ETH zürich

D-BIOL



Tissue Repair Part IV

Prof. Dr. Joel Zindel
Assistant Professor (TT) for Tissue Repair
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Notes for this lecture



Central concepts — exam-relevant



How we know: We look at the experimental data behind central paradigms. These slides are epistemologic in nature—**how we know what we know**—and should not be memorized for the exam.



Nerd factor: Historical or medical perspective or fun. Not to be committed to memory—although sometimes the most random facts stick best.

Resources: Robbins Basic Pathology, Tenth Edition, Chapter TISSUE REPAIR

Agenda – Tissue Repair

This agenda organises key concepts by when they are discussed — not as strict biological boundaries.

LECTURE 1

Injury

seconds – minutes

- **Definitions:** homeostasis, injury, regeneration, repair, and failure modes.
- The molecular basis of injury and injury detection: DAMPs, PAMPs, and LAMPs.

LECTURE 2

Inflammation

min – hours – days

- Injury detection
- macrophage cloaking and threshold gating
- Coagulation and Complement
- Thromboinflammation

LECTURE 3

Granulation tissue

hours – days – weeks

- The macrophage switch: macrophages subtypes in repair
- Macrophage-fibroblast circuit
- Provisional Matrix
- Angiogenesis
- Neural regulation of repair
- Collagen III
- Failure modes

LECTURE 4

Remodelling

days – weeks – months

- Pre primam vs. per secundam
- Provisional Matrix
- Collagen III
- MMP/TIMP balance
- Collagen I
- Remodeling in different tissues
- Failure modes

Phases are overlapping and tissue-dependent — complement, macrophages, and adaptive immunity span multiple lectures and are discussed in context.

Learning Objectives — Lecture 4: Remodelling

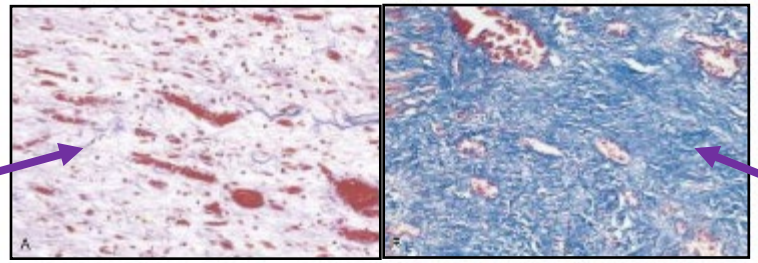
- Students can distinguish between **sanitatio per primam** and **per secundam intentionem** — explaining how gap size, DAMP load, and mechanical stability determine the scale of scaffold formation and remodelling required.
- Students can describe the **sequential matrix composition during remodelling** — from fibrin/fibronectin scaffold through collagen III to mature collagen I — and explain what drives each transition.
- Students can explain how **MMP/TIMP balance controls ECM degradation** — including the cysteine switch mechanism of proMMP activation and why net ECM remodelling equals expression × activation – inhibition.
- Students can apply the concept of **organ-specific remodelling goals** — articulating why the physiological scar differs between bone, liver, lung, heart and skin, and predicting the failure mode when remodelling overshoots in each tissue.
- Students can explain why **fibrosis represents a failure of myofibroblast resolution** — identifying TGF-β and persistent DAMP signalling as the common drivers across organs, and giving organ-specific examples (cirrhosis, IPF, cardiac fibrosis, keloid).

Recap: Phases of Repair

Lecture 1 and 2

Lecture 3

Lecture 4



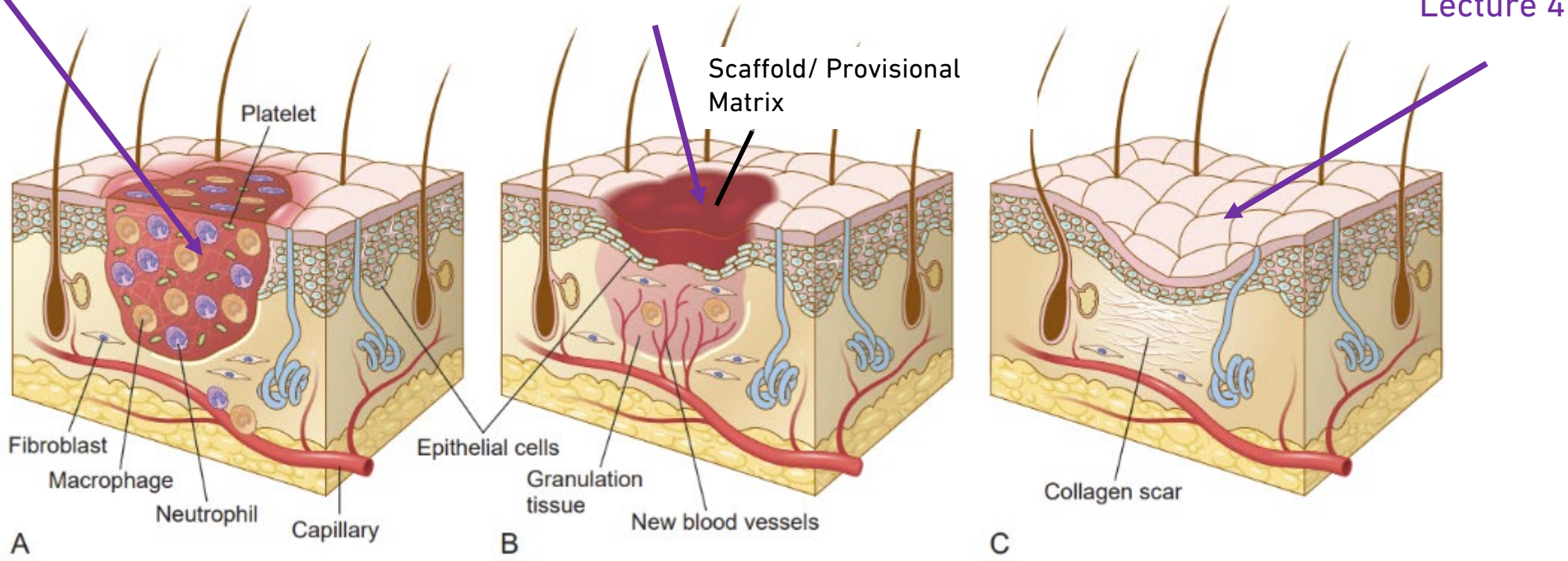
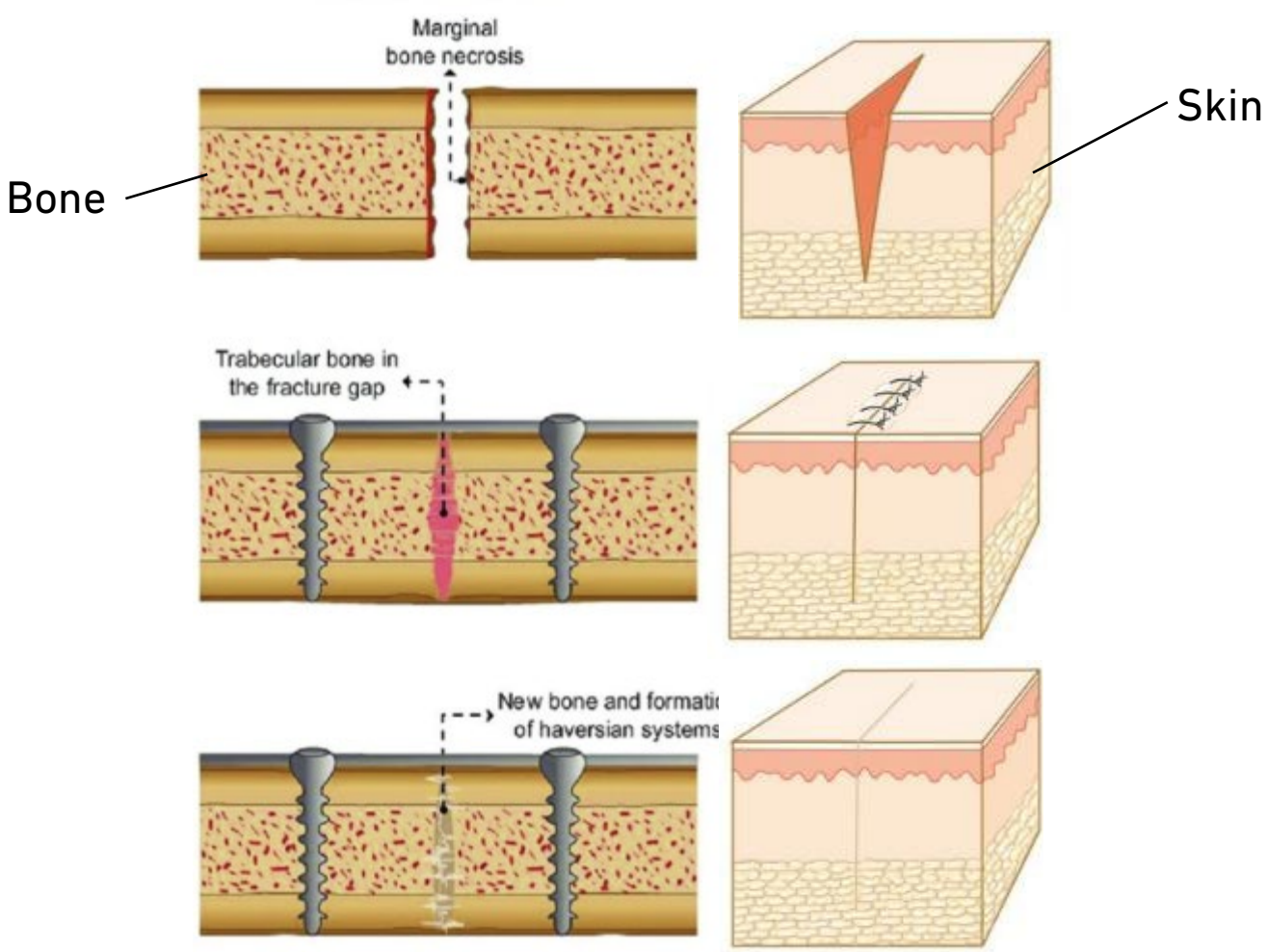


Fig. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is an example of healing by second intention. (A) Hemostatic plug and inflammation. (B) Proliferation of epithelial cells; formation of granulation tissue by vessel growth and proliferating fibroblasts. (C) Remodeling to produce the fibrous scar.

Sanitatio per primam vs. per secundam

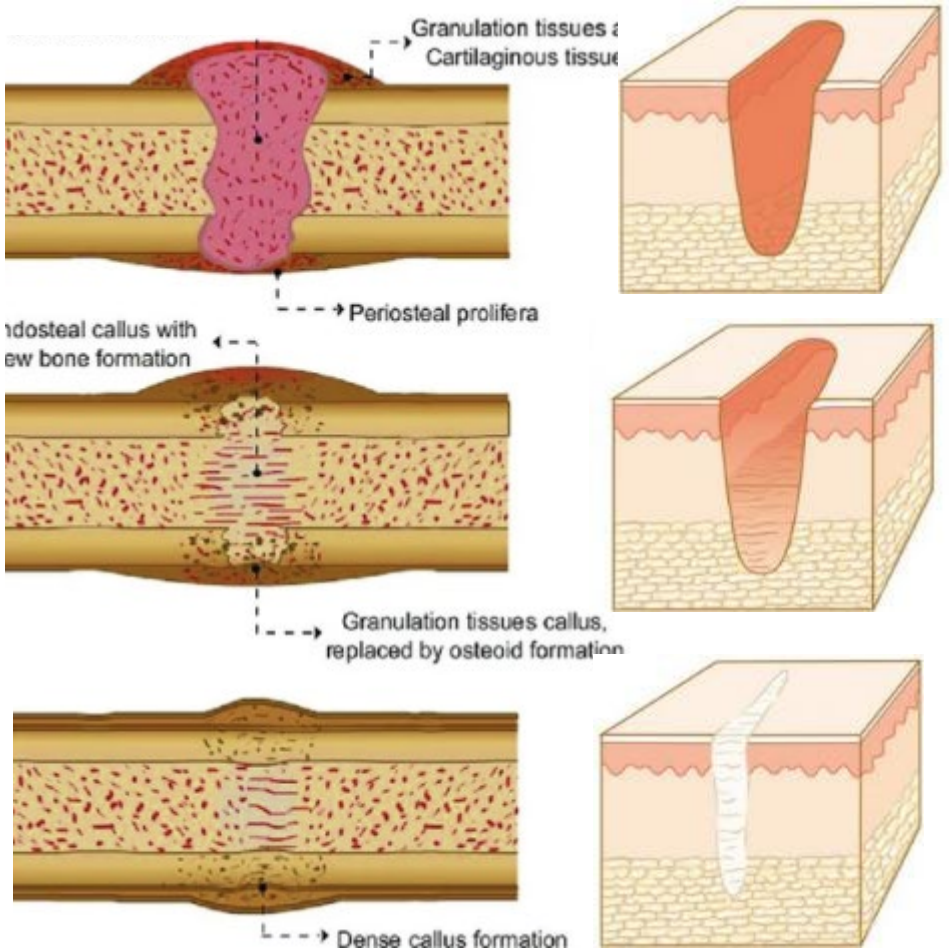
Primary intention healing

Why: ↓*DAMP*, ↓ *gap* → ↓scaffold, ↑mech. stability



Secondary intention healing

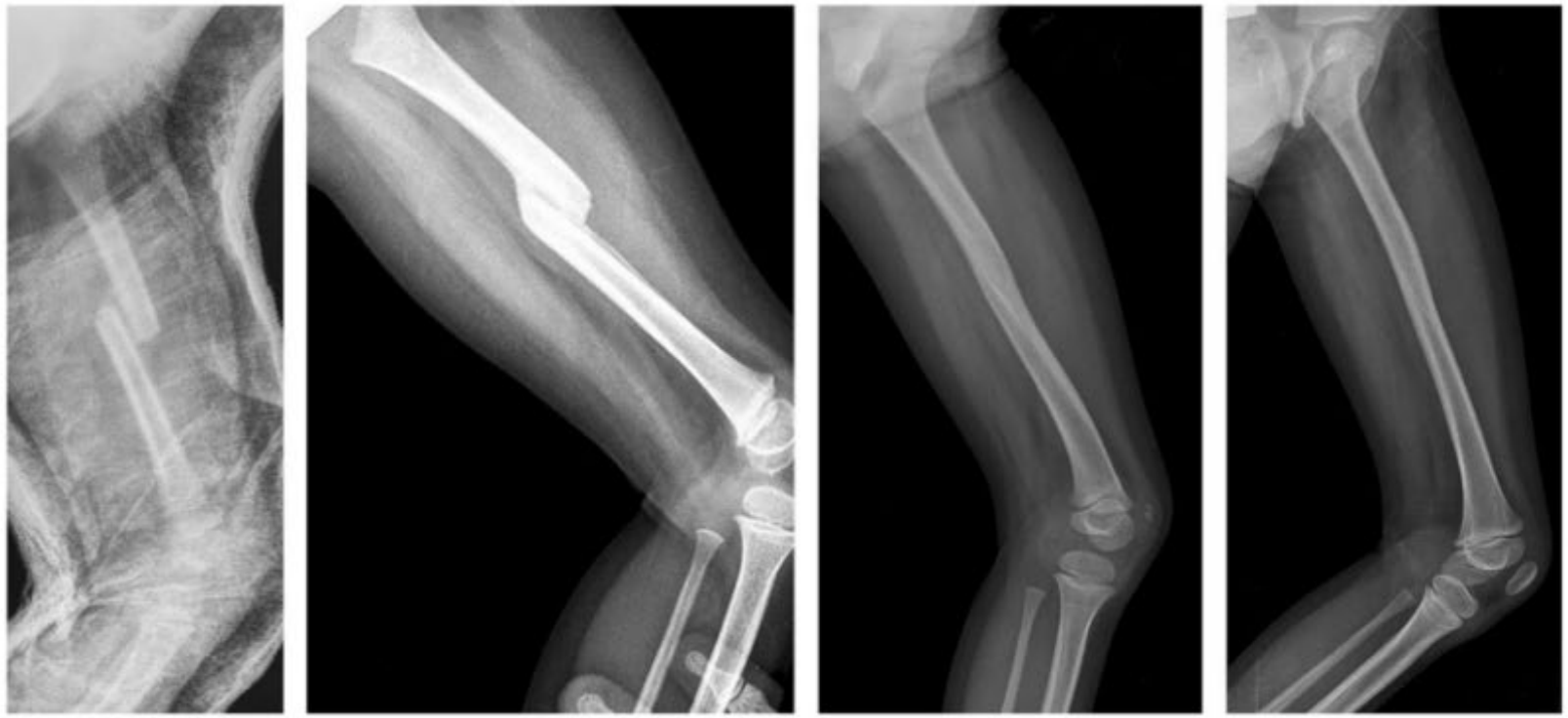
Why: ↑DAMP, ↑*gap* → ↑*scaffold*, ↓mech. stability



https://doi.org/10.1007/978-3-319-92055-9_21, DOI:10.25259/IJMSR_43_2022

Case study bone

Fig. 3 Full correction of complete translation of femur shaft fracture in 2-year-old girl over one and a half years



https://doi.org/10.1007/s43465-020-00320-2

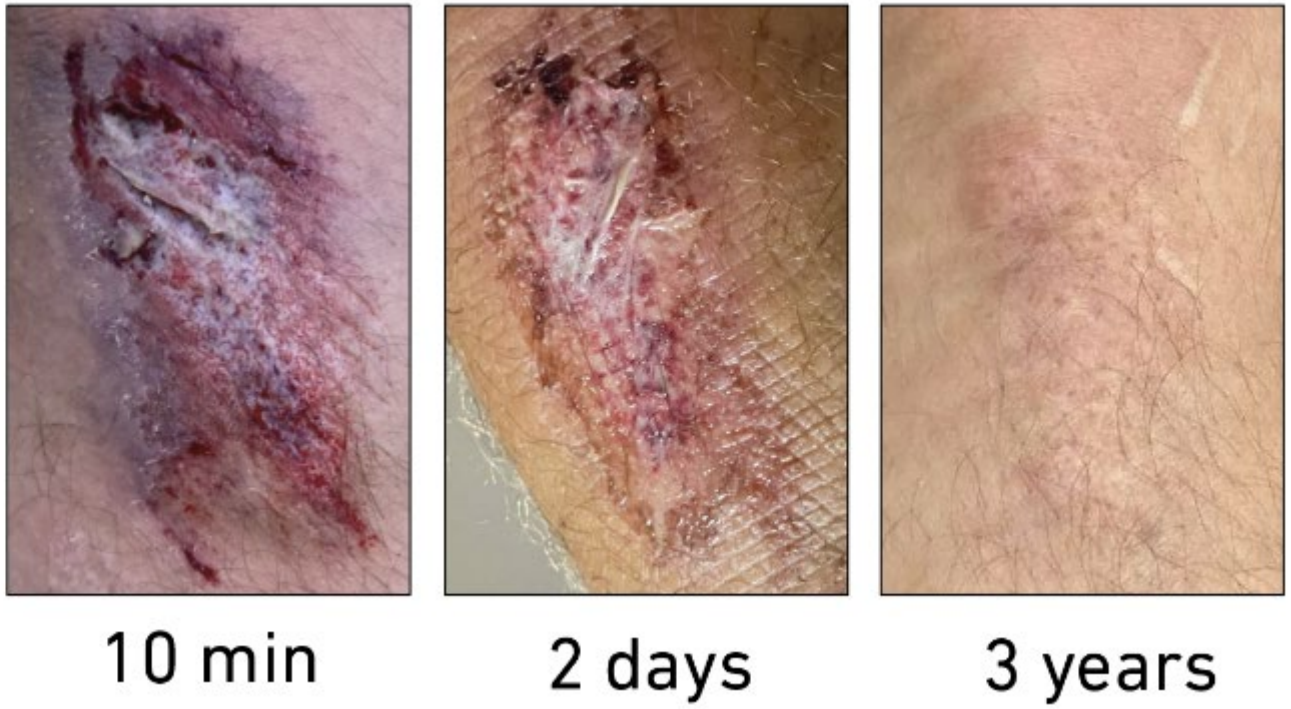
This (valid) example is no treatment advice. The treatment chosen varies depending on age, comorbidities, and fracture pattern and will affect **primary vs. secondary** bone repair.



https://www.orthobullets.com/pediatrics/4019/femoral-shaft-fractures--pediatric

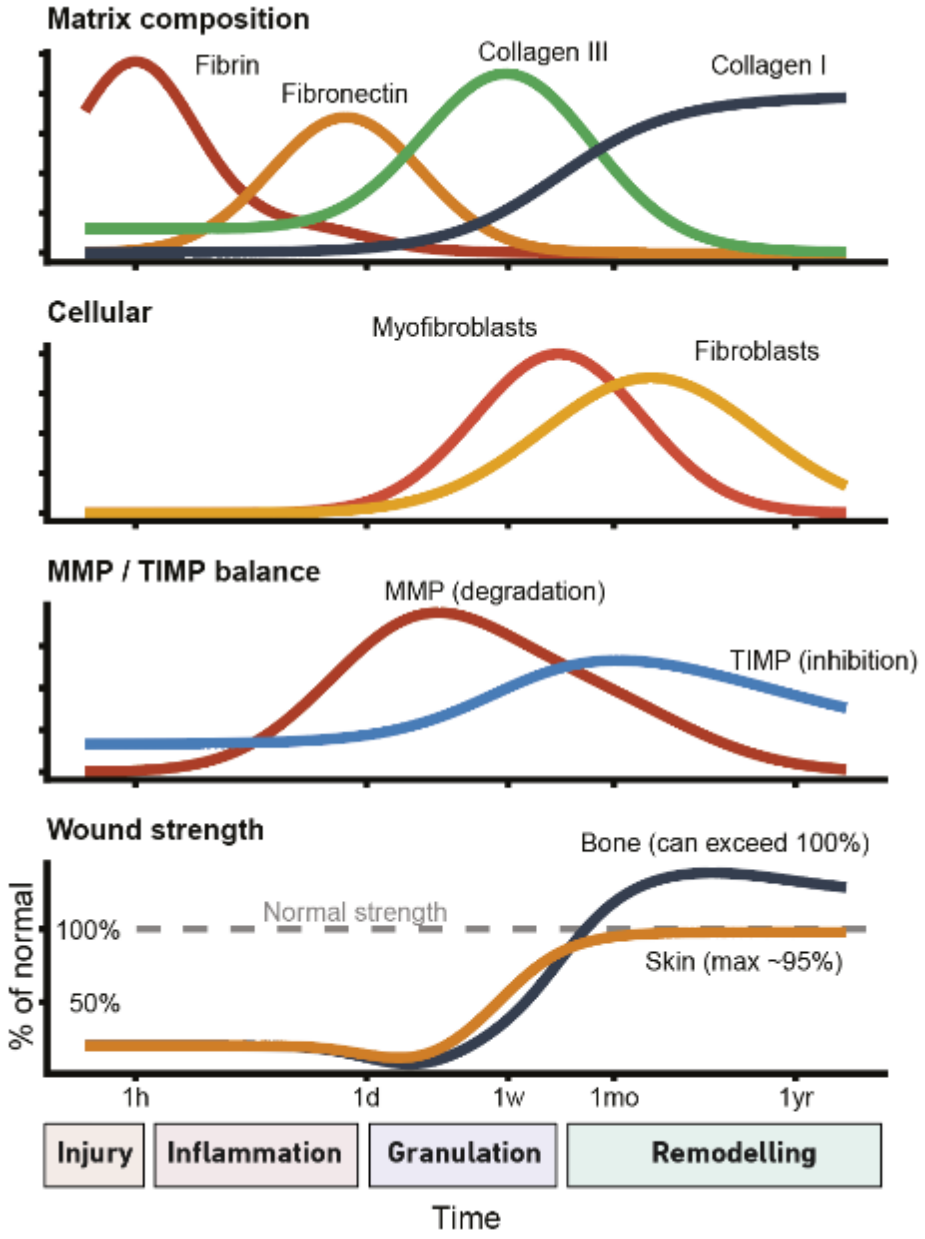
Case study skin

Fig.1 High-function correction of contaminated wound in 34-year-old man.



Take home: secondary intention healing (repair) can lead **to highly functional outcomes** → this is the main role of remodelling.

Remodelling Overview

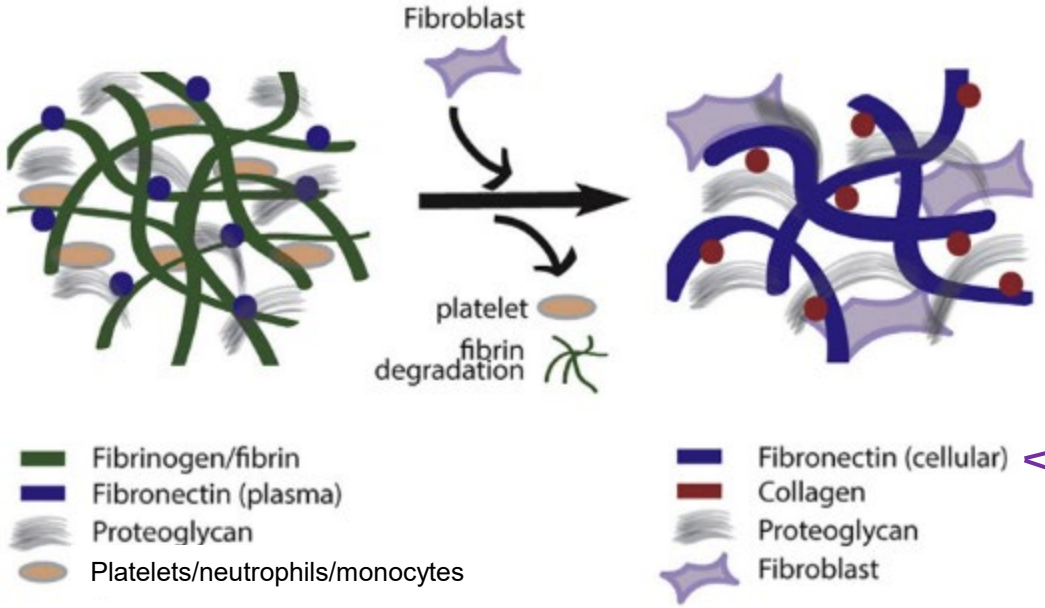


Schematic based on review of the literature (not based on experimental data)

Provisional matrix

Early Provisional Matrix

Late Provisional Matrix



Adapted from:
https://doi.org/10.1016/j.matbio.2017.04.003

Teaching note—early provisional matrix = thromboinflammation (link to previous lecture)

Fibronectin the key player

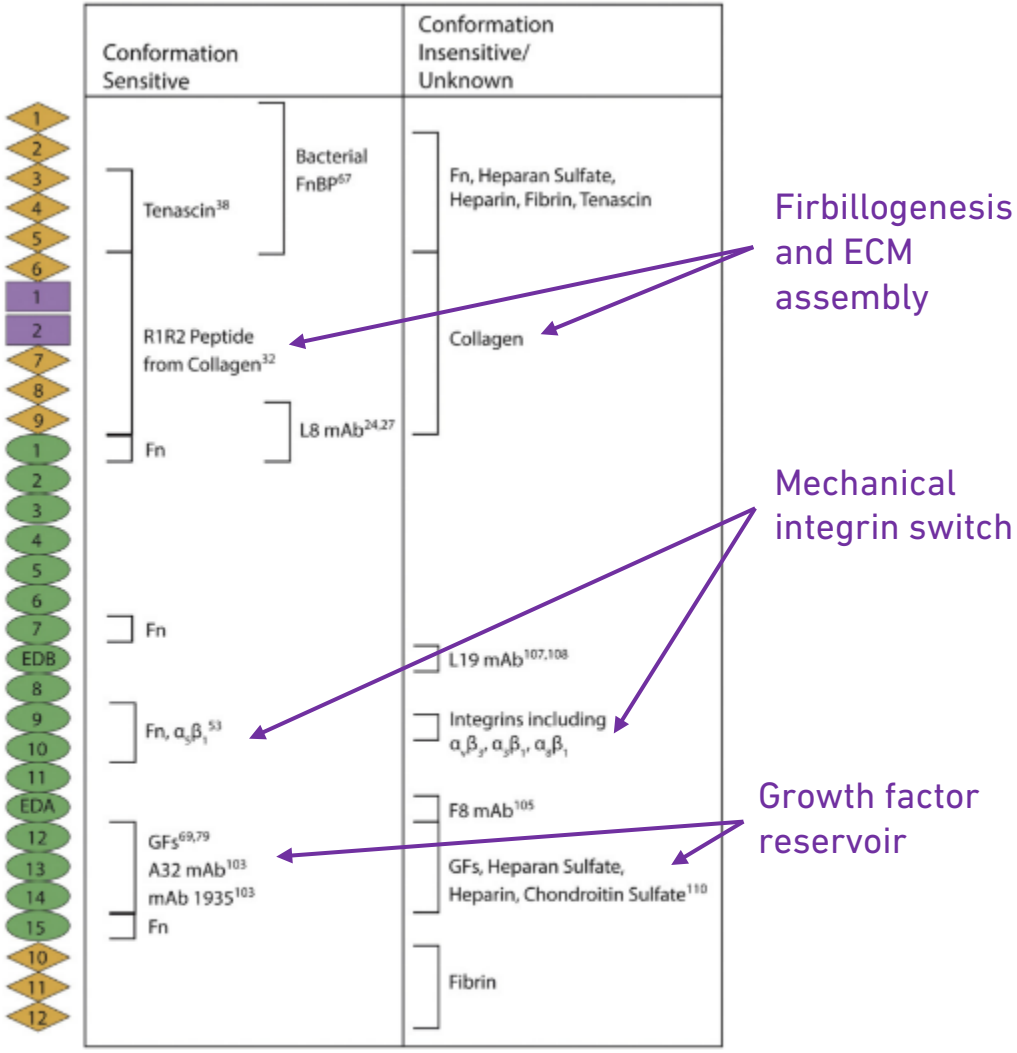
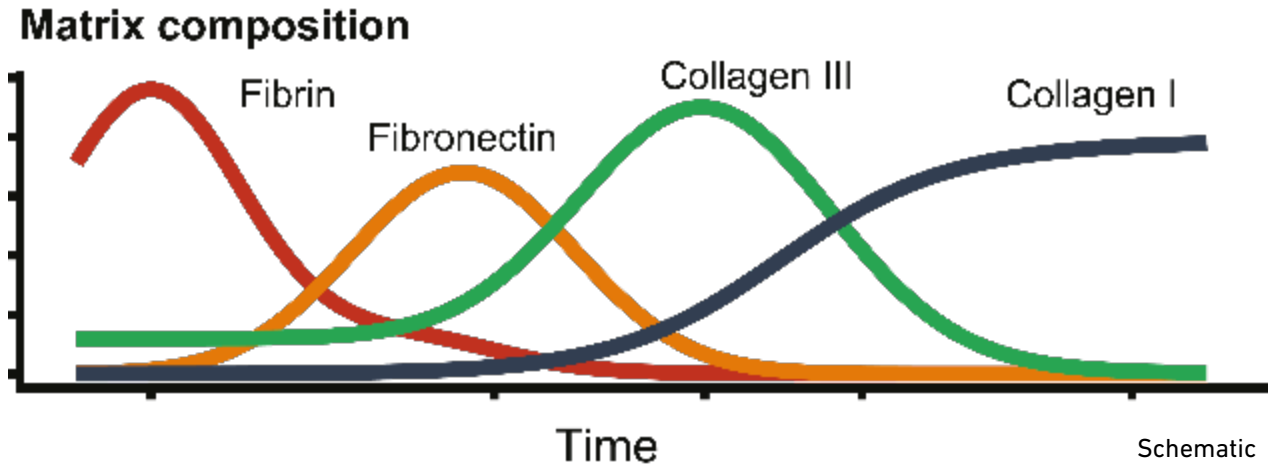


Fig. 2. Conformation dependent binding. Fn conformation is an important determinant of molecular binding. The arrangement of Fn's type I (diamonds), type II (rectangles), and type III (oval) modules is shown. Binding partners are shown with categorization according to whether binding is dependent or independent/unknown on Fn conformation. References provided for binding are noted in superscript; otherwise, commonly recognized binding sites are noted with references in this classic review article [1].

https://doi.org/10.1016/j.matbio.2016.07.011

Intermediate Matrix (Collagen III) → Final Matrix (Collagen I)



Schematic

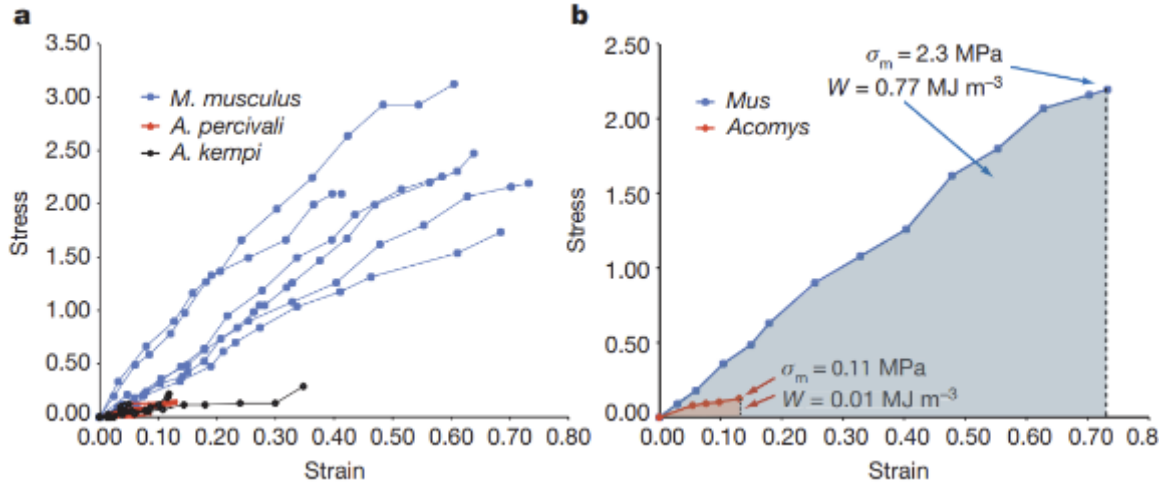
Property	Collagen III	Collagen I
Gene	COL3A1	COL1A1, COL1A2
Chain composition	$[\alpha1(III)]_3$ homotrimer	$[\alpha1(I)]_2\alpha2(I)$ heterotrimer
Fibril diameter	Thin, reticulin (~15–50 nm)	Thick (100–500 nm)
Mechanical properties	Flexible, compliant, disulfide-stabilized	High tensile strength, stiff, heavily cross-linked
Normal tissue distribution	Blood vessels, gut, fetal skin (~27% adult skin)	Bone, tendon, skin (~85% of adult skin)

Species specificity Collagen I and III

Mus musculus

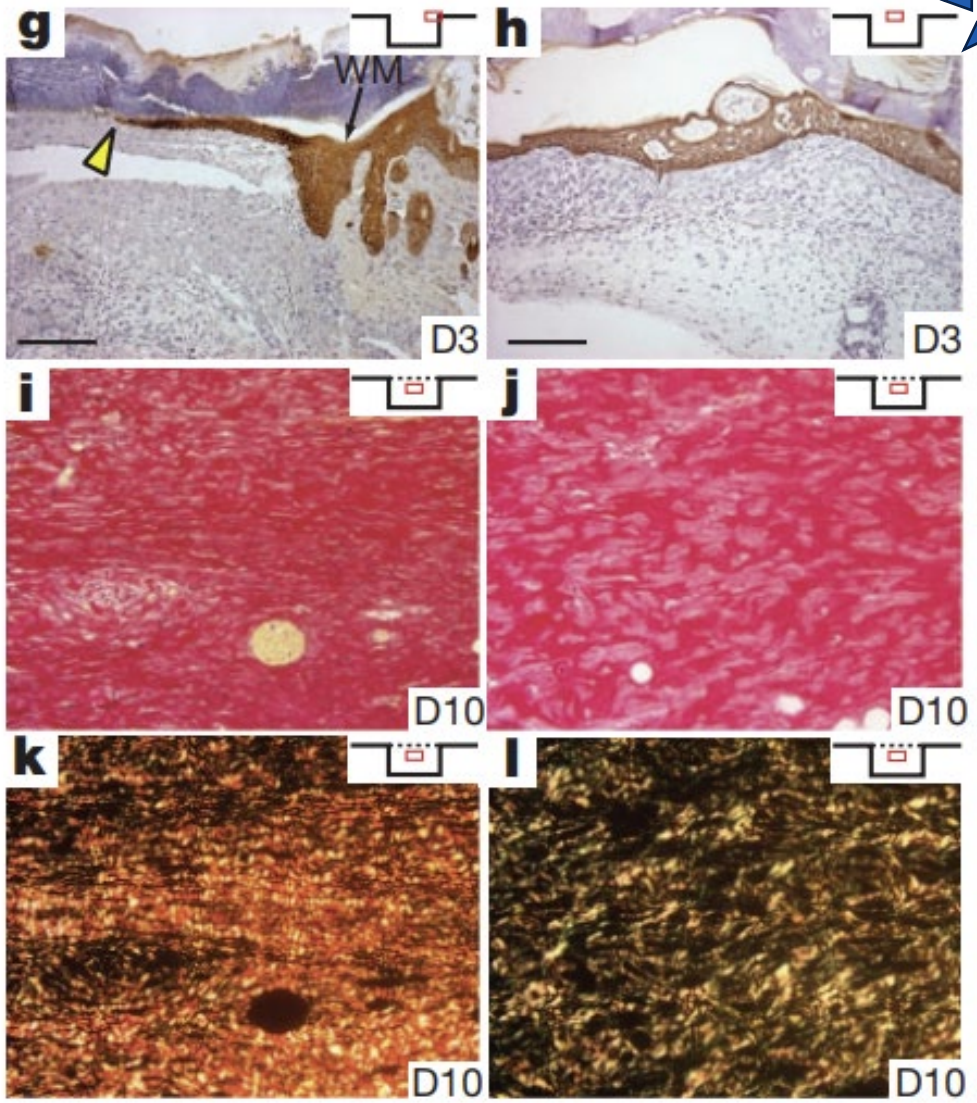


Acomys Spp.



https://doi.org/10.1038/nature11499

M. musculus **A. percivali**



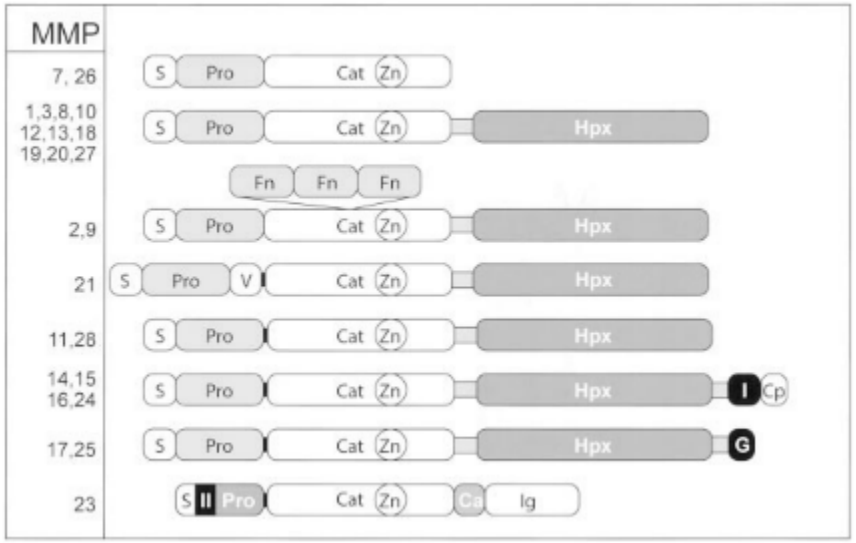
↑Scarring
Dense Collagen
↑ Collagen I

Regeneration
Less Dense
Collagen

MMP/TIMP balance (I)

Many different substrate-specific forms

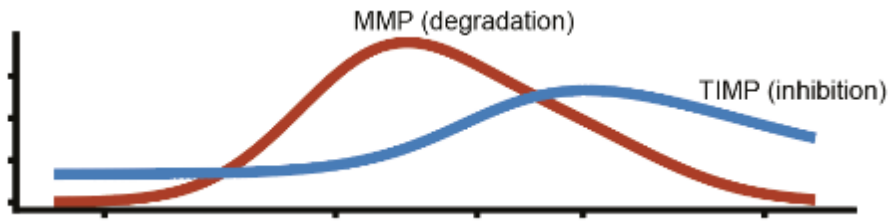
Class	Members	Key substrates
Collagenases	MMP-1, -8, -13	Fibrillar collagens I, II, III (¾ + ¼ fragments)
Gelatinases	MMP-2, -9	Denatured collagen (gelatin), collagen IV, fibronectin
Stromelysins	MMP-3, -10, -11	Proteoglycans, laminin, fibronectin, amorphous collagen
MT-MMPs	MMP-14, -15, -16, -17, -24, -25	Membrane-anchored; degrade ECM at cell surface; MT1 (MMP-14) cleaves collagen I directly
Matrilysins	MMP-7, -26	ECM components, cell surface molecules (Fas-L, TNF-α, E-cadherin) — **no Hpx domain**
Inhibitors	TIMP-1, -2, -3, -4	Inhibit all MMPs (1:1 stoichiometry, Ki in the picomolar range 10^{-12}M)



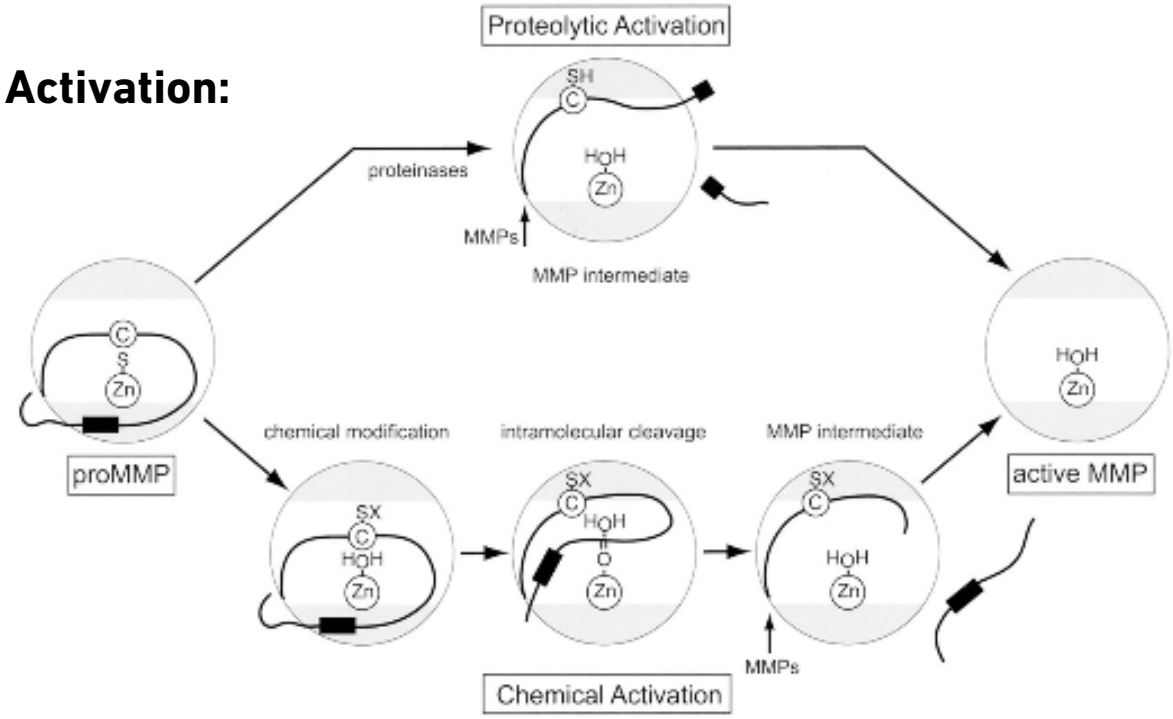
Simplified from doi: 10.1161/01.RES.0000070112.80711.3D

MMP/TIMP balance (II)

$$\text{Net Remodelling} \propto \frac{(\text{Expression} \cdot \text{Activation} \cdot \text{Localization})}{\text{Inhibition}} \cdot f(\text{Substrate})$$



Activation:



Simplified from doi: 10.1161/01.RES.0000070112.80711.3D

Are all collagenases MMPs?

Enzyme	Class	pH optimum	Key substrate	Key cell
MMP-1	MMP	7.4	Collagen I, II, III	Fibroblasts
MMP-8	MMP	7.4	Collagen I, II, III	Neutrophils
MMP-13	MMP	7.4	Collagen II > I, III	Chondrocytes
MMP-14	MMP	7.4	Collagen I, II, III	Fibroblasts, osteoclasts
Cathepsin K	**Cysteine protease**	4.5-6	Collagen I, II	Osteoclasts only
Cathepsin L/B	**Cysteine protease**	4.5-6	Broad collagen	Macrophages, lysosomes

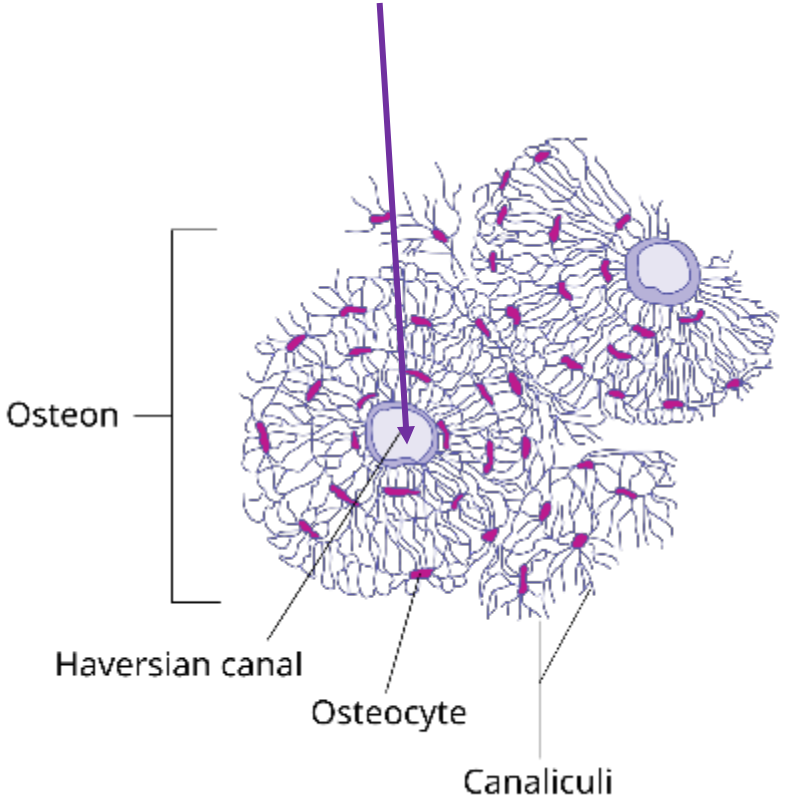
Bone remodelling

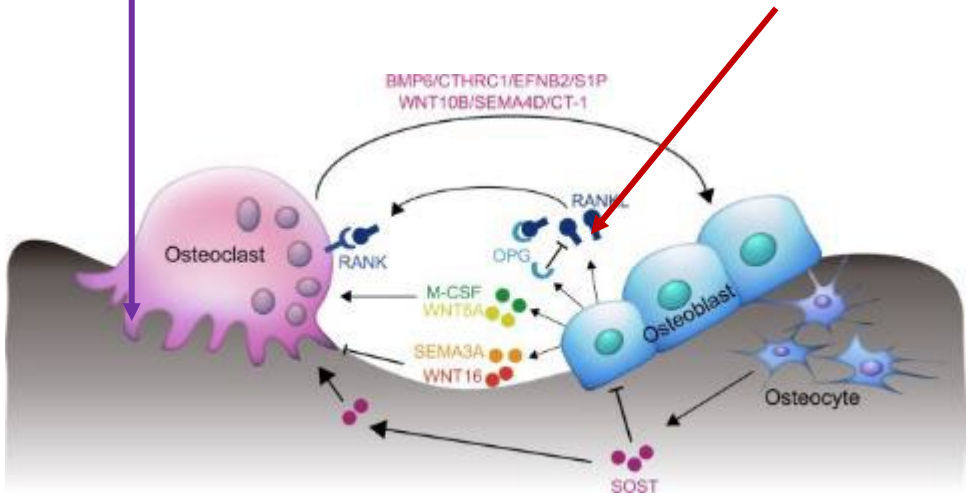
Cathepsin K — the main collagenase in osteoclasts (not an MMP), MMP-9 and MMP-14, acid phosphatase (TRAP), Hydrochloric acid

Fracture



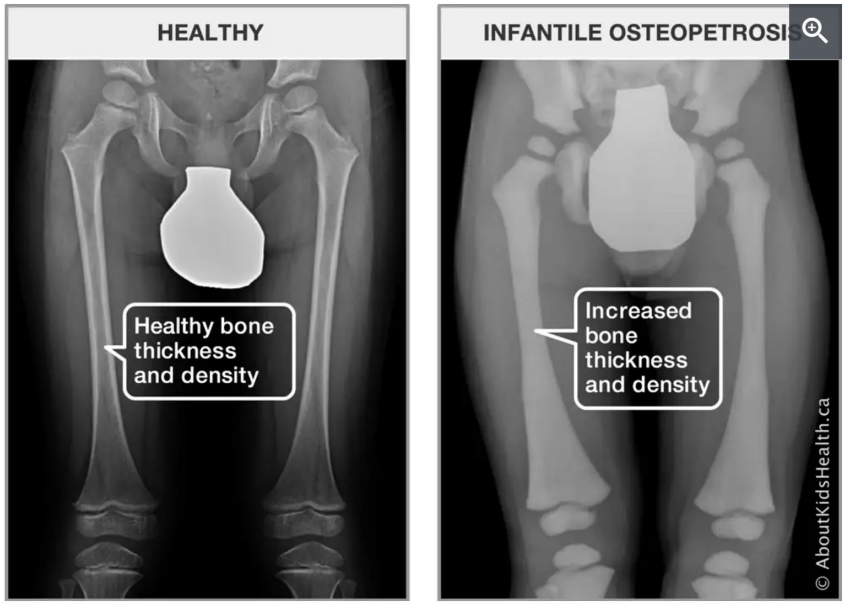
Haversian channels





https://www.nature.com/articles/s41413-018-0019-6

Osteopetrosis – Link to Immunology III





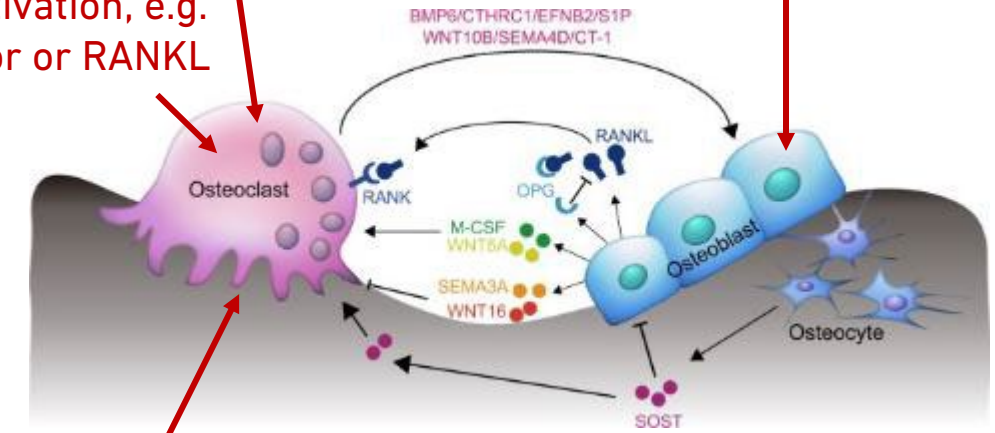
«At the Moulin Rouge» **Toulouse-Lautrec**

CSF1/CSF1R mutations, i.e. no osteoclasts

Infantile, Severe!!

Osteoblast gain of function: e.g. OPG gain of function mutation

Loss of function osteoclast activation, e.g. RANK receptor or RANKL

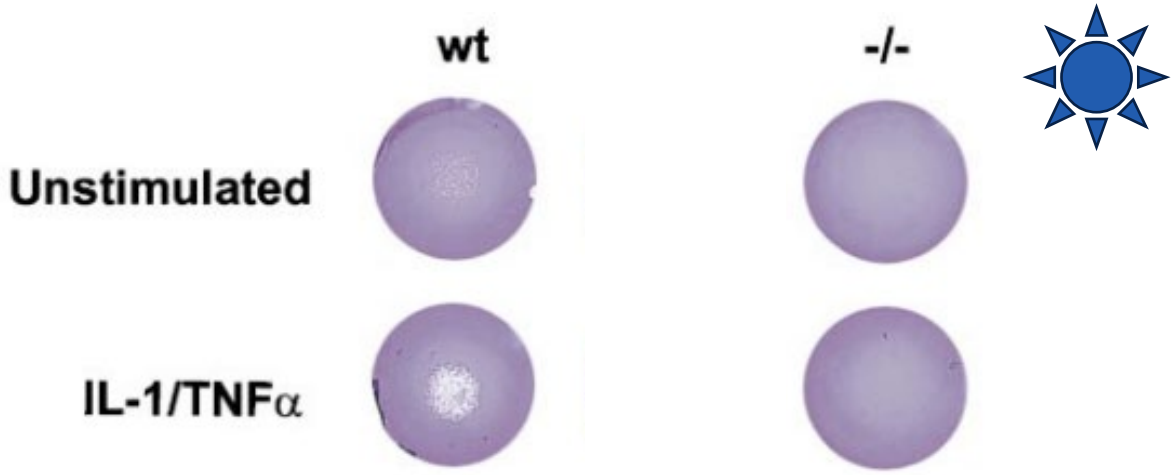


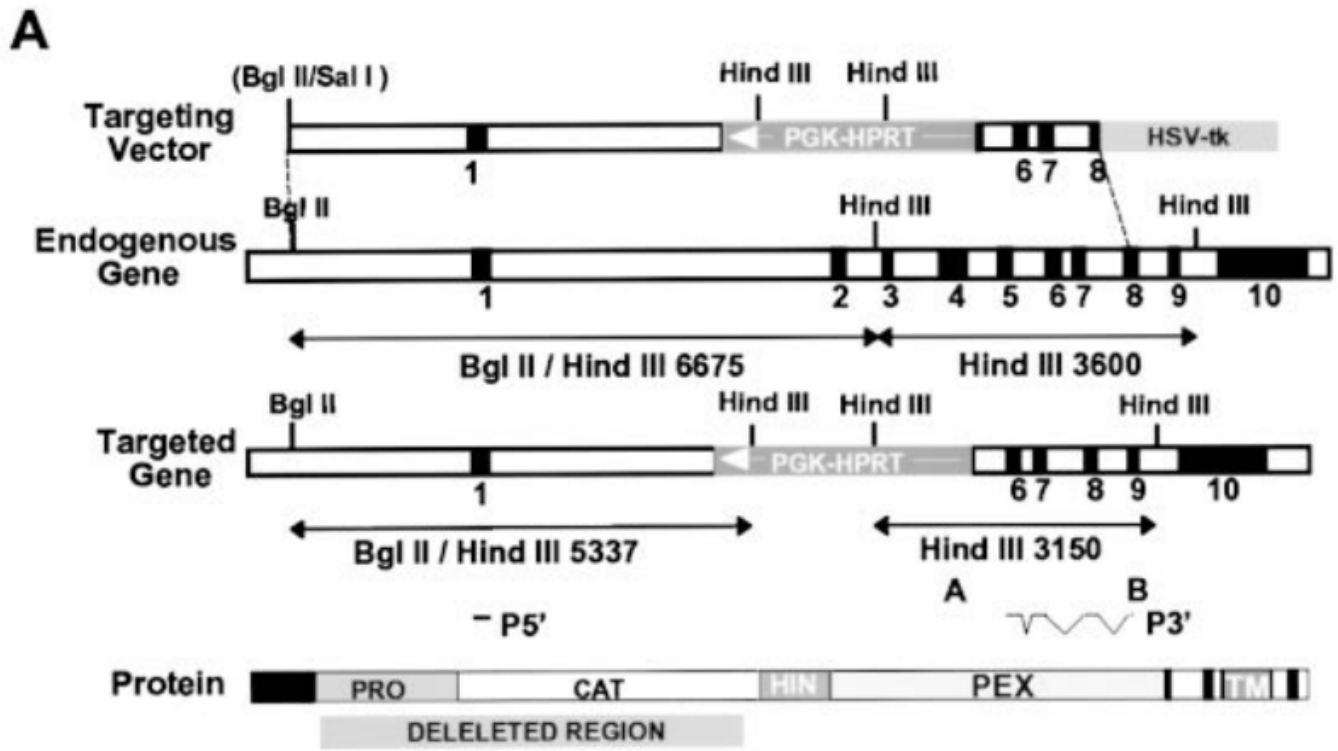
https://www.nature.com/articles/s41413-018-0019-6

Loss of function resorption, e.g.:

- ***CTSK* Cathepsin K (Pycnodysostosis, much milder!)**
- *CLCN7* chloride channel (severe!)

Osteopenia in MT1-MMP (MMP14) KO

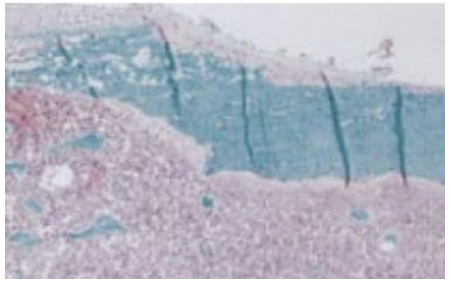


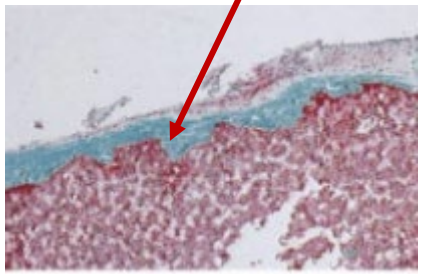






Osteopenia and Fibrosis

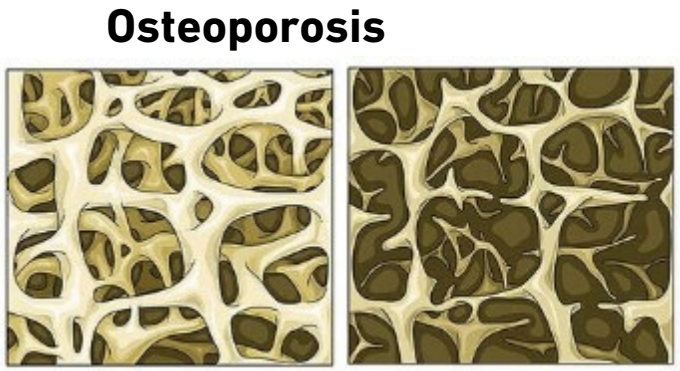


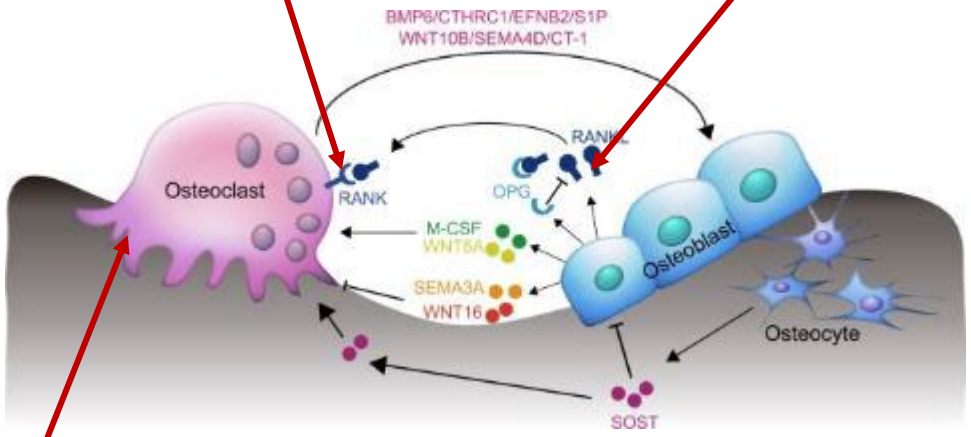


Osteoporosis

Selective estrogen receptor modulators/hormone therapy: normalize RANKL/OPG ratio

RANKL-Antibody



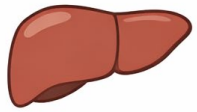


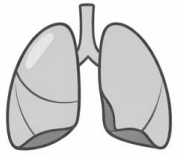
https://www.nature.com/articles/s41413-018-0019-6

Bisphosphonates (e.g. Clodronate, Alendronate): osteoclast apoptosis

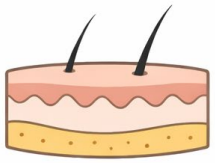
Remodelling Goal







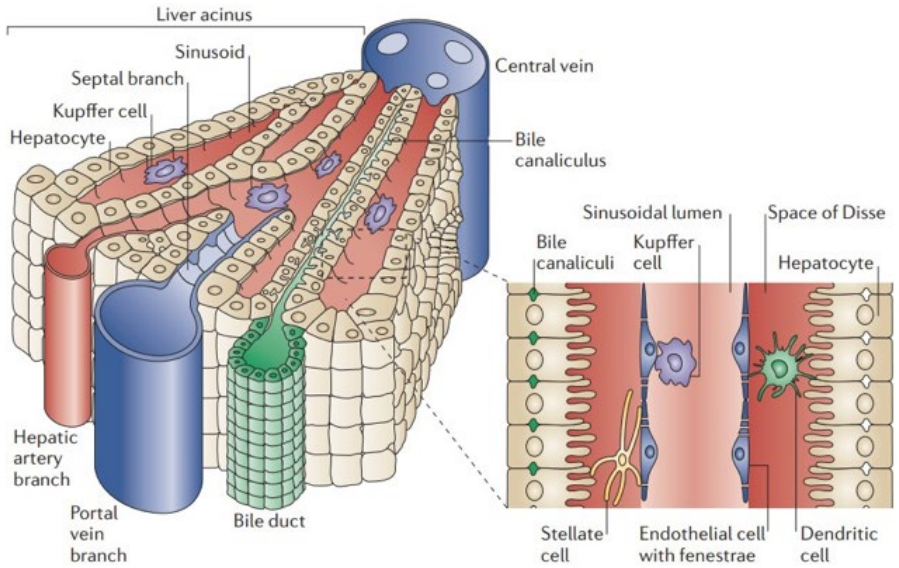




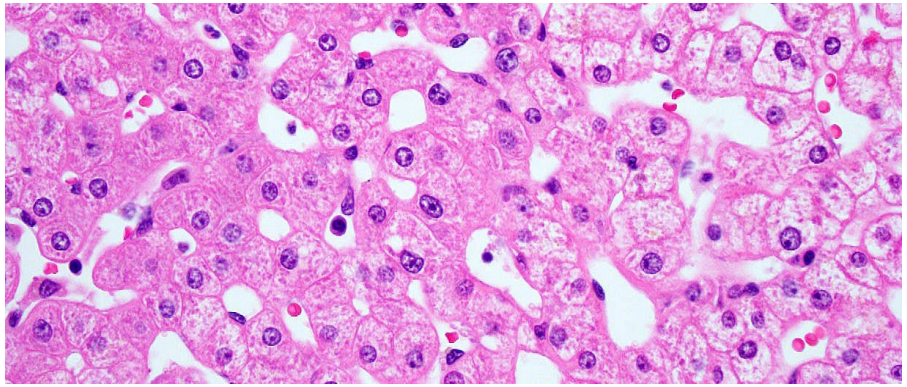
Organ	Key parenchymal function	Critical ECM architecture	Physiological scar	Failure mode
Bone	Load bearing, locomotion haematopoiesis	Haversian systems, medullary cavity, mineralized collagen I	Callus → remodelled lamellar bone, restored cortex	**Osteopetrosis (**too little resorption) / **Osteopenia** (too little organisation) — as we just saw, Osteoarthritis.
Liver	Metabolism, detoxification, immunology	Fenestrated sinusoidal endothelium, space of Disse — minimal interstitial collagen	Near zero — regeneration preferred over repair	**Cirrhosis** — bridging fibrosis, loss of sinusoidal fenestrations, pseudonodules, portal hypertension
Lung	Gas exchange (O_2/CO_2 diffusion)	Thin alveolar basement membrane (1-2 cell layers), elastic recoil	Minimal — walls must stay thin for diffusion	**Pulmonary fibrosis** — honeycombing, fibroblastic foci, stiff inelastic alveoli, diffusion block
Heart	Pump function	Aligned cardiomyocytes, minimal interstitial ECM, intact electrical pathways	Firm focal scar at infarct site — necessary, not optional	**Heart failure** after Myocardial infarction, **Diffuse interstitial fibrosis** — stiff ventricle, diastolic dysfunction, arrhythmia
Skin	Barrier, locomotion, sensation	Basket-weave collagen I + elastin, thin dermis	Thin flat pale scar, partial elastin restoration	Keloid/hypertrophic scar — thick disorganized collagen III, no elastin, contracture

Liver – Stellate cells

Sinusoids: Illustration

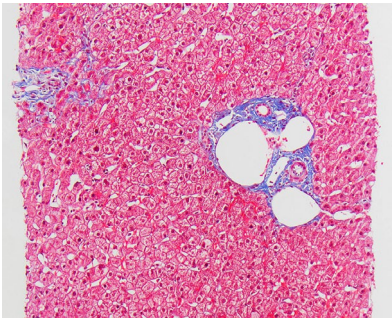


Sinusoids: H&E healthy



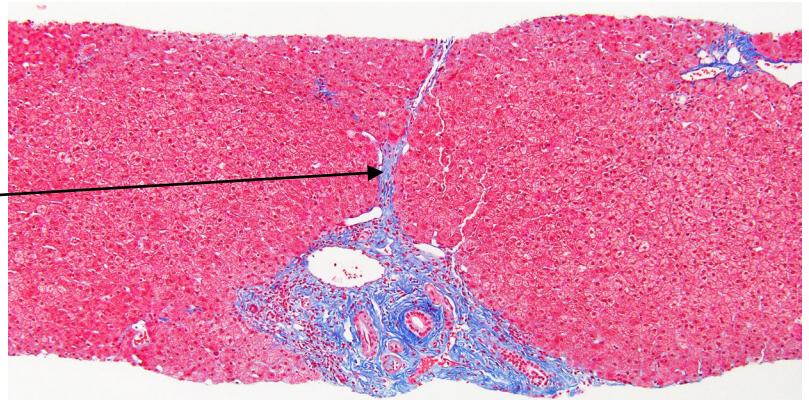
Masson Trichrome Staining

Healthy: collagen (blue) in portal tract

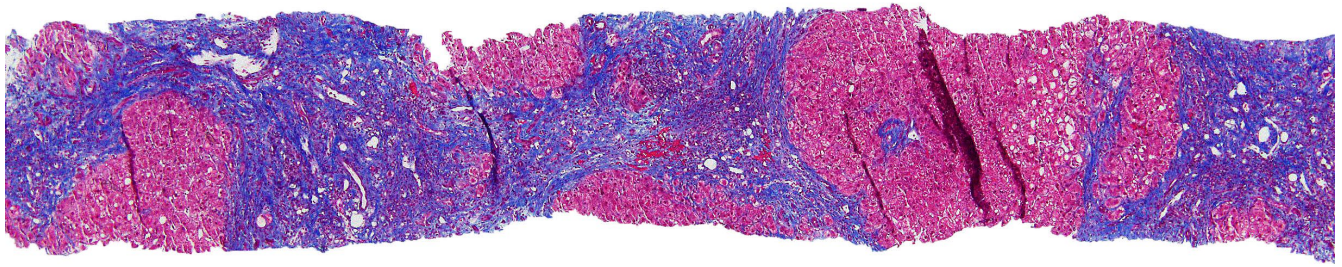


Stage 1 Fibrosis: fibrous portal expansion

Stage 3-4 increasing fibrotic bridges here



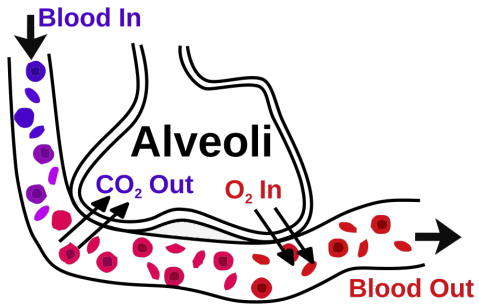
Stage 4 Fibrosis: cirrhosis, regenerative nodules surrounded by fibrous bands



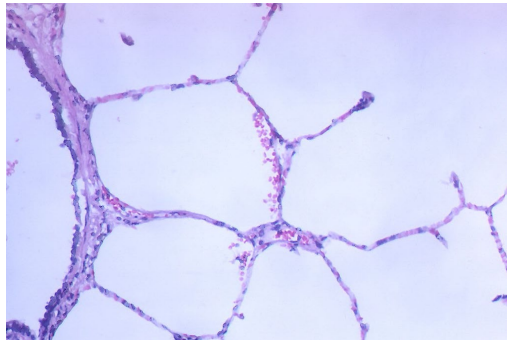
Lung remodelling

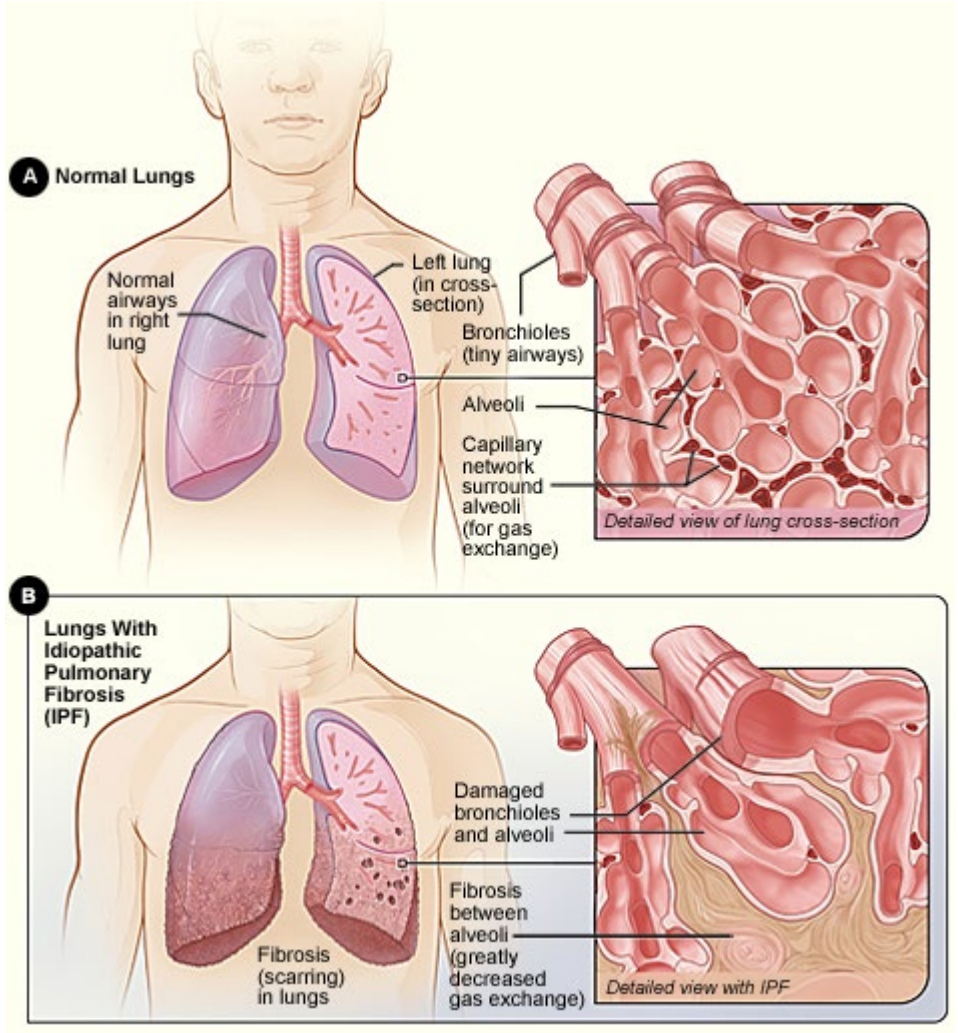
Failure Mode: Idiopathic Pulmonary Fibrosis

Alveolus: Illustration

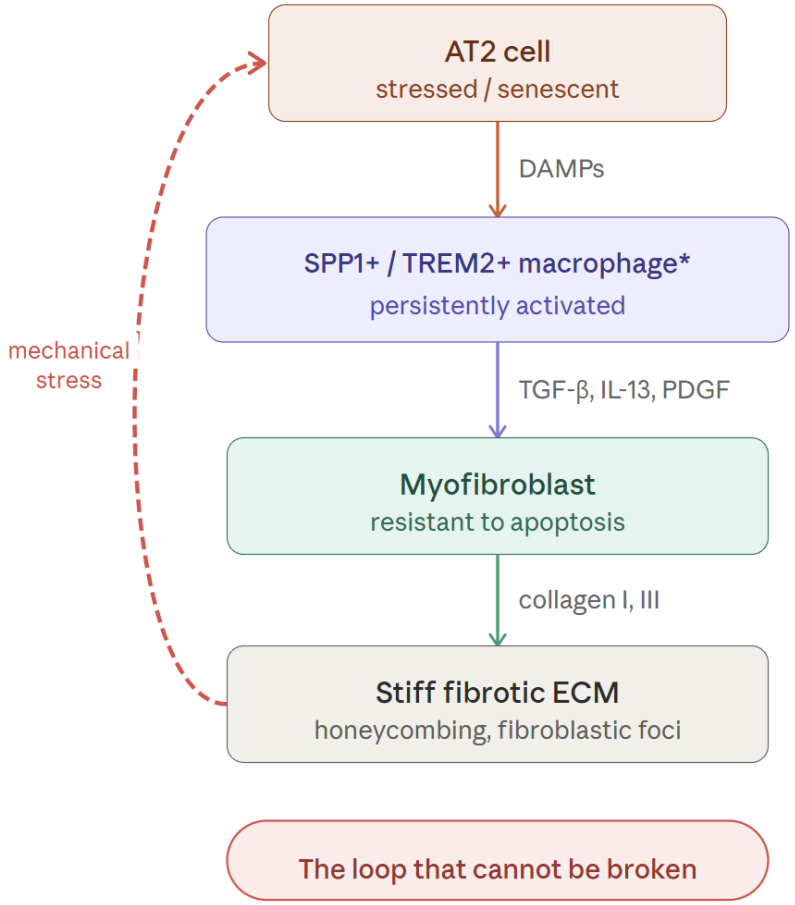


Alveoli: H&E healthy



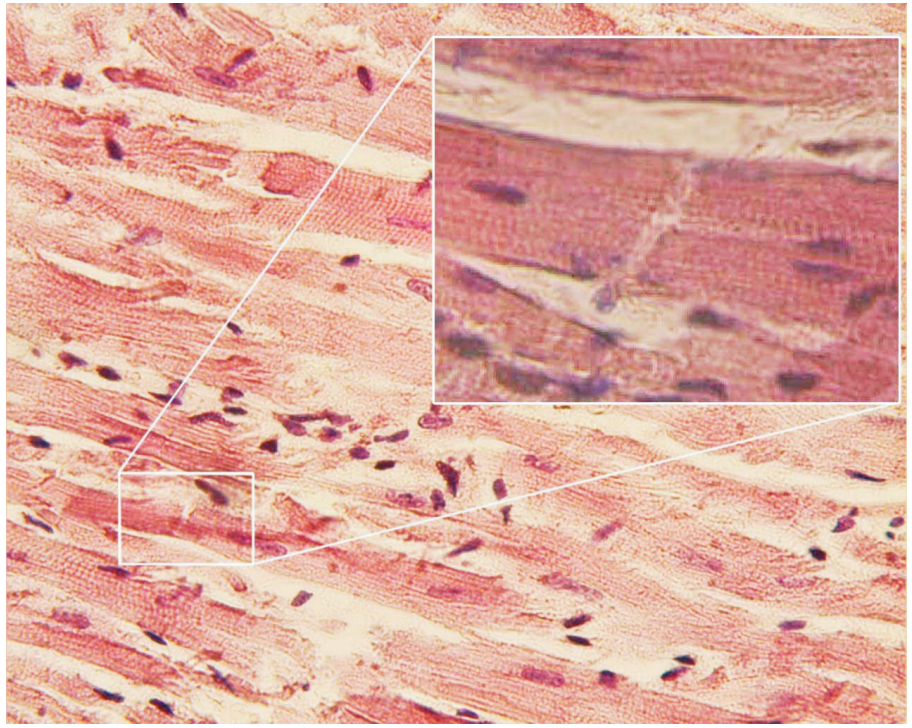


Macrophage Fibroblast Circuit

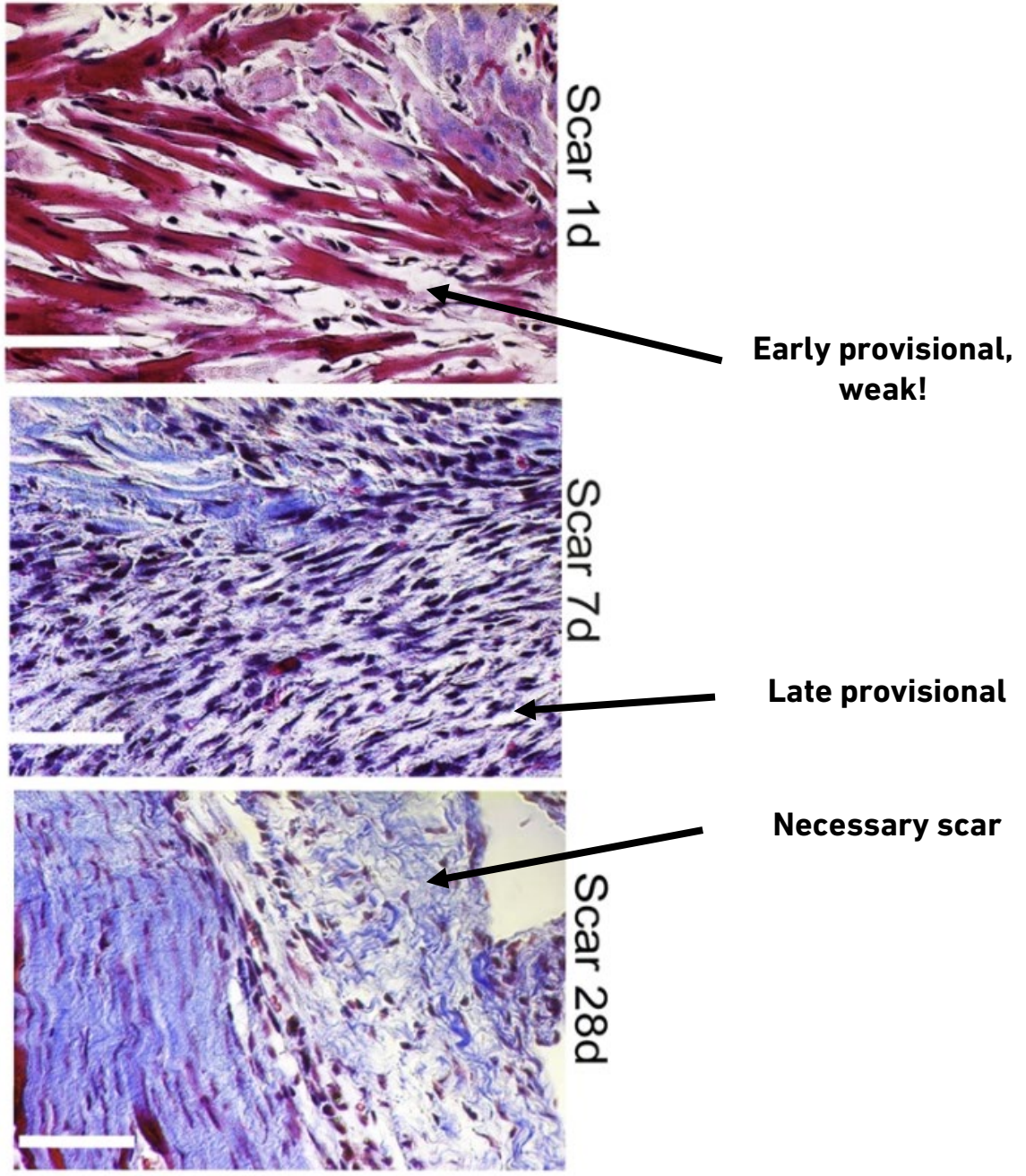


Heart remodelling

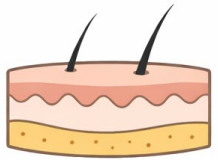
Healthy heart muscle



https://en.wikipedia.org



https://doi.org/10.1038/s41598-019-53351-7



Skin



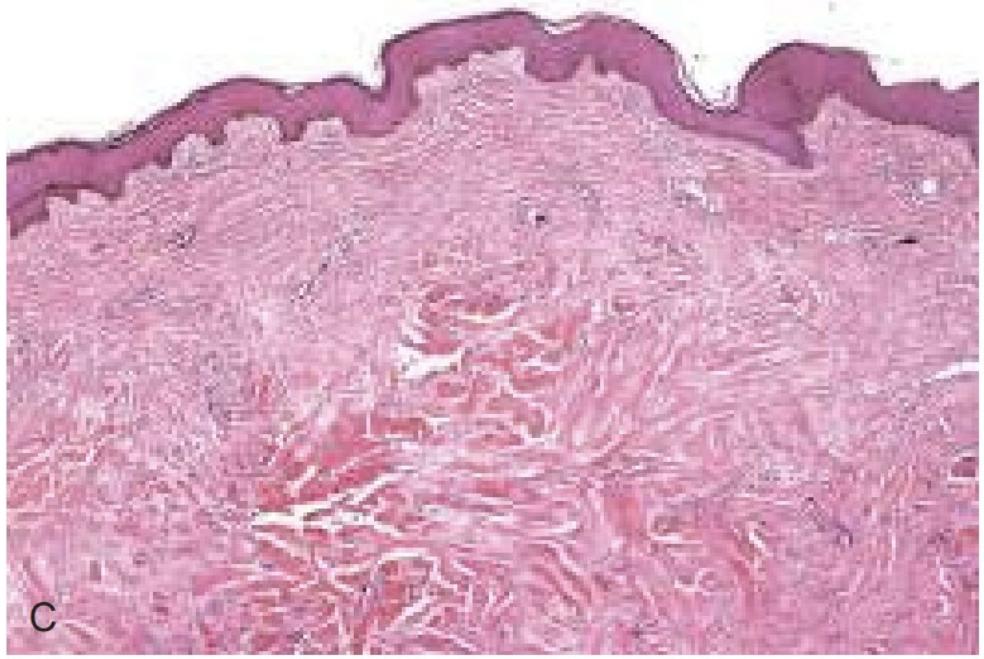


Fig. 3.28 Clinical examples of excessive scarring and collagen deposition. (A) Hypertrophic scar. (B) Keloid. (C) Microscopic appearance of a keloid. Note the thick connective tissue deposition in the dermis. *(A–B from Eming SA, Margin P, Tomic-Canic M: Wound repair and regeneration: mechanisms, signaling, and translation,* Sci Transl Med *6:265, 2014, p. 2.)*

Learning Objectives — Lecture 4: Remodelling

- Students can distinguish between **sanitatio per primam** and **per secundam intentionem** — explaining how gap size, DAMP load, and mechanical stability determine the scale of scaffold formation and remodelling required.
- Students can describe the **sequential matrix composition during remodelling** — from fibrin/fibronectin scaffold through collagen III to mature collagen I — and explain what drives each transition.
- Students can explain how **MMP/TIMP balance controls ECM degradation** — including the cysteine switch mechanism of proMMP activation and why net ECM remodelling equals expression × activation – inhibition.
- Students can apply the concept of **organ-specific remodelling goals** — articulating why the physiological scar differs between bone, liver, lung, heart and skin, and predicting the failure mode when remodelling overshoots in each tissue.
- Students can explain why **fibrosis represents a failure of myofibroblast resolution** — identifying TGF-β and persistent DAMP signalling as the common drivers across organs, and giving organ-specific examples (cirrhosis, IPF, cardiac fibrosis, keloid).

ETH zürich

Prof. Dr. Joel Zindel
Assistenzprofessor
Joel.zindel@biol.ethz.ch

ETH Zürich
Institut für Molekulare Gesundheitswissenschaften (IMHS), D-BIOL
HPL F32.2
Otto-Stern-Weg 7
8098 Zürich