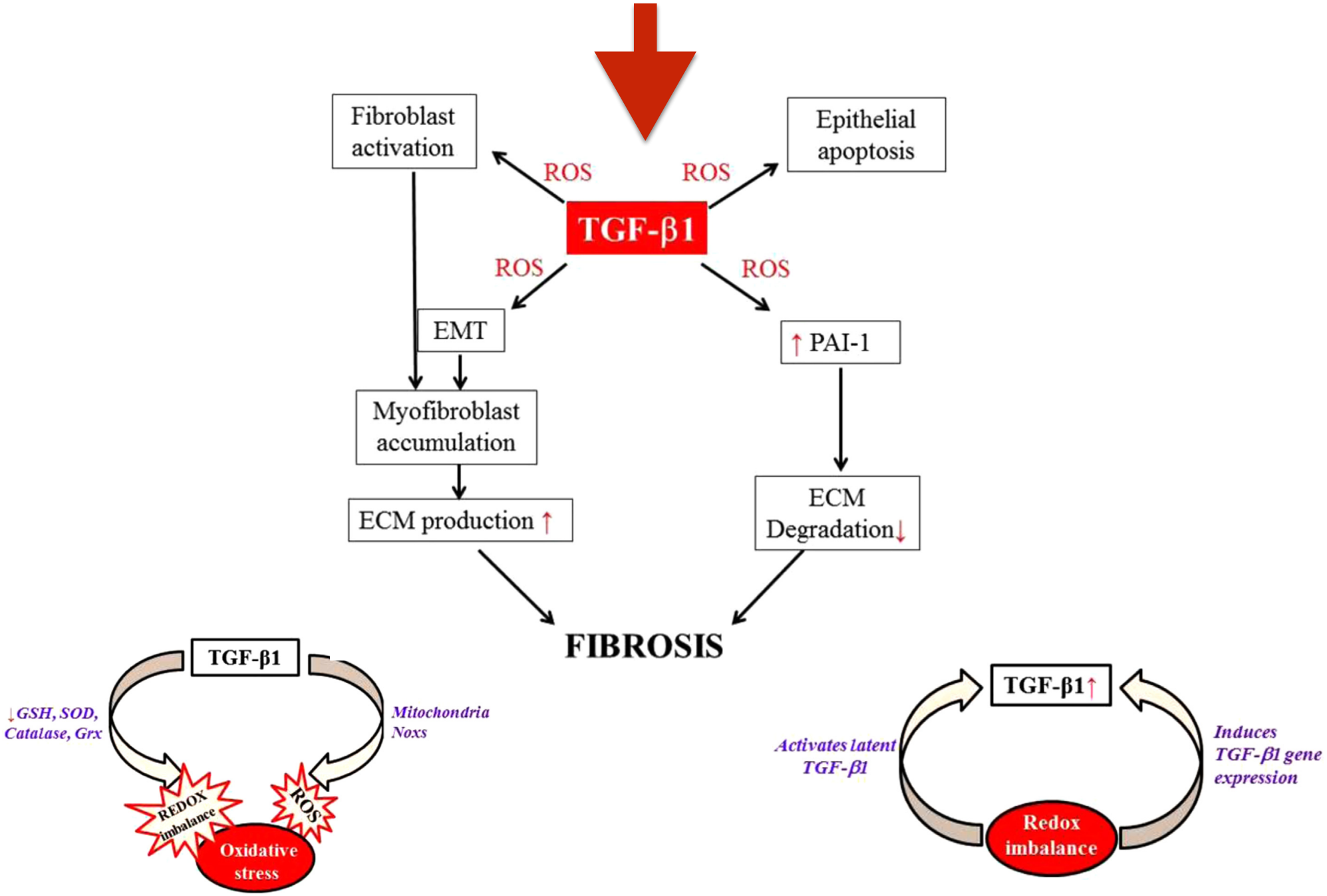
Wynn and Ramalingham 2012 Nature





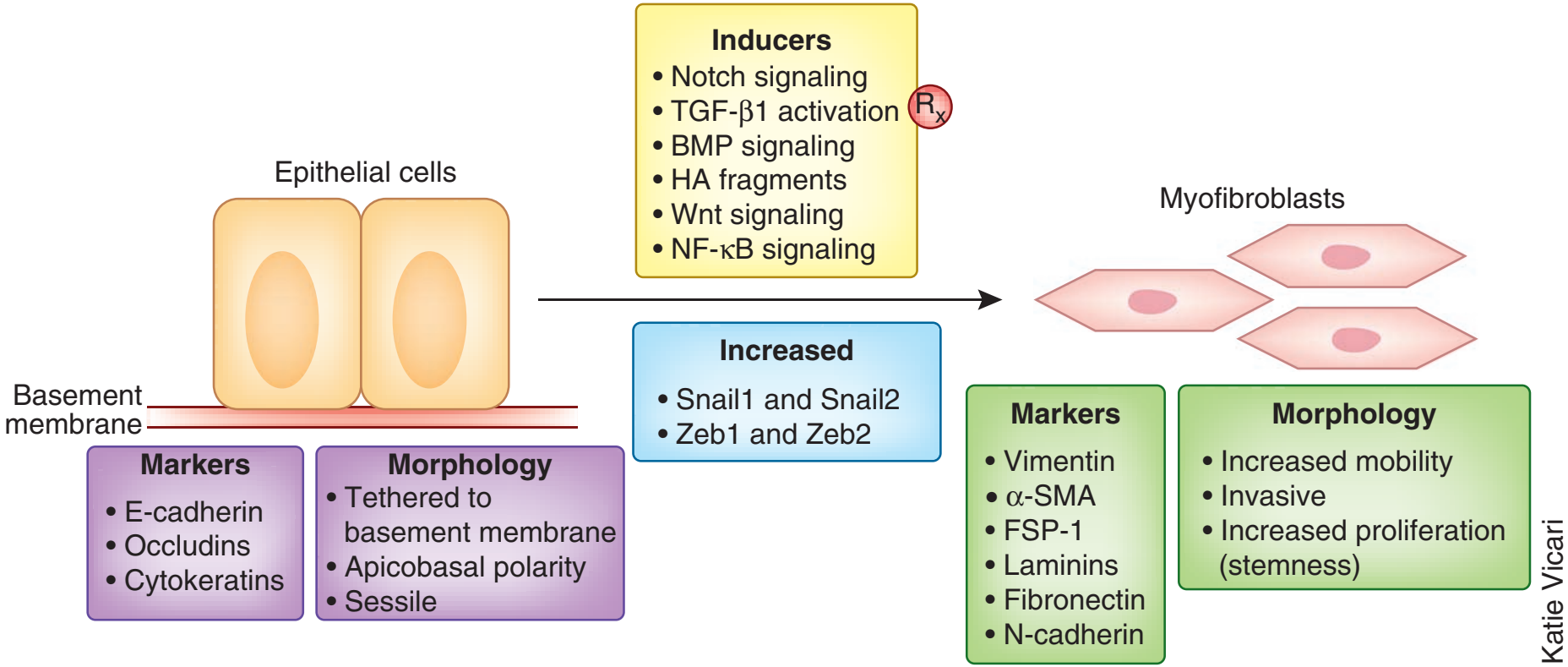
Wong and Peck 2014 PRS

Tissue Injury

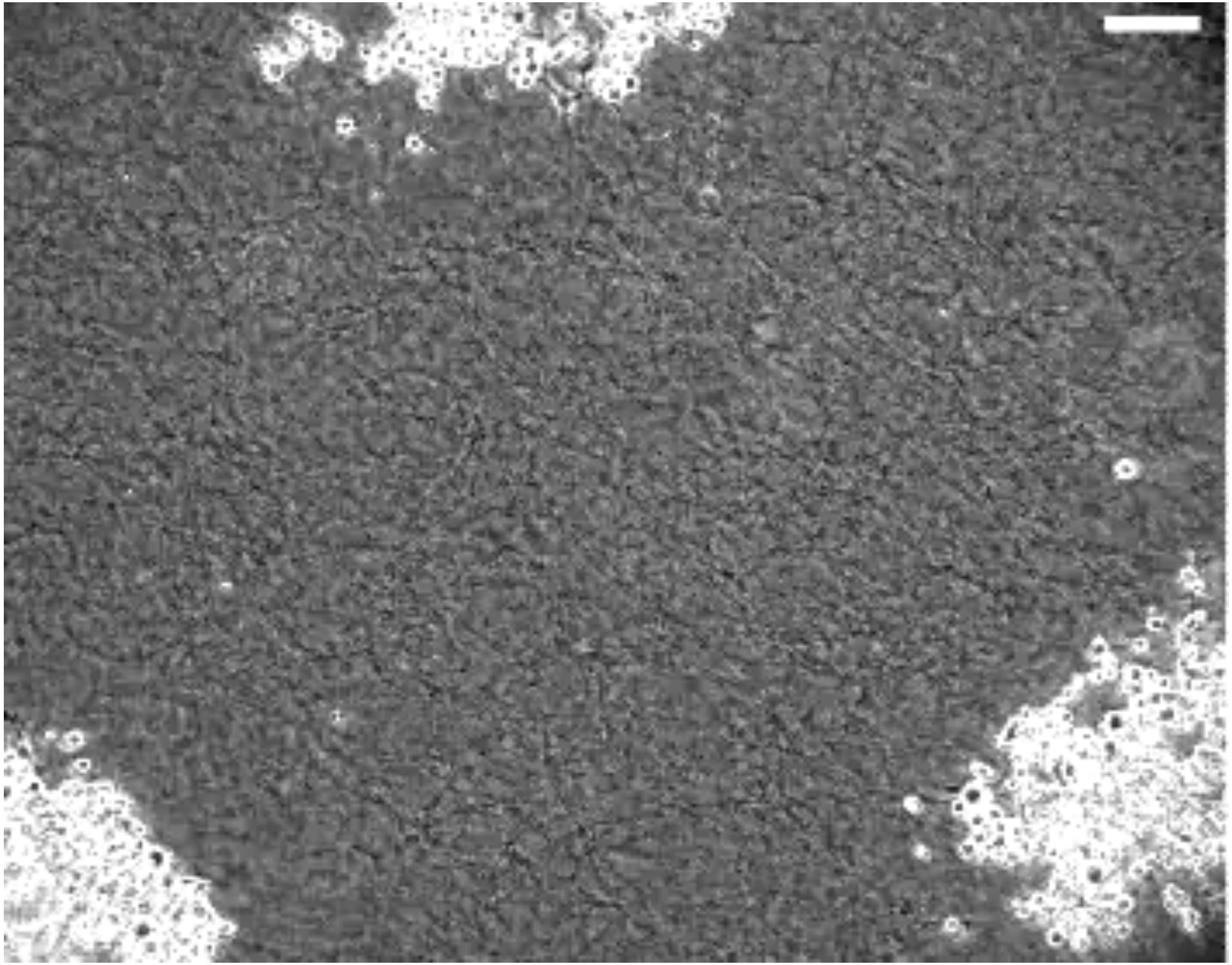


Liu and Desai 2015

Epithelial to mesenchymal transformation

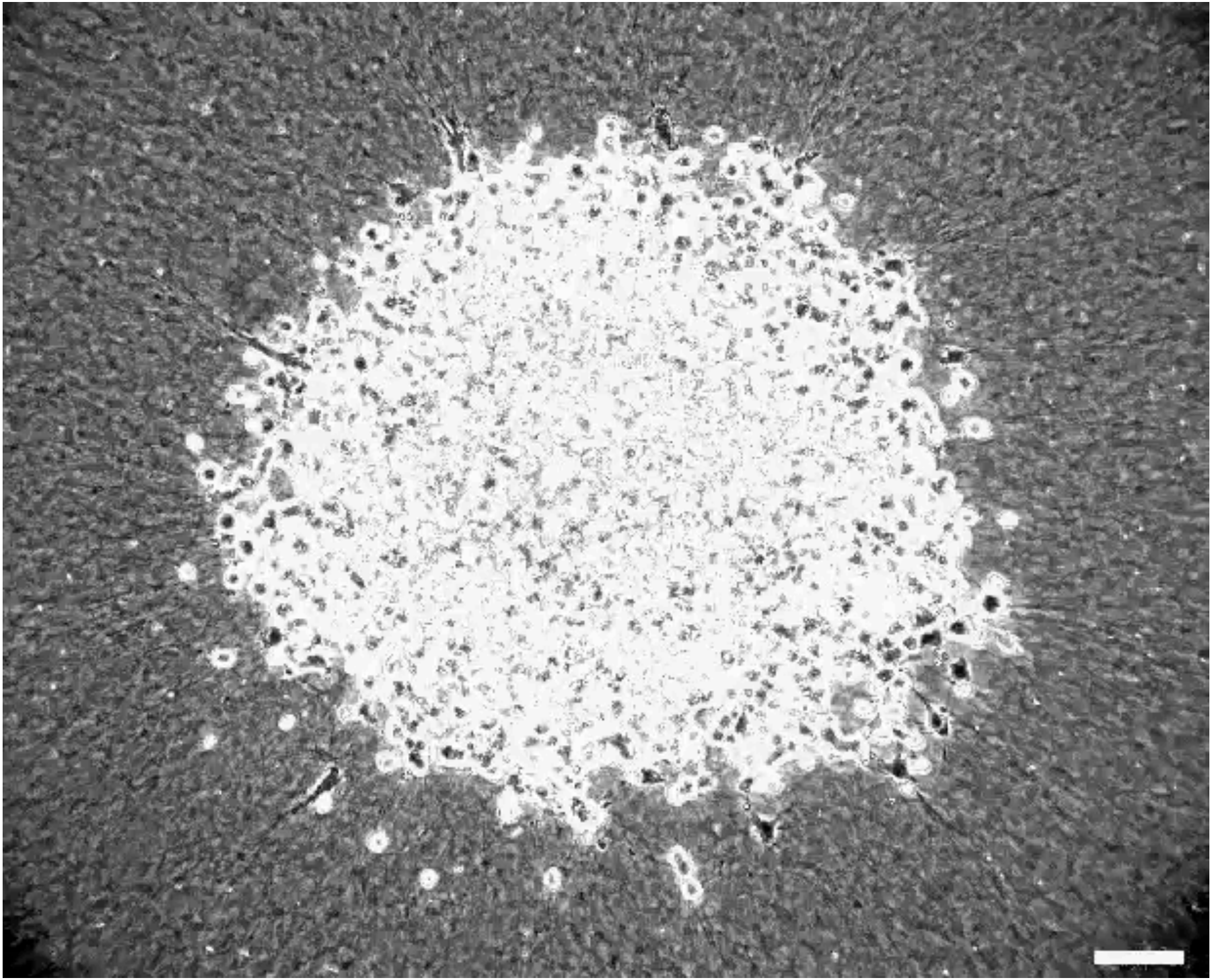


Wynn and Ramalingham 2012

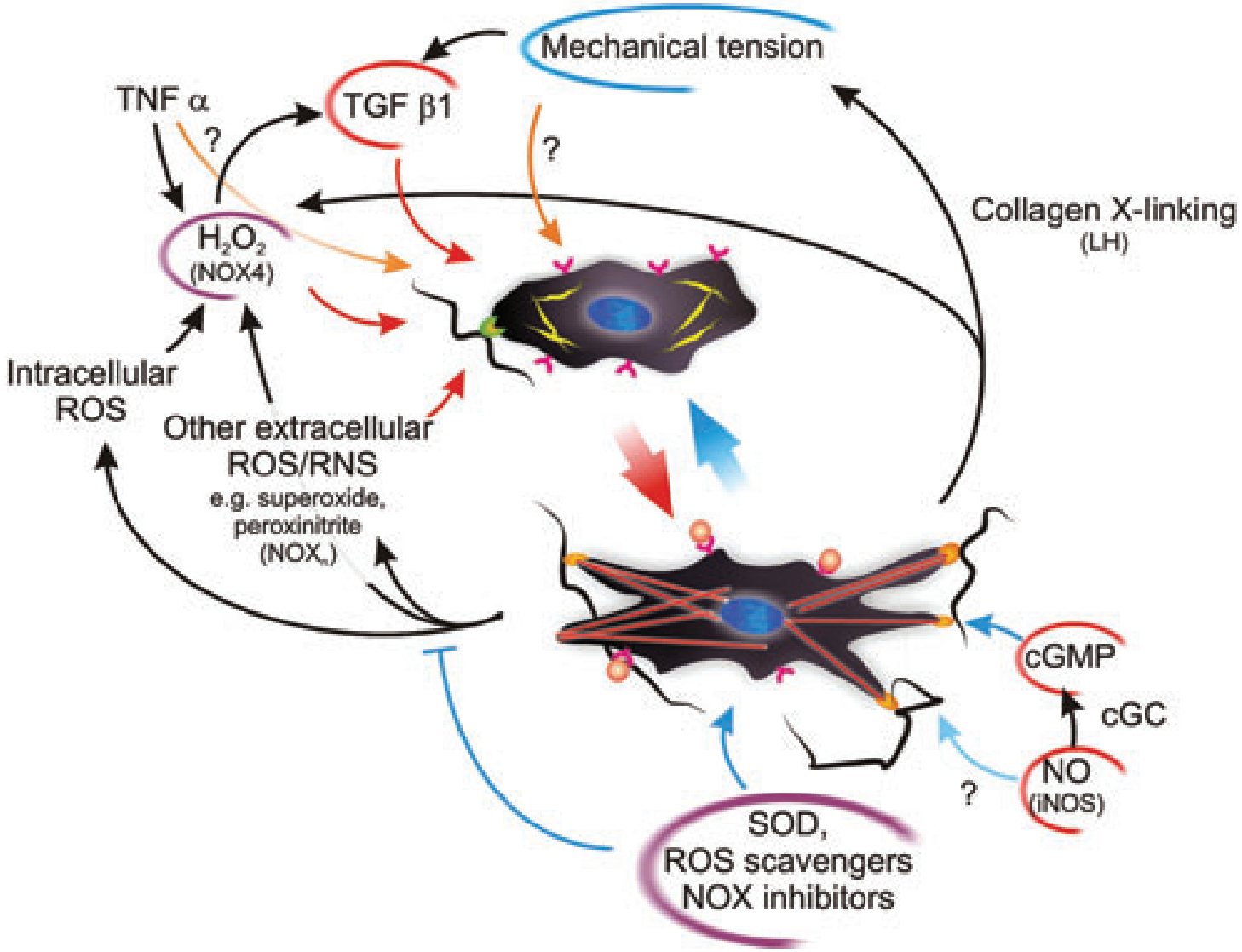


Fibroblasts on a fibrin gel

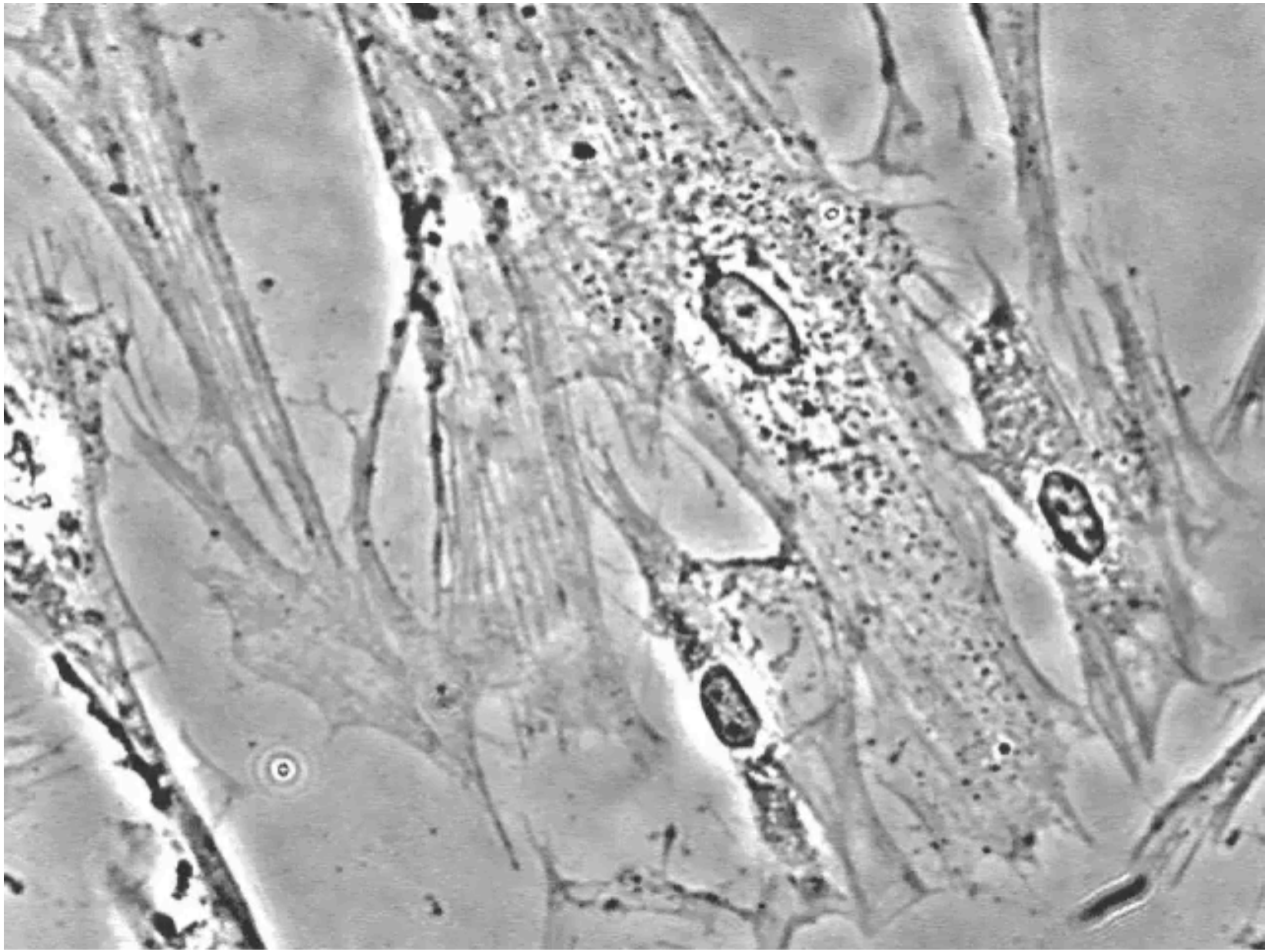
Sawhney et al, J.Cell Biol 2002

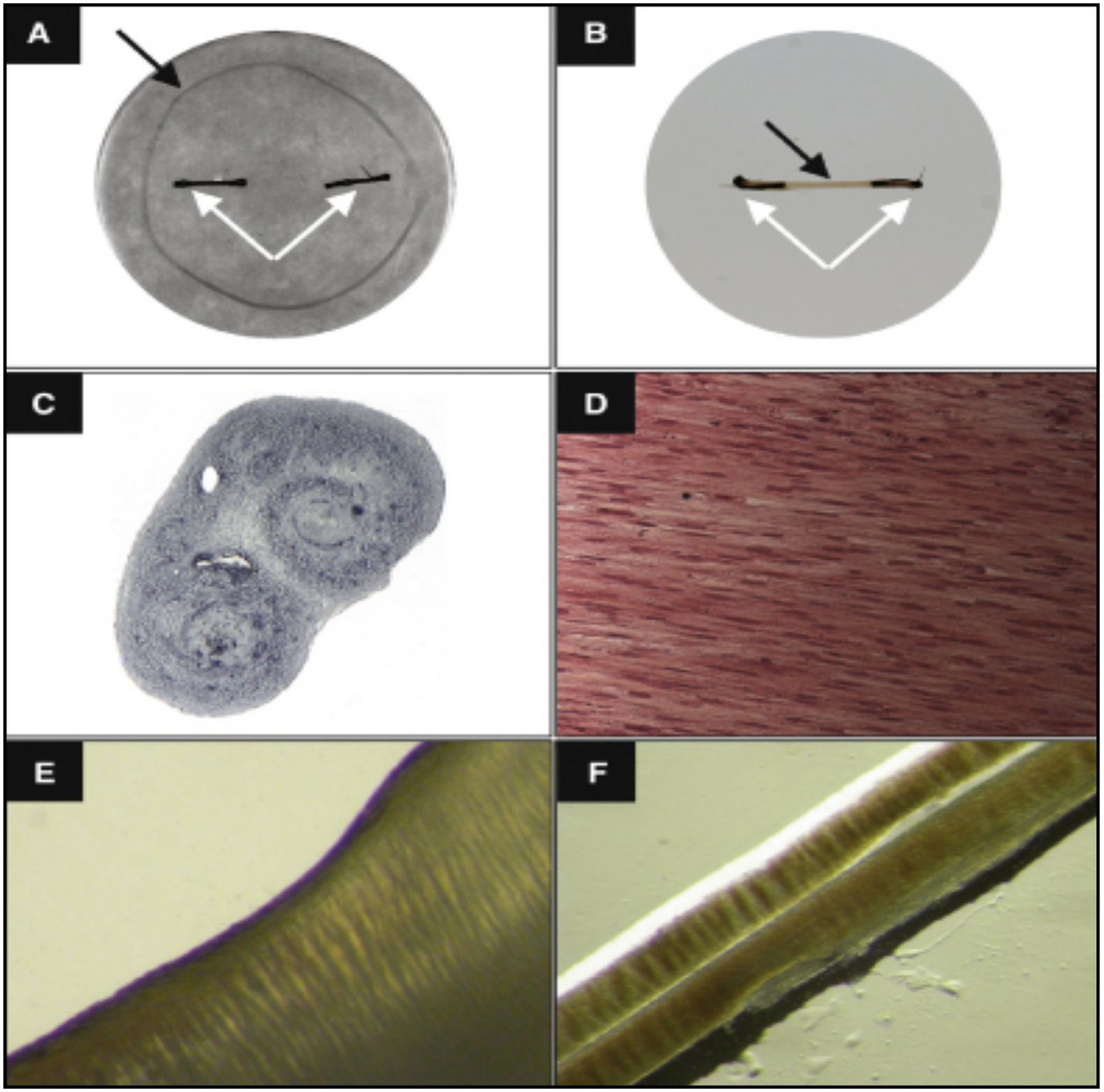


Collagen Assembly



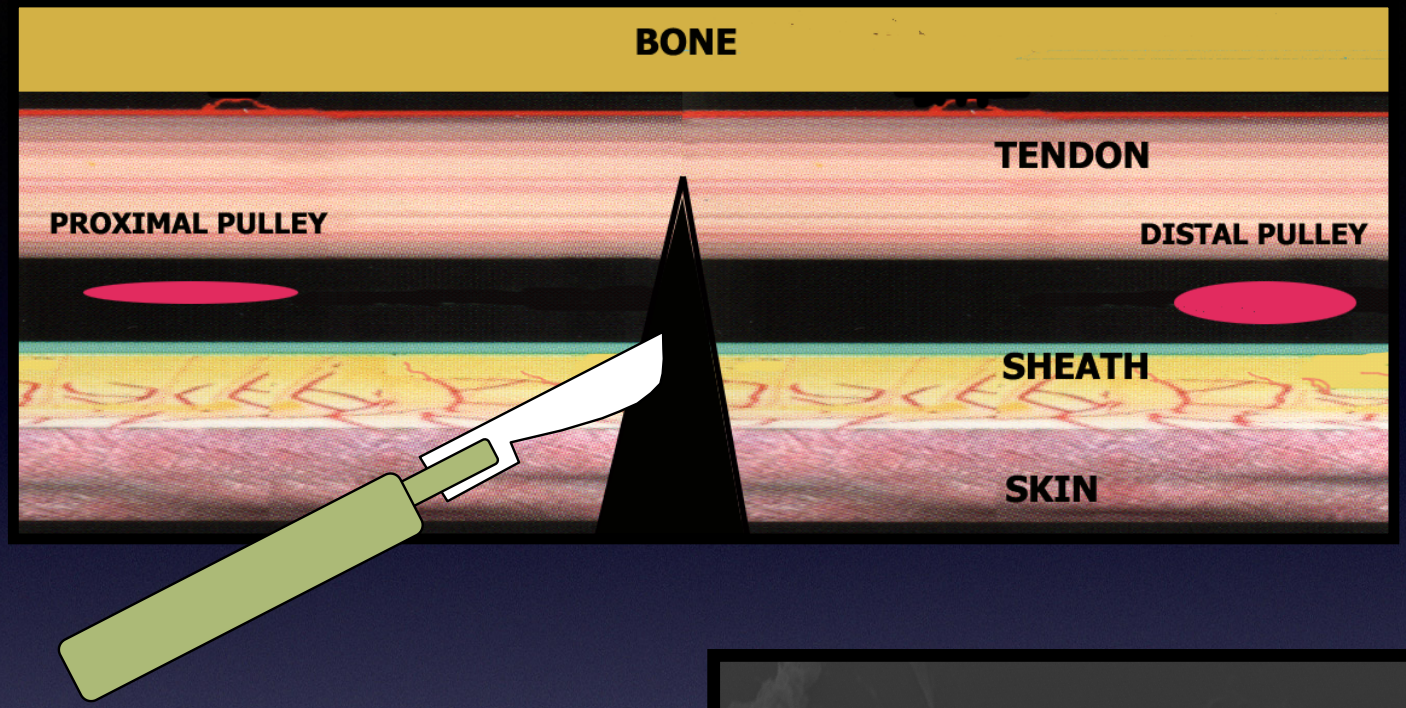
Siani and Tirelli 2014



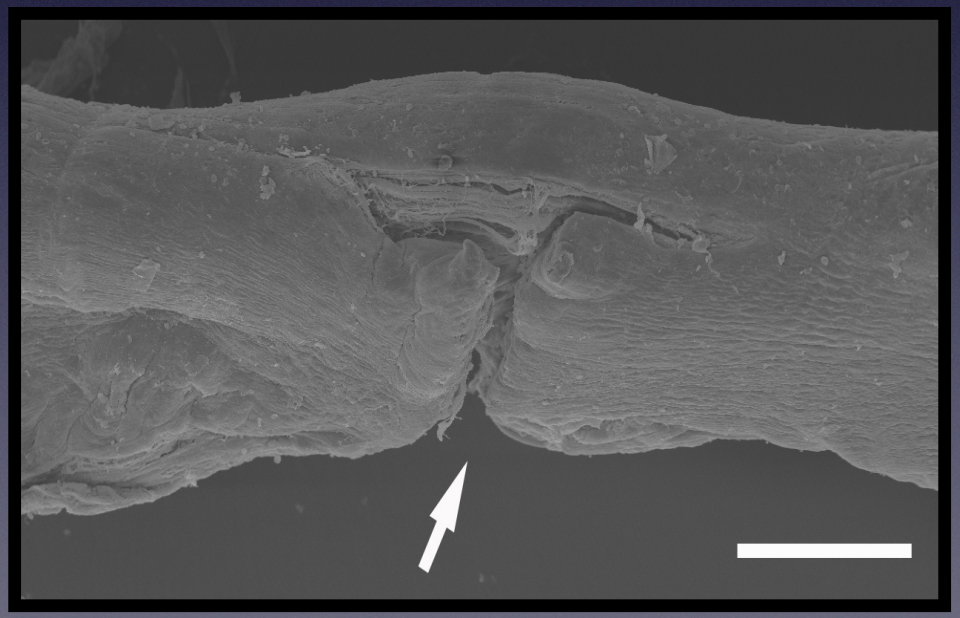


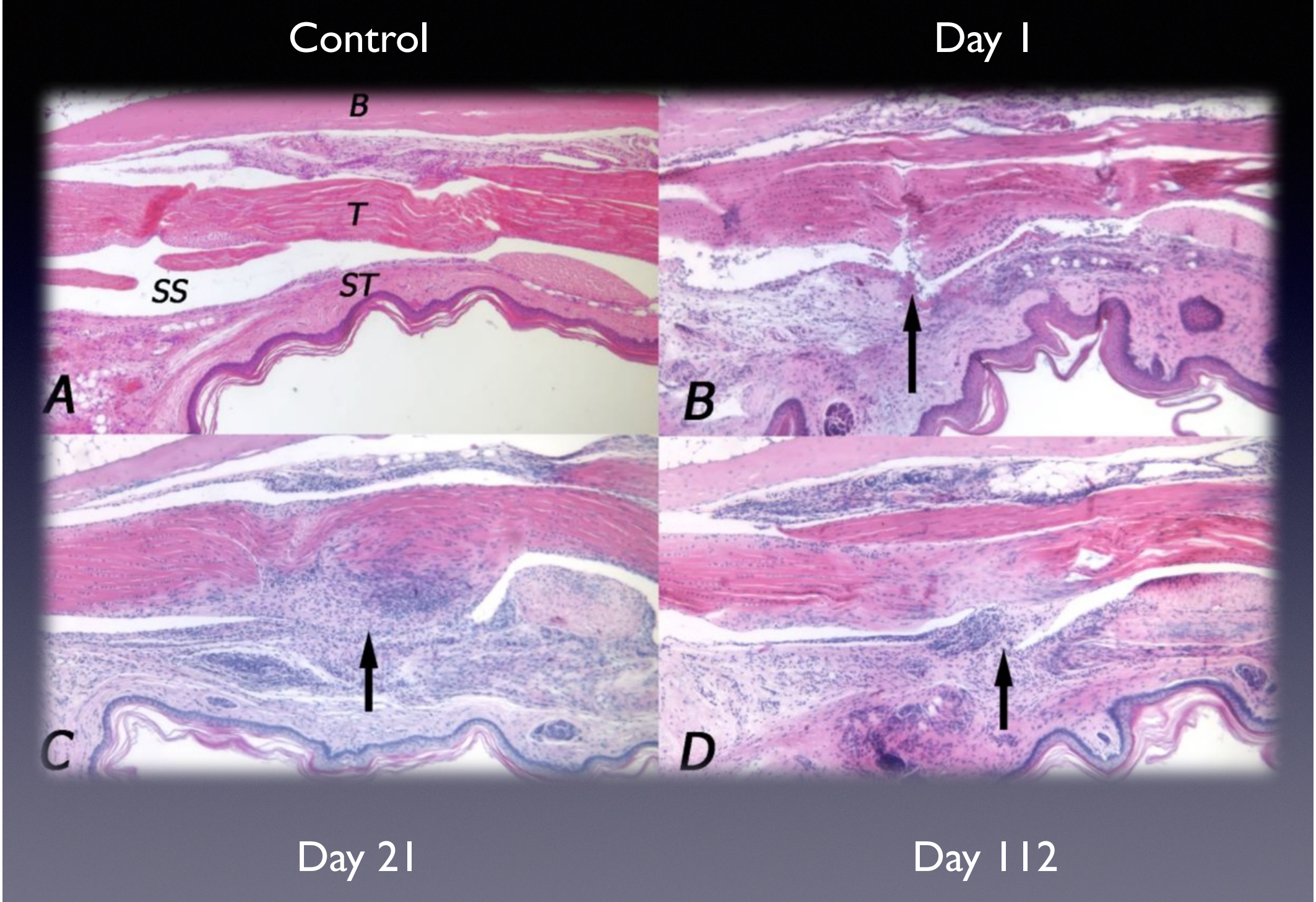
Kapacee et al 2010 Matrix Biology

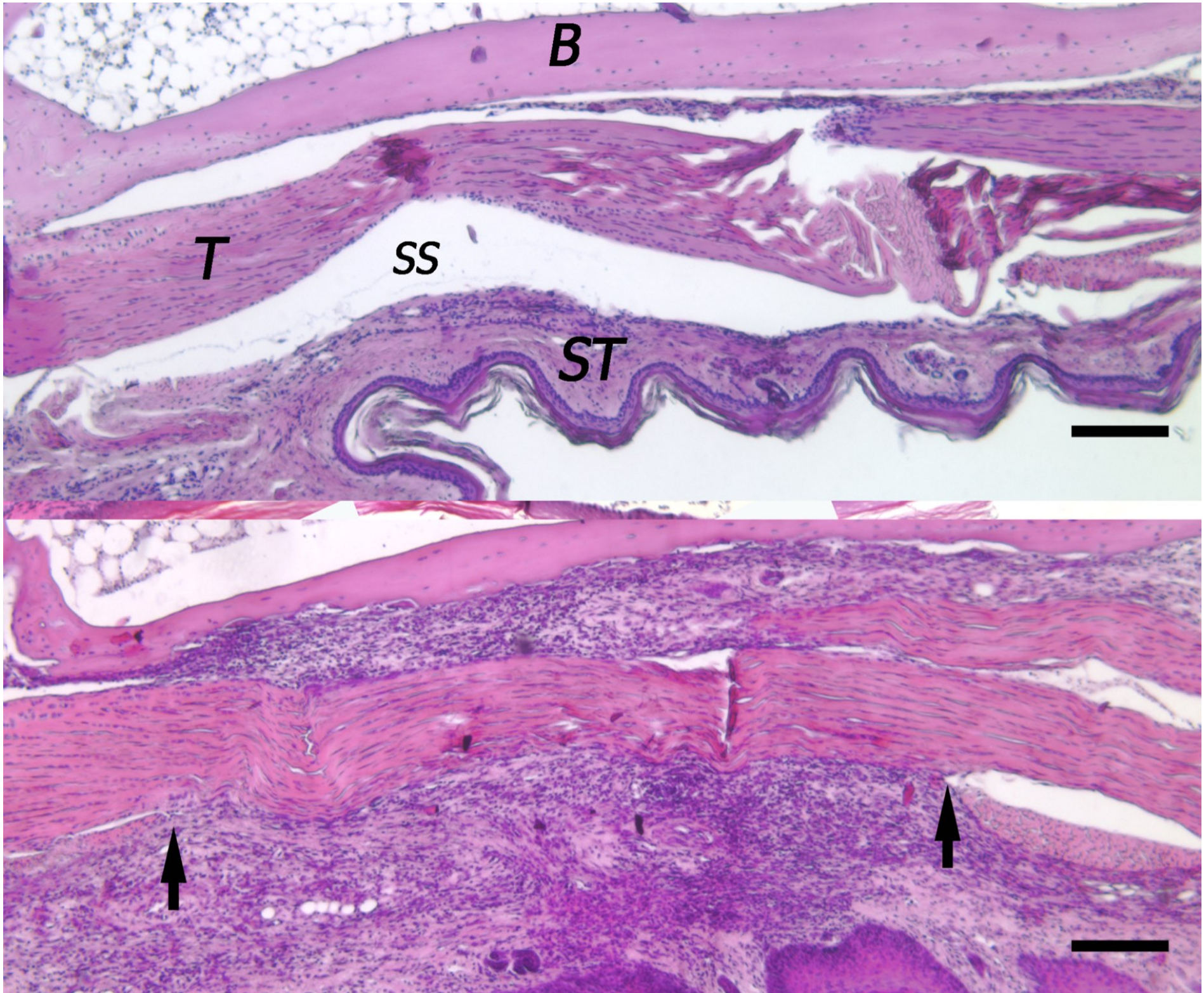
What about the systemic response?

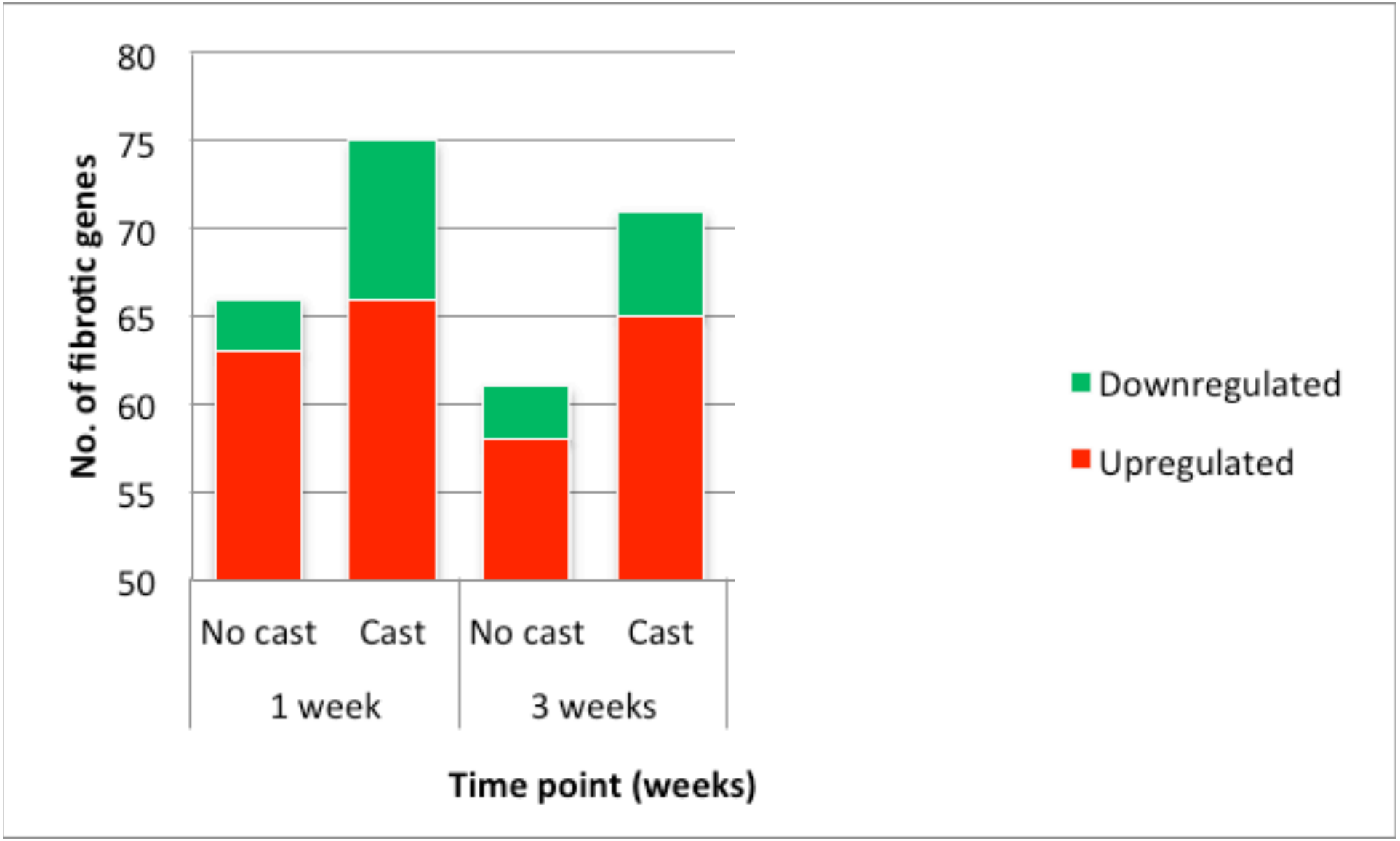


Scanning electron microscopy of the injured tendon. A simple partial laceration through 50% of the tendons diameter under operating microscope guidance. This was used as a model for healing.

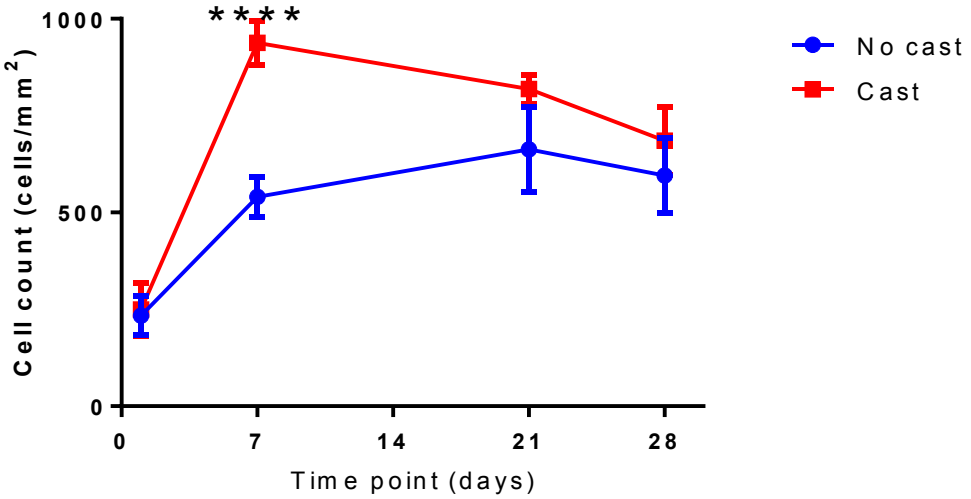



Control
Day 1
B
T
SS
ST
A
B
C
D
Day 21
Day 112

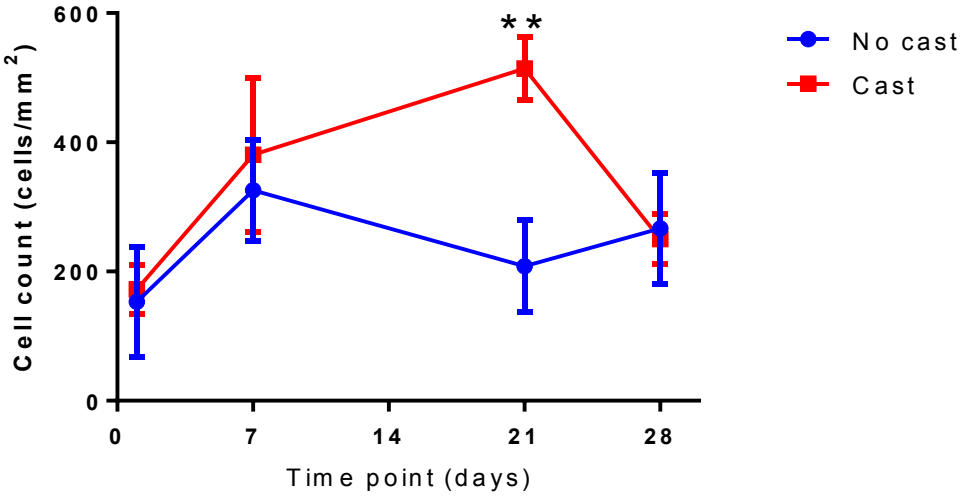

B
T
SS
ST

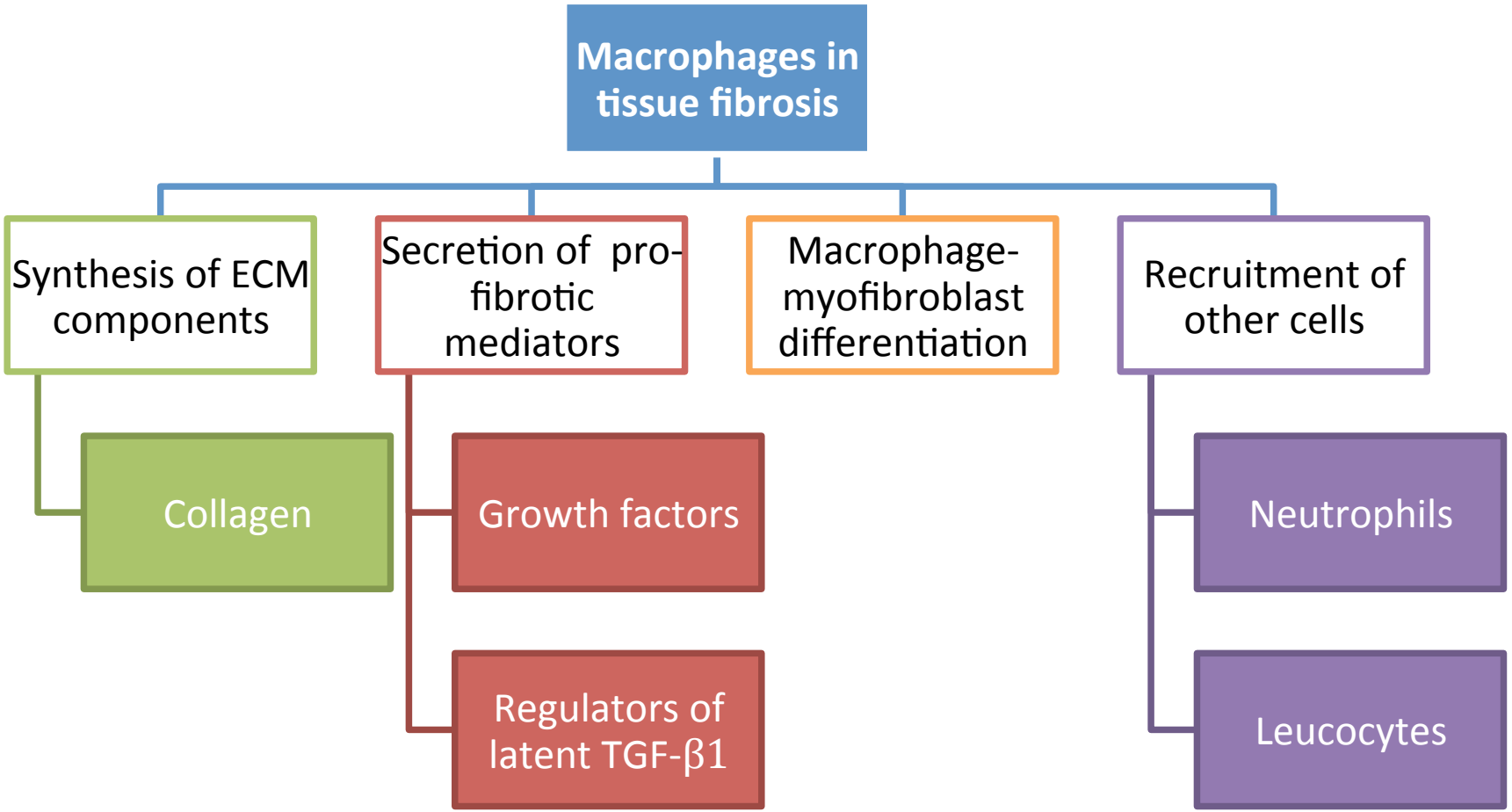

80
75
70
65
60
55
50
No. of fibrotic genes
No cast
Cast
No cast
Cast
1 week
3 weeks
Time point (weeks)
Downregulated
Upregulated

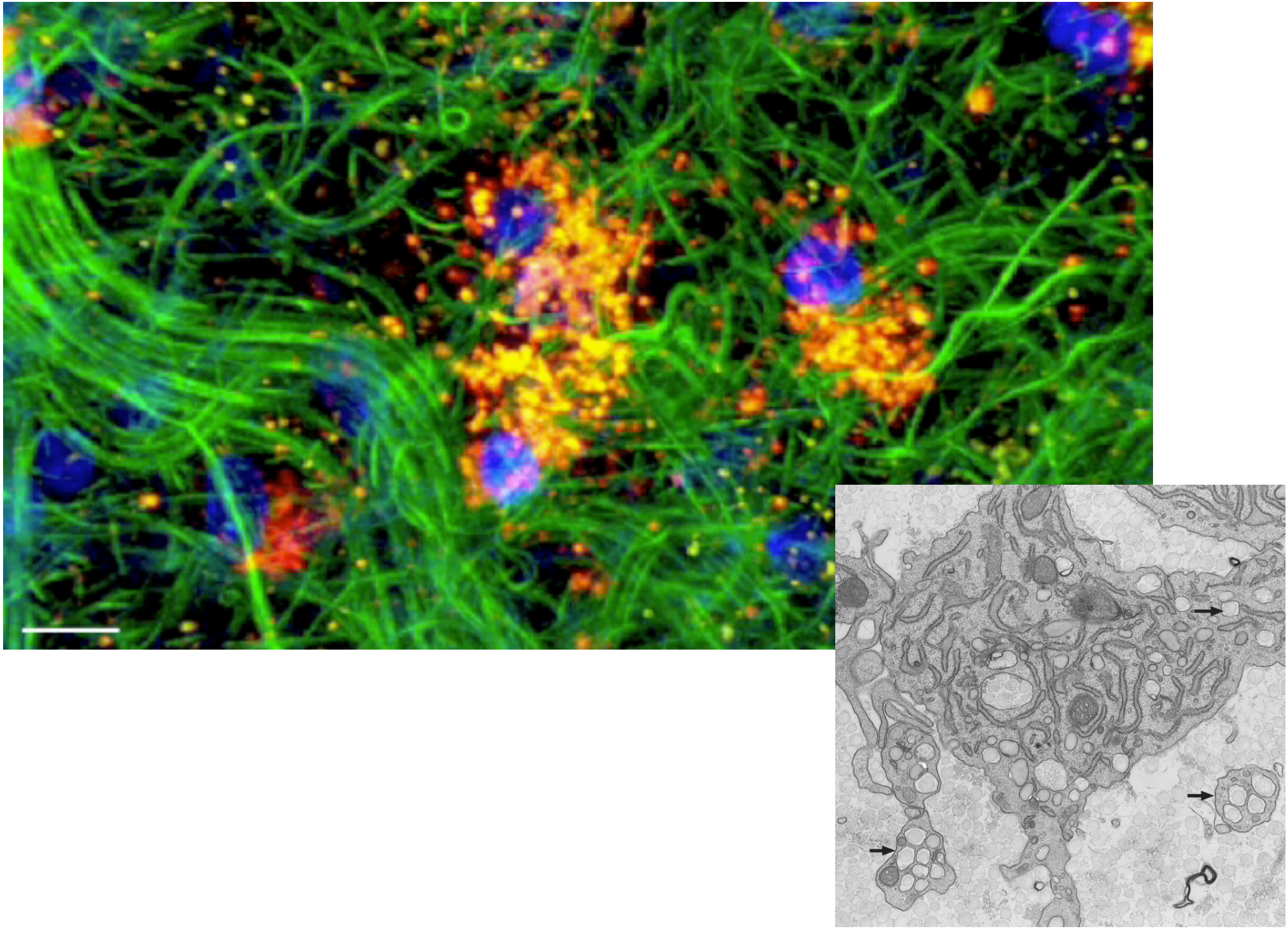
Macrophages

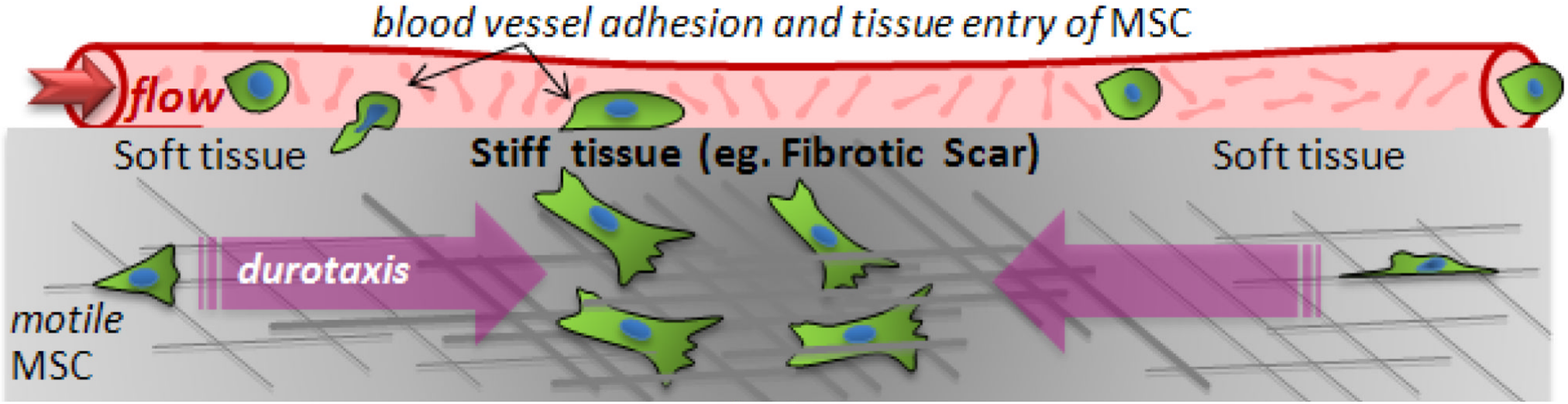


Myofibroblasts



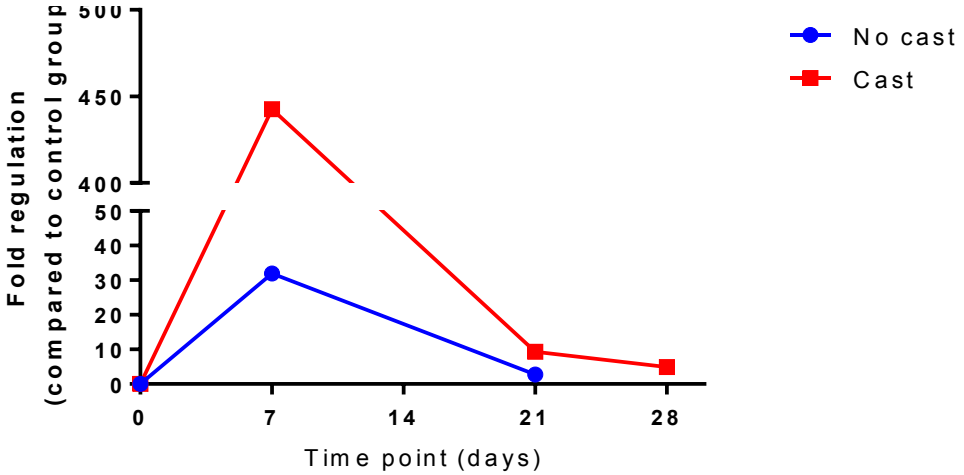

Macrophages in tissue fibrosis
Synthesis of ECM components
Secretion of pro-fibrotic mediators
Macrophage-myofibroblast differentiation
Recruitment of other cells
Collagen
Growth factors
Regulators of latent TGF-β1
Neutrophils
Leucocytes



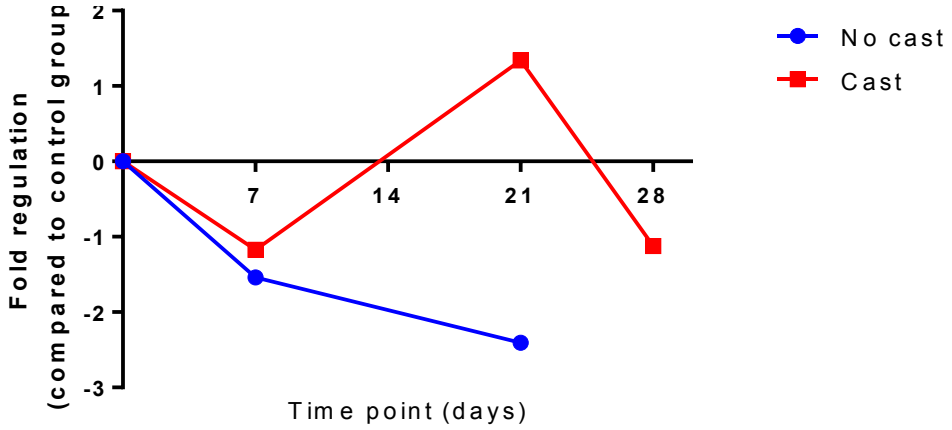

blood vessel adhesion and tissue entry of MSC
flow
Soft tissue
Stiff tissue (eg. Fibrotic Scar)
Soft tissue
durotaxis
motile
MSC

Gene expression

Collagen type 1

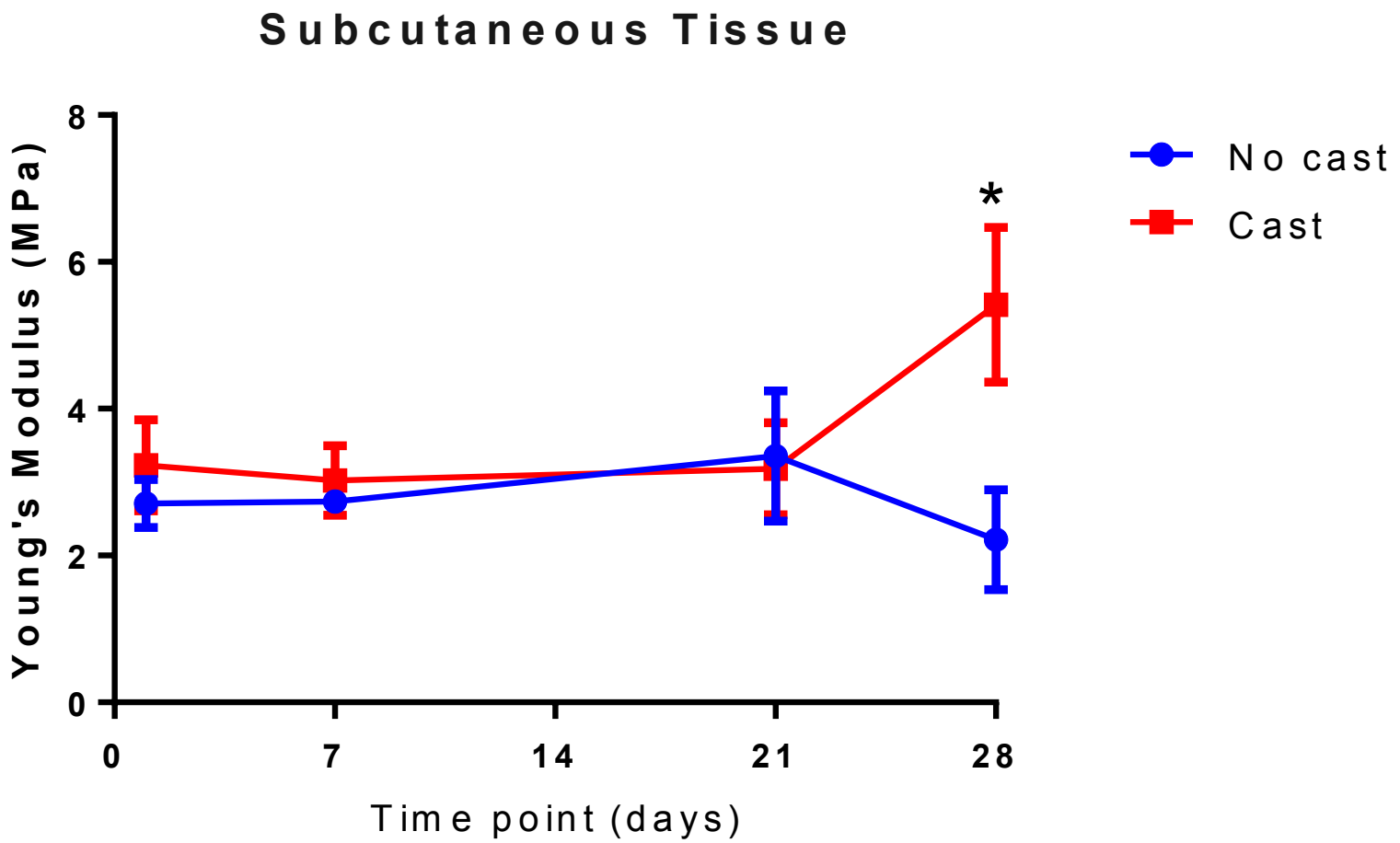


Collagen type 3

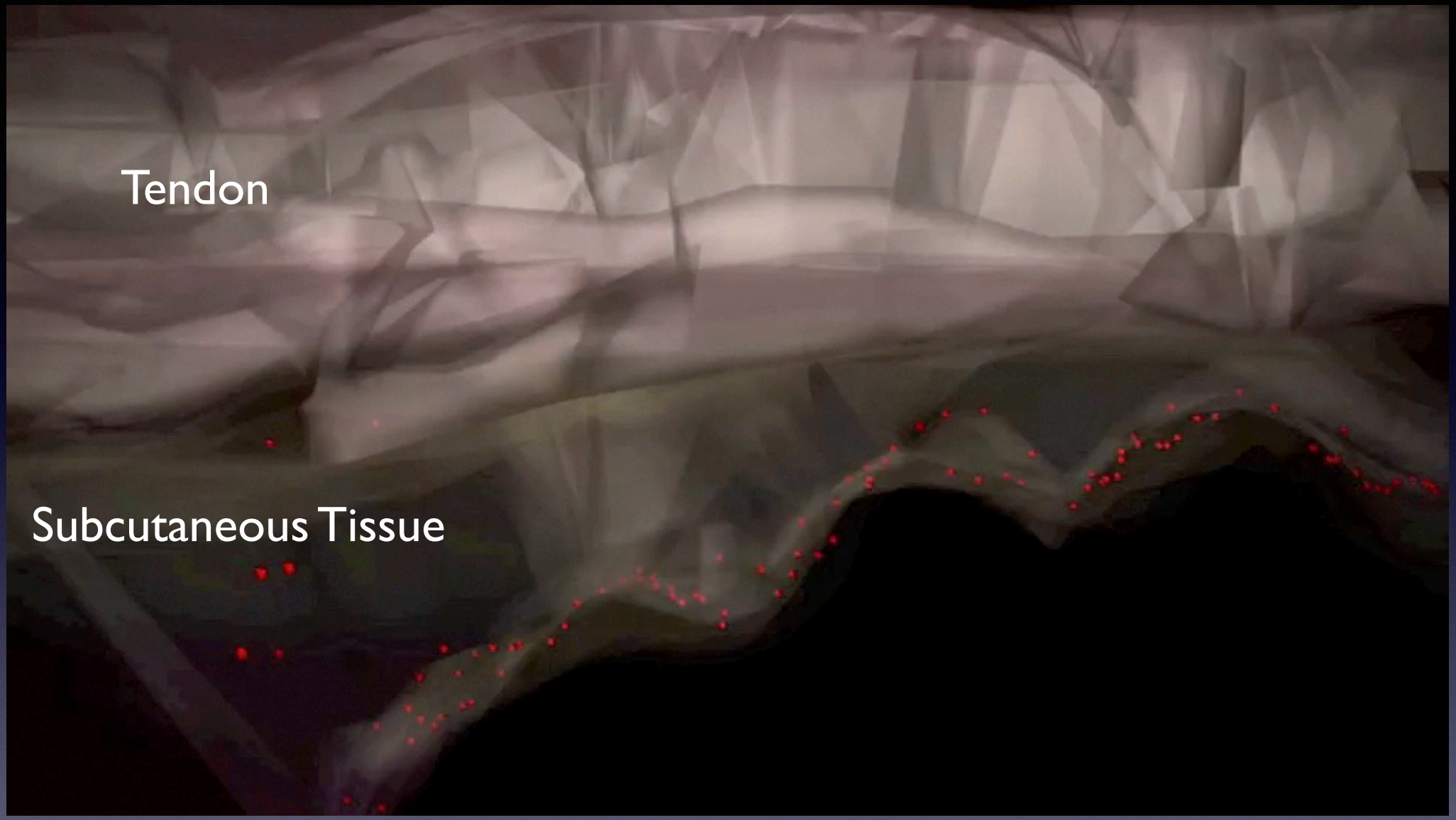


Atomic force Microscopy

Nanoindentation

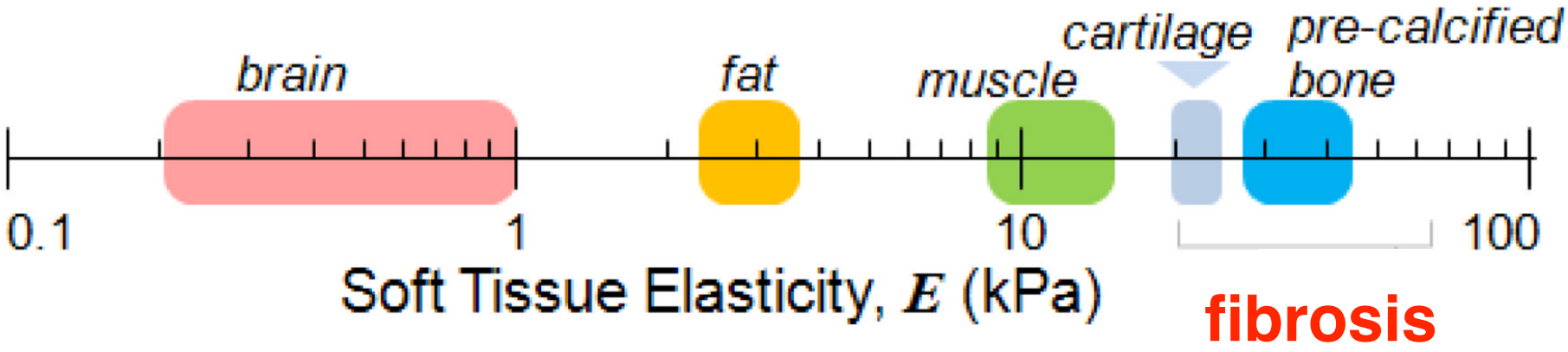


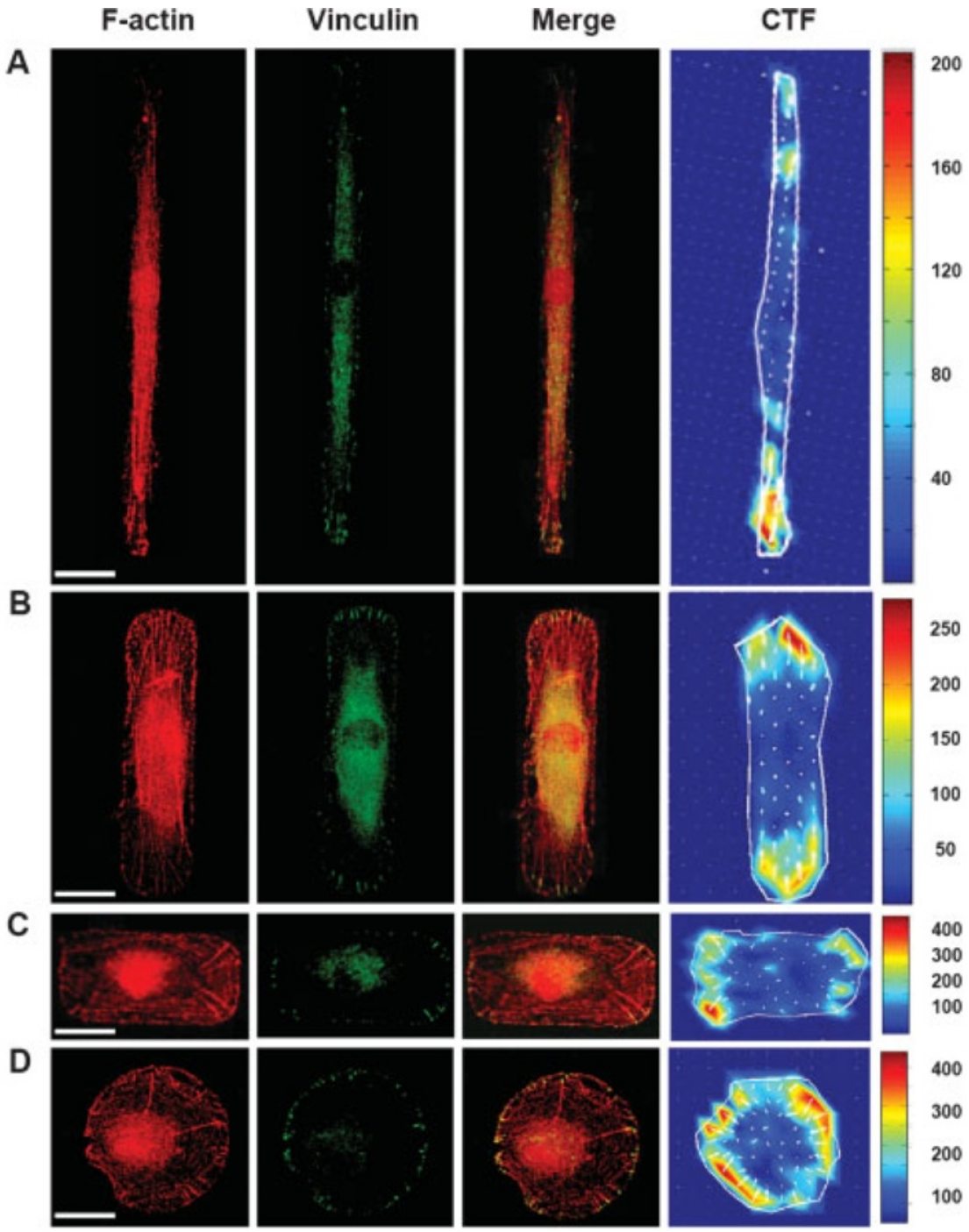
So how does fibrosis / adhesions form?



Inflammatory cells
Macrophages
Adhesion
Fibroblasts

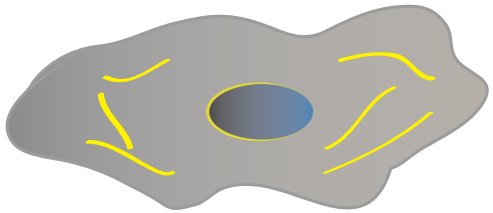
American Journal of Pathology 2009


brain
fat
muscle
cartilage
pre-calcified bone
0.1
1
10
100
Soft Tissue Elasticity, E (kPa)
fibrosis

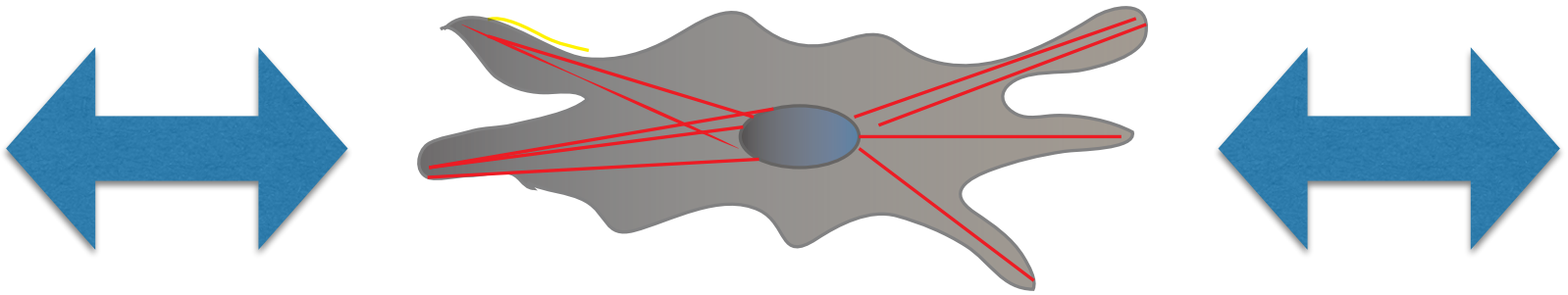


Cells under
tension express Coll1

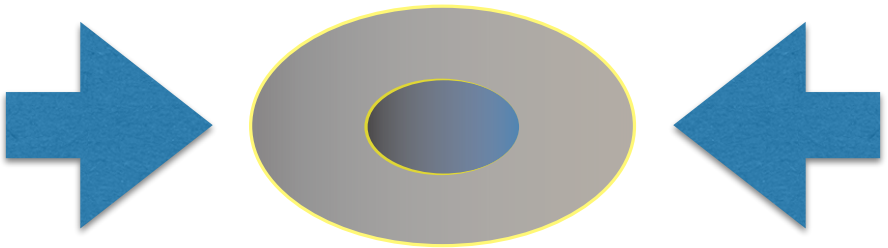
Cells under
compression express MMP1



cyclic load



compression



Current Work

Ex vivo perfusion

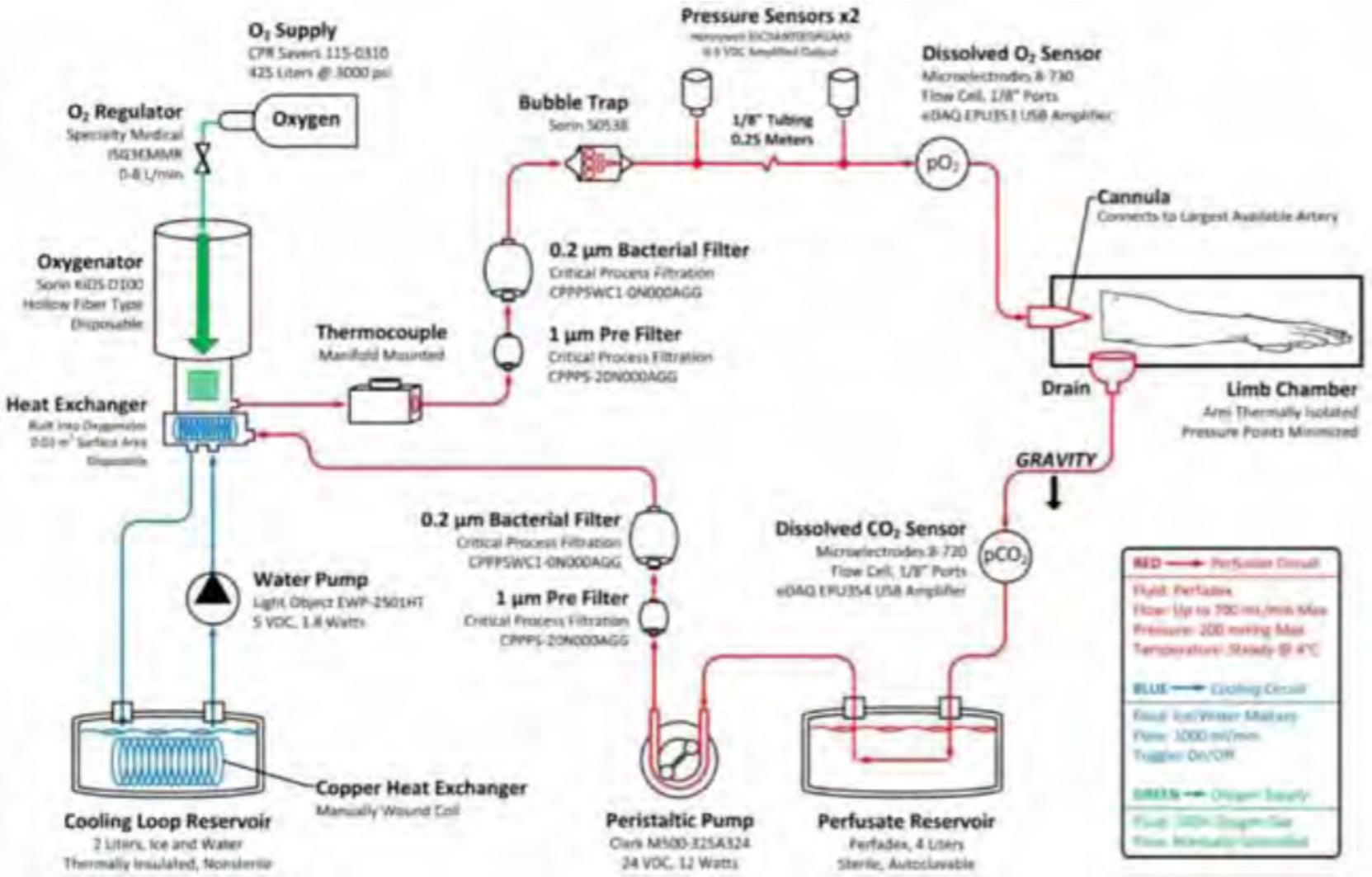
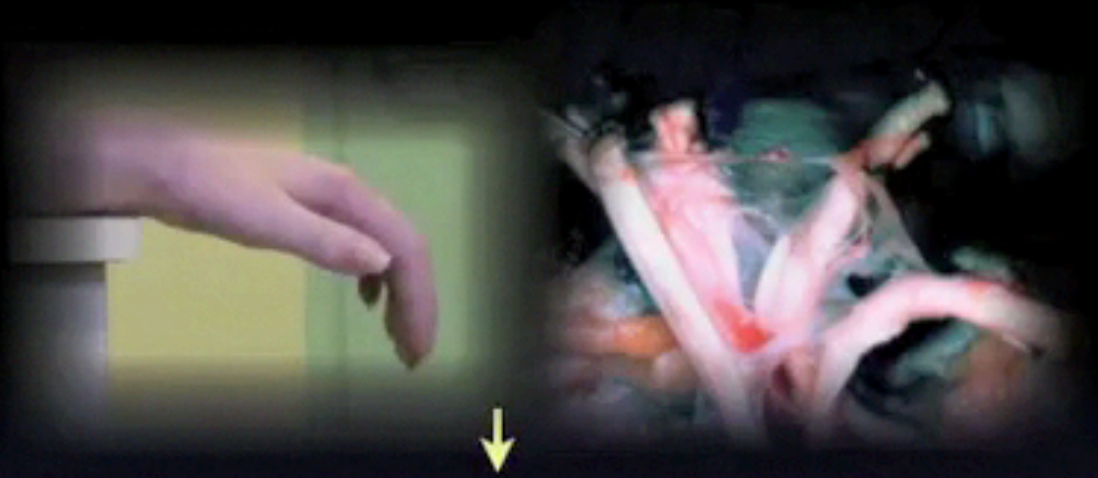


Figure 1. Schematic of the upper extremity perfusion device used in the planning stages of development.

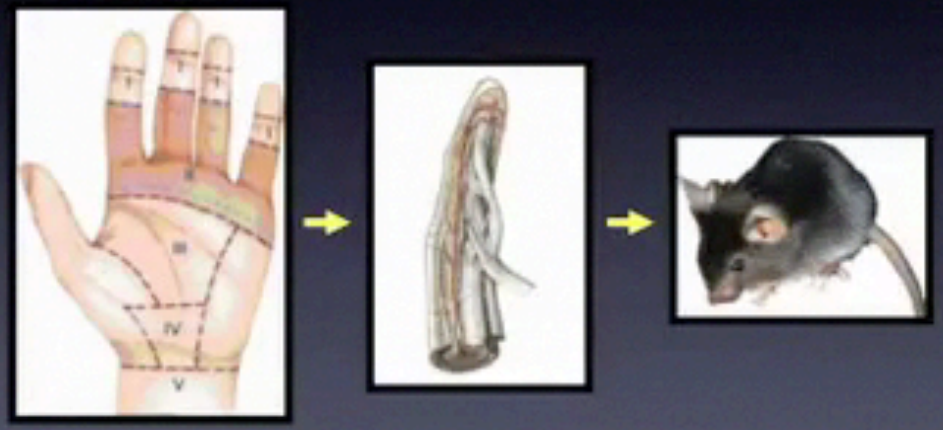
Clinical observations

IDEAS



Take observation to the lab

MODELS



Take it back to the patient

RAPID or Traditional TRANSLATION

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