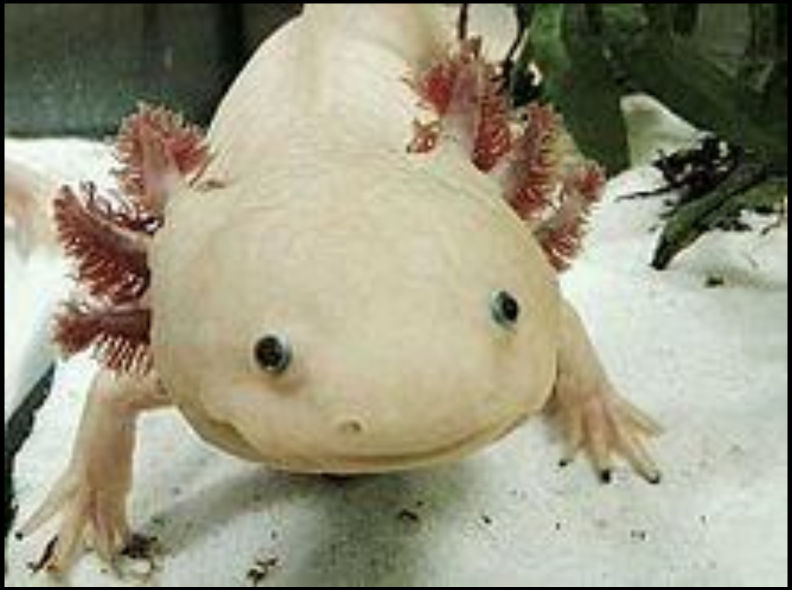
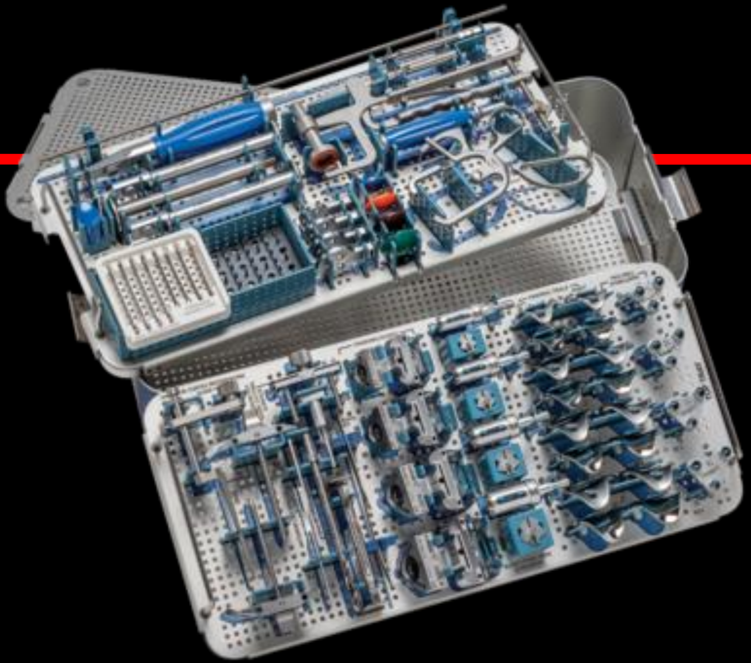
Re-growing the Skeleton:
Approaches in Tissue Engineering and Regenerative Medicine

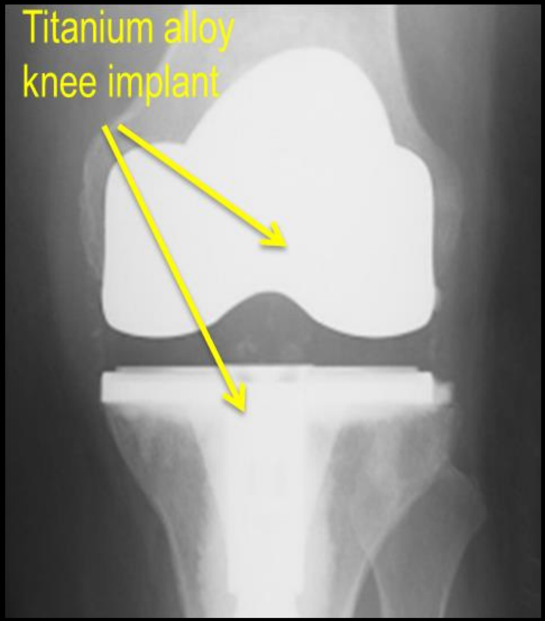
Orthopaedic Trauma Institute
UCSF + SAN FRANCISCO GENERAL HOSPITAL



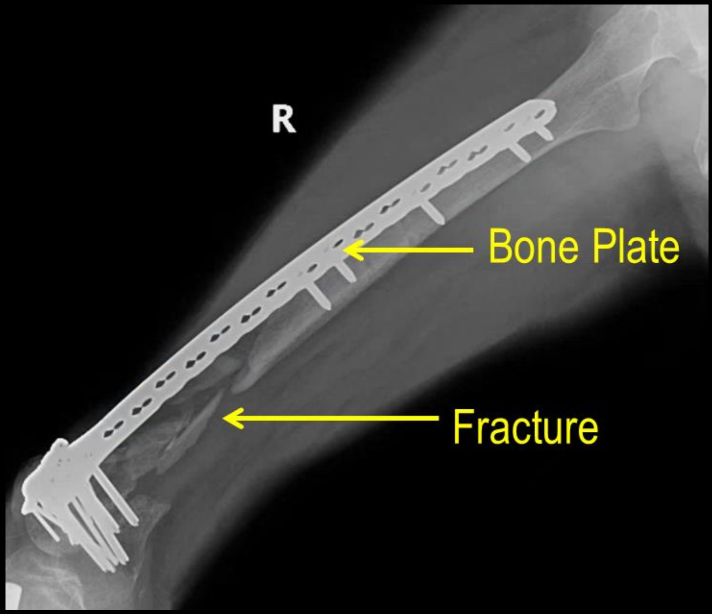
How we fix things now



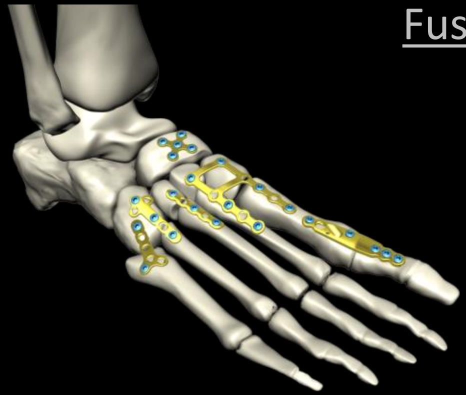
Total Knee Replacements



Fracture Plates

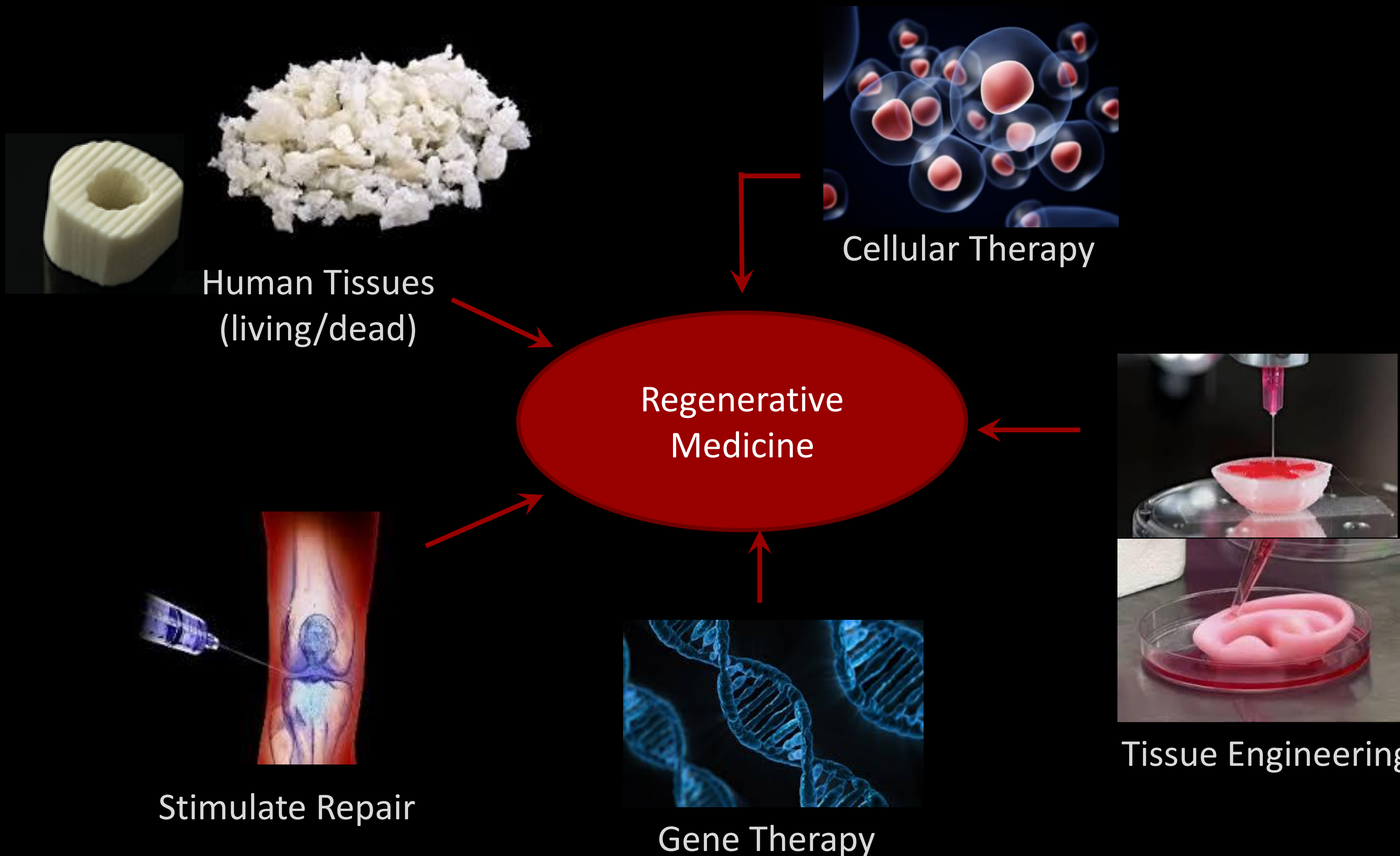


Fusing Joints



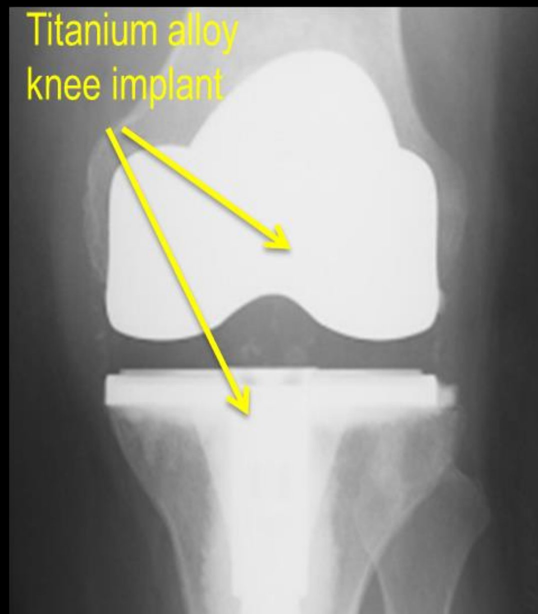
Defining Regenerative Medicine

restore form and function to damaged and diseased tissue through biological approaches



Applications of Regenerative Medicine in Cartilage Repair

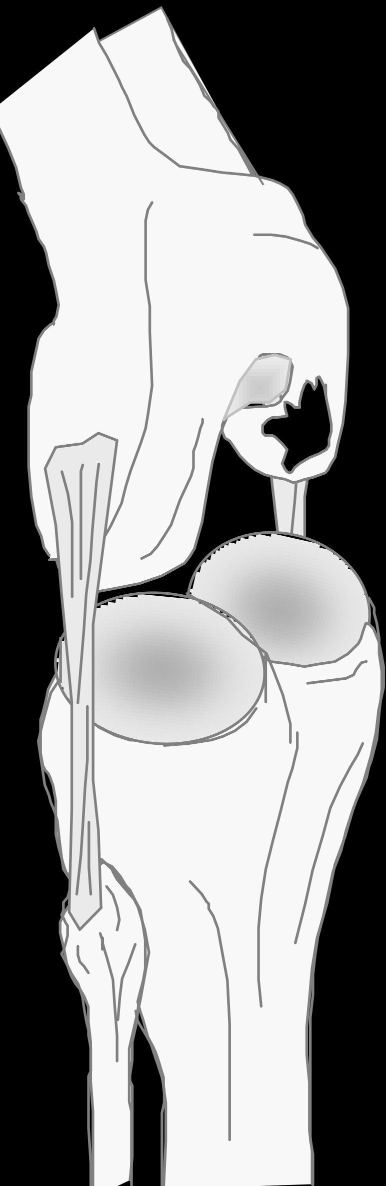
Joint Replacements



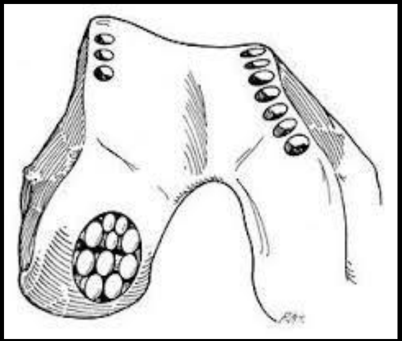
Where it all starts….

CHALLENGE: Cartilage has no innate regenerative capacity

Current Regenerative Medicine in Cartilage Repair



Transplanting Tissue



Mosaciplasty

- ✓ Improves biomechanics
- ✓ Does not activate repair

Injecting Biologics

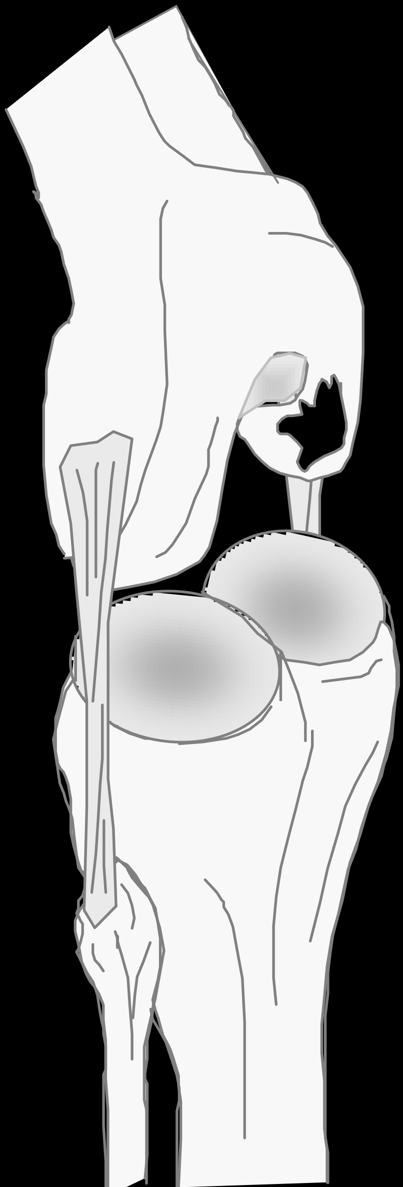
Hyaluronic Acid

- ✓ Mimics synovial fluid (lubrication)
- ✓ Temporary relief
- ✓ Does not activate repair

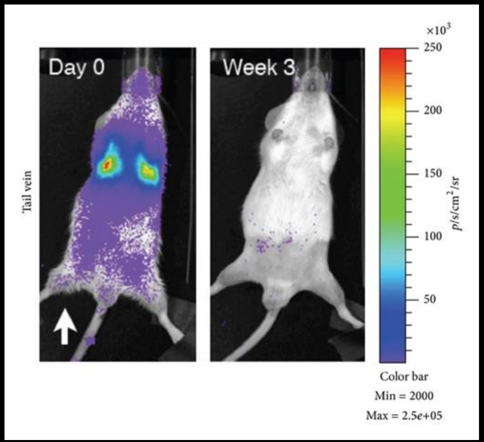
Platelet Rich Plasma (PRP)

- ✓ May stimulate repair
- ✓ Highly variable results
- ✓ Biologically not well characterized

Current Regenerative Medicine in Cartilage Repair



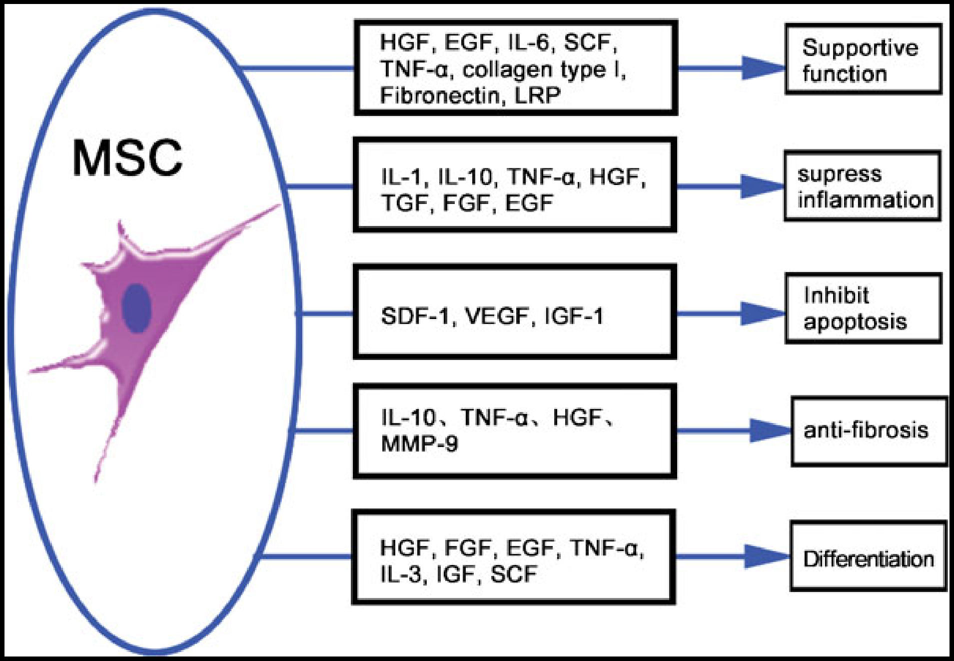
Stem Cell Injections



Interarticular injection to knees

- ✓ Minimal cell engraftment

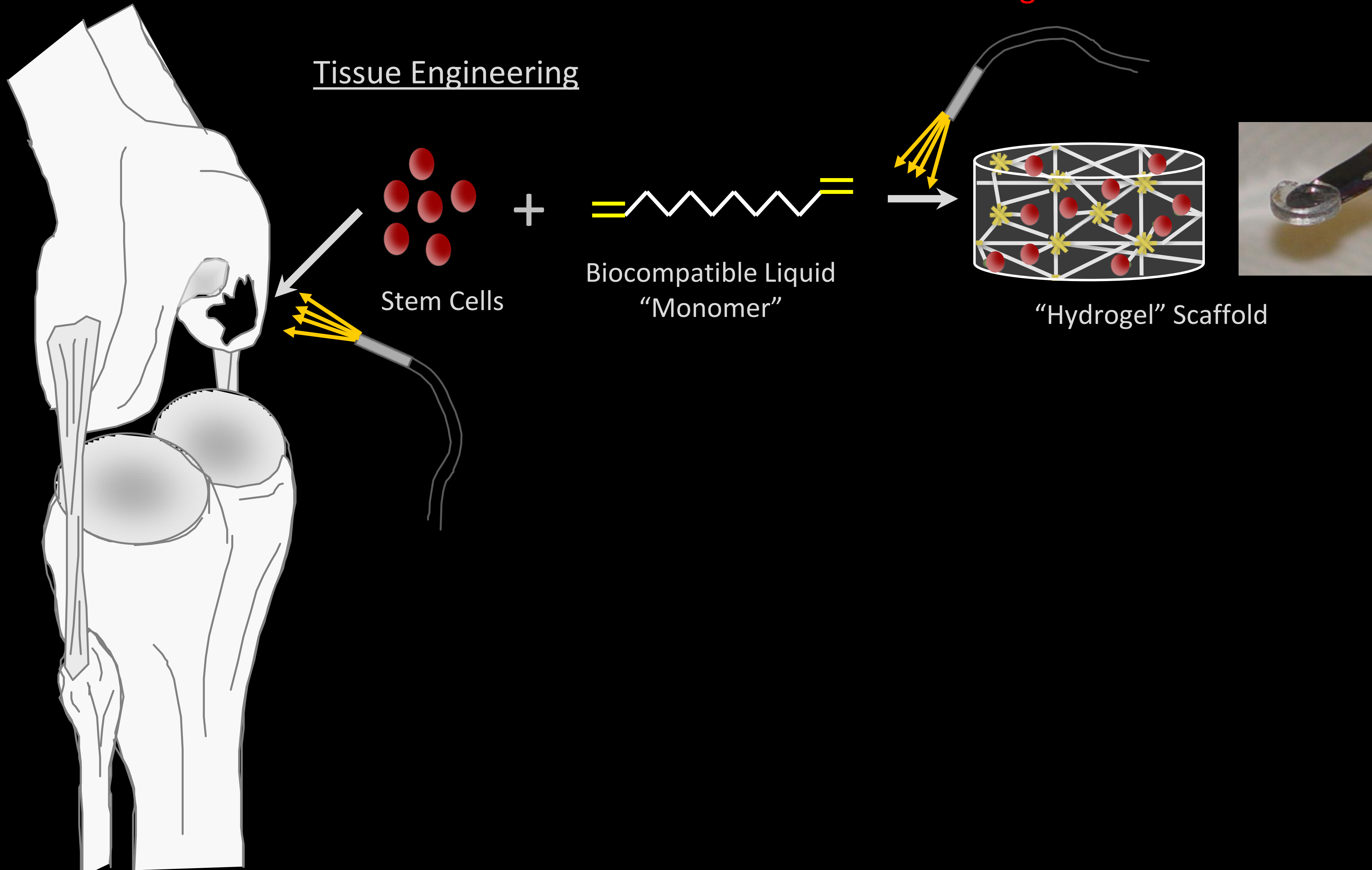
- ✓ Protects subchondral bone
- ✓ May stimulate cartilage repair
- ✓ Reduces inflammation



Lin *et al*. Cellular & Molecular Immunology 8(1):19-22 2010

Future of Regenerative Medicine in Cartilage Repair

PROBLEM: skeletal tissues have a biomechanical and biologic function



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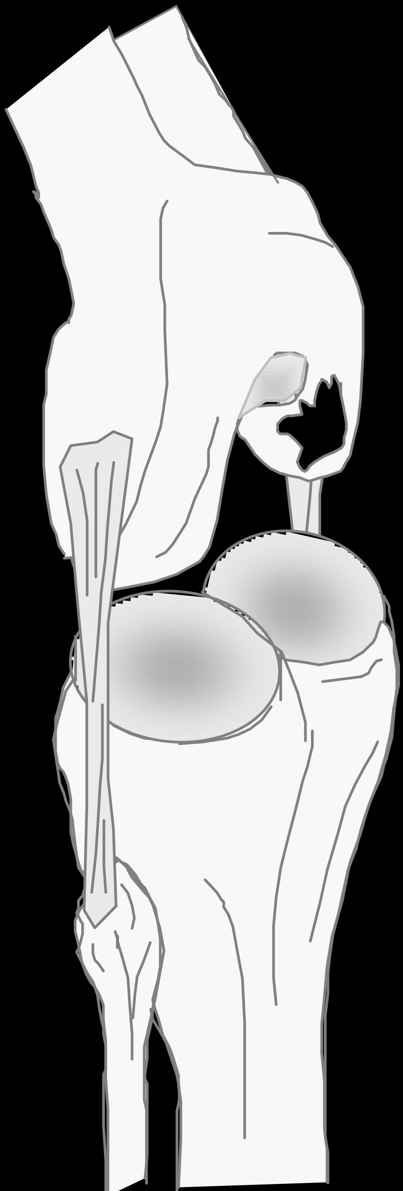


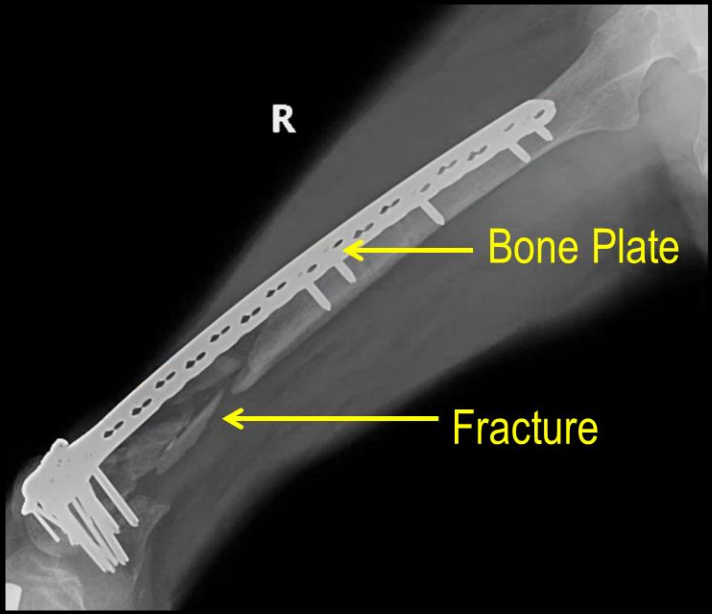
3D-Biodegradable Woven Scaffold

Molded to shape of joint, seeded with stem cells taken from fat

https://source.wustl.edu/2016/07/stem-cells-engineered-grow-cartilage-fight-inflammation/

Applications of Regenerative Medicine in Bone Repair

Fracture Plates



Magnitude of the problem

15 million fractures ($45B)
1.6 million trauma patients
1.6 million bone graft procedures

- 10-20% of normal fractures don't heal
- 47% of fractures with co-morbidities don't heal

ADVANTAGE: Bone has good innate regenerative capacity

CHALLENGE: Bone is a complex tissue (bone, vasculature, nerves, marrow space)

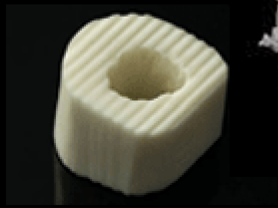
Current Regenerative Medicine in Bone Repair

Gold Standard = Autograft

- ✓ Limited ability to accelerate remodeling of bone
- ✓ Limited availability of material for large bone defects
- ✓ Donor site morbidity (20-40 % pain or complication)
- ✓ Difficulty of repeated procedures

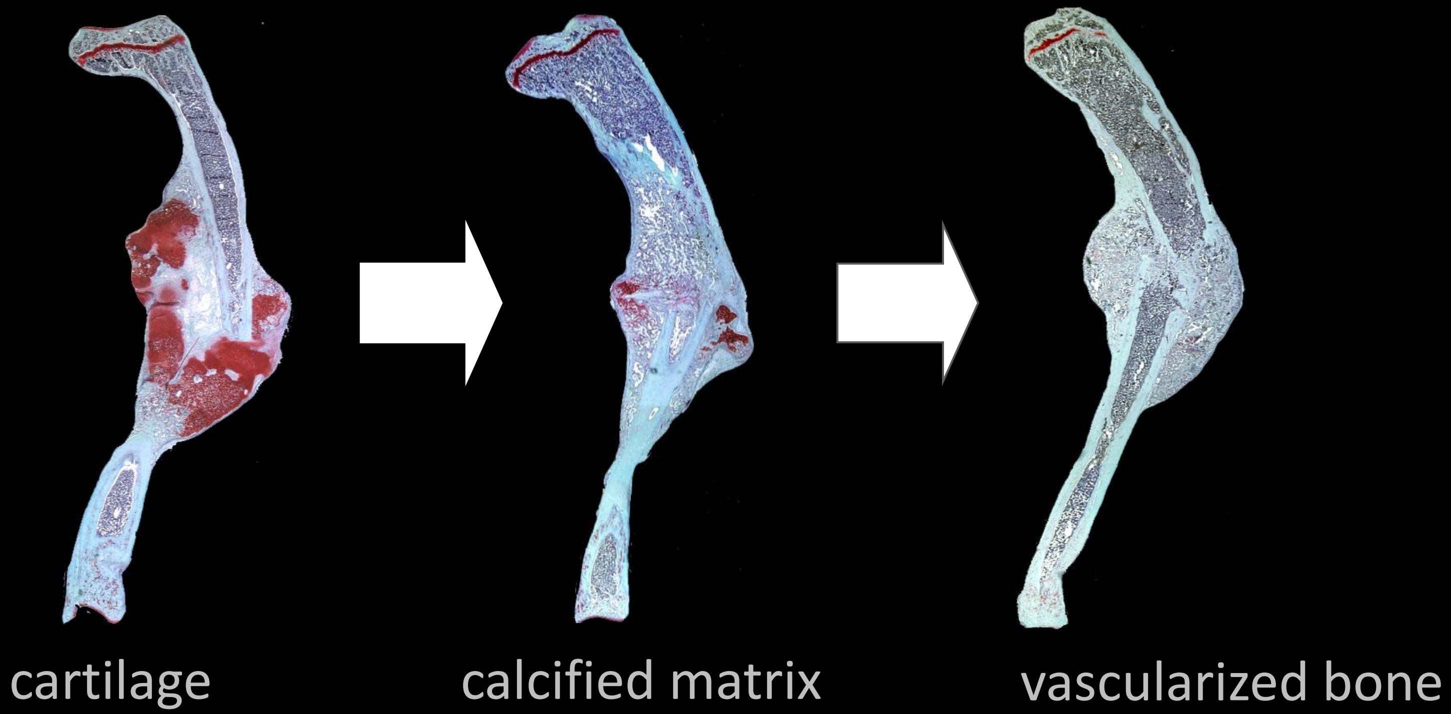
Alternatives = Allograft (Dead Bone)

- ✓ Synthetic materials – difficult to attach soft tissues
- ✓ Loss of bone and tissue near graft
- ✓ Poor graft vascularization → osteonecrosis
- ✓ Poor integration
- ✓ Allograft failure due to resorption and fracture



Future of Regenerative Medicine in Bone Repair

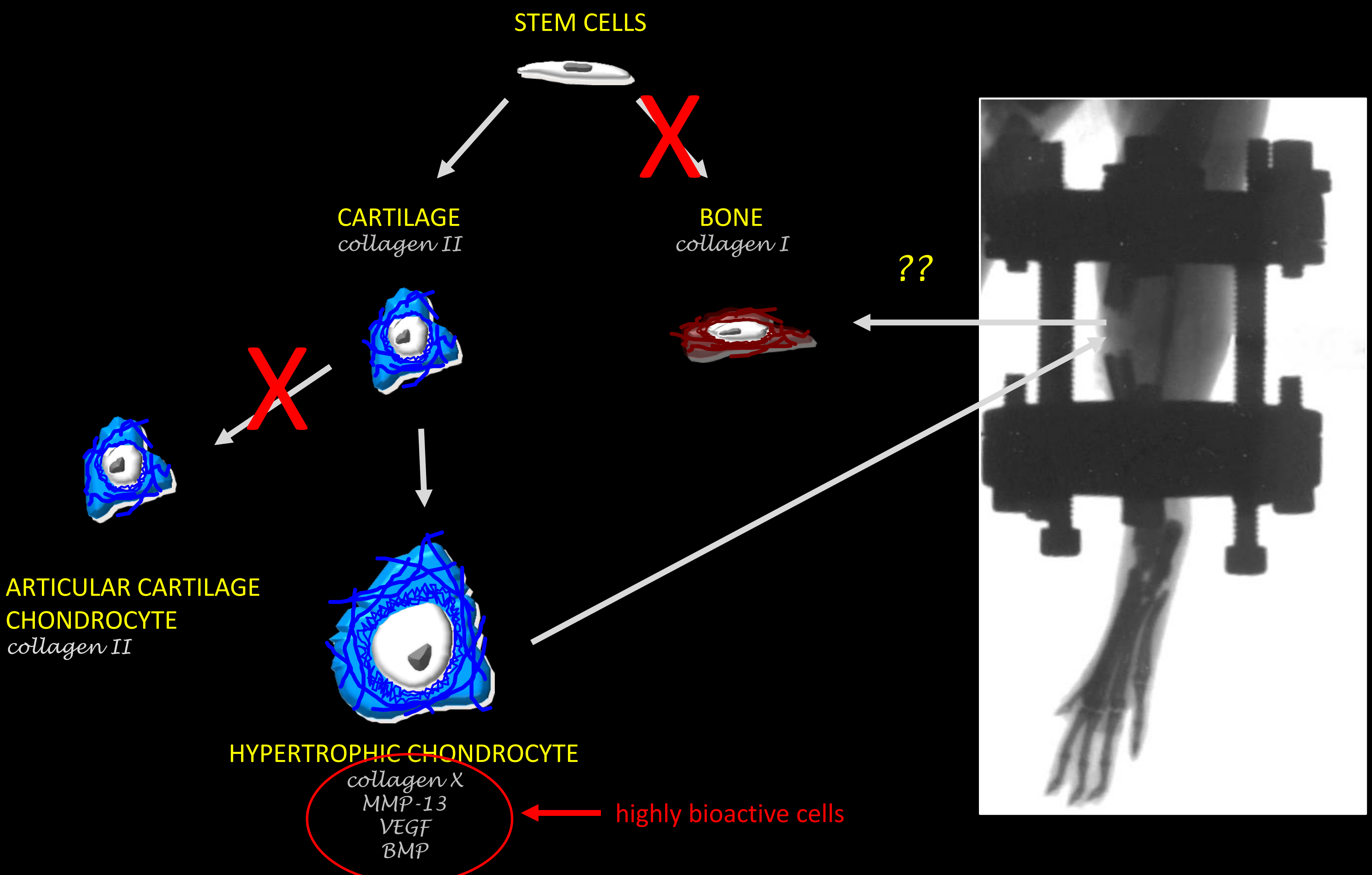
PROBLEM: Current technologies promote bone repair/regeneration through direct bone formation (intramembranous ossification), yet development and repair proceed through cartilage intermediate (endochondral ossification).



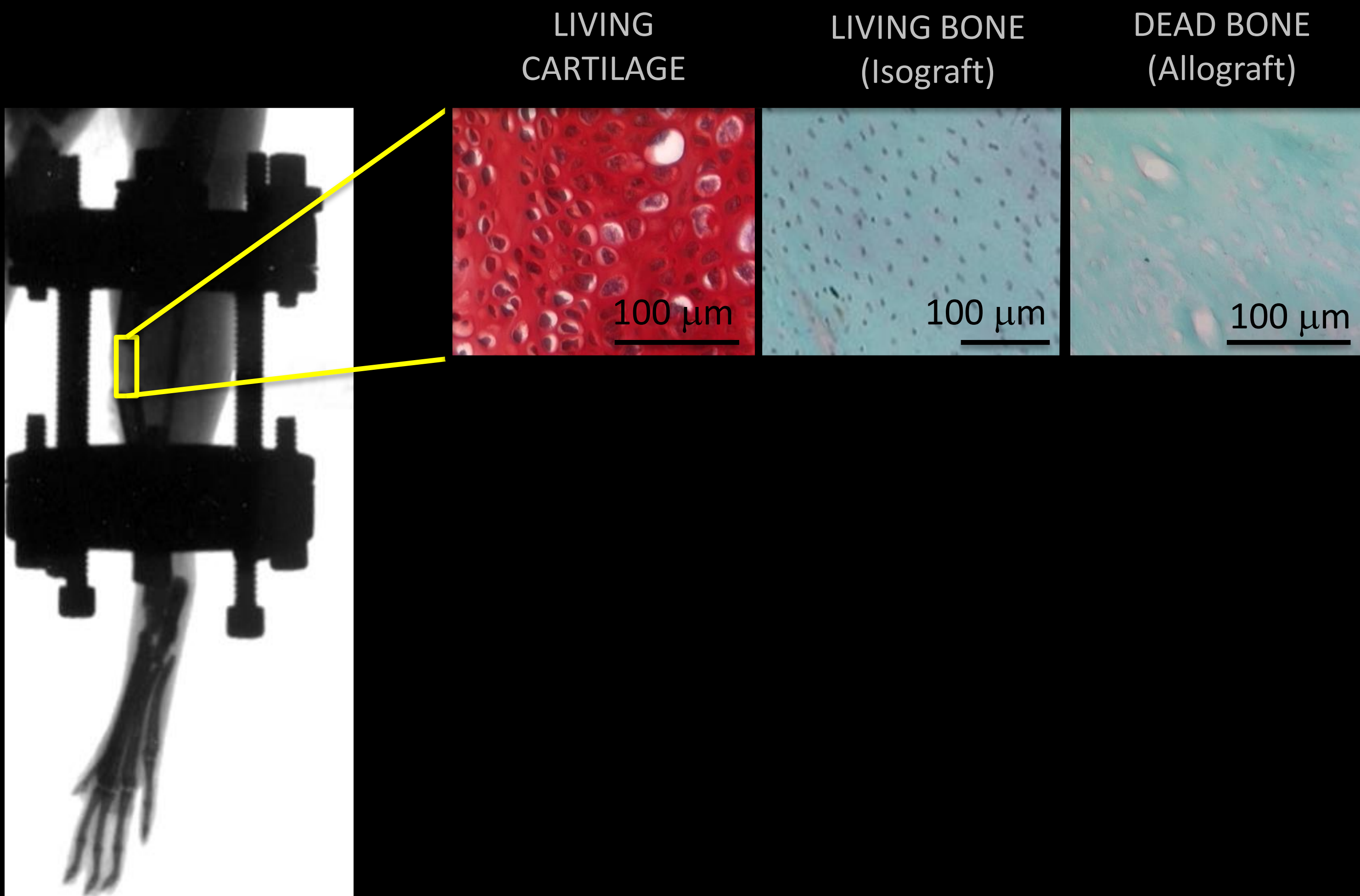
Developmental Engineering

Engineer a system that attempts that models tissue developmental or repair

Indirect bone formation as a better regeneration strategy?

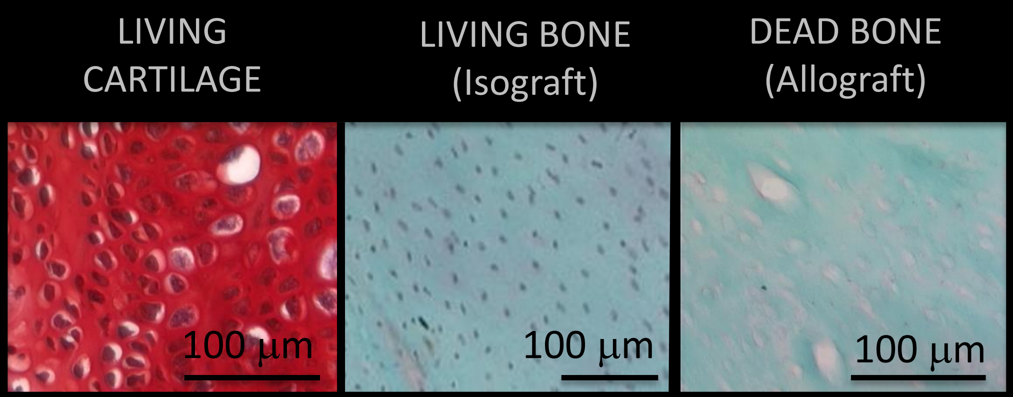


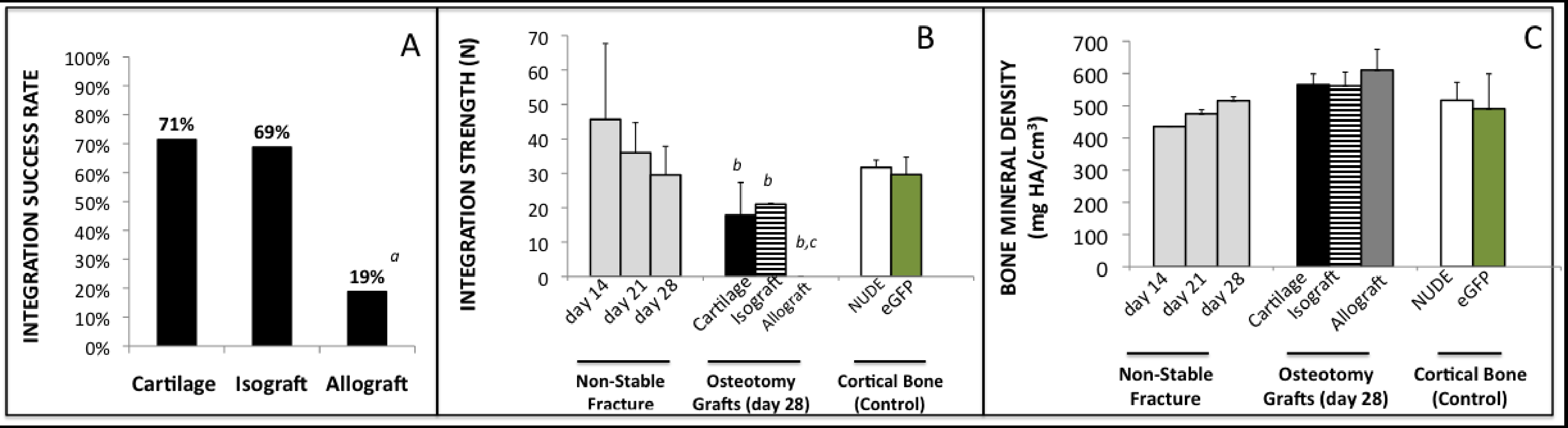
Cartilage Graft Produces Integrated Bone



Bahney *et al*. Stem cell-derived endochondral cartilage stimulates bone healing by tissue transformation. JBMR 2014

Cartilage Graft Produces Integrated Bone





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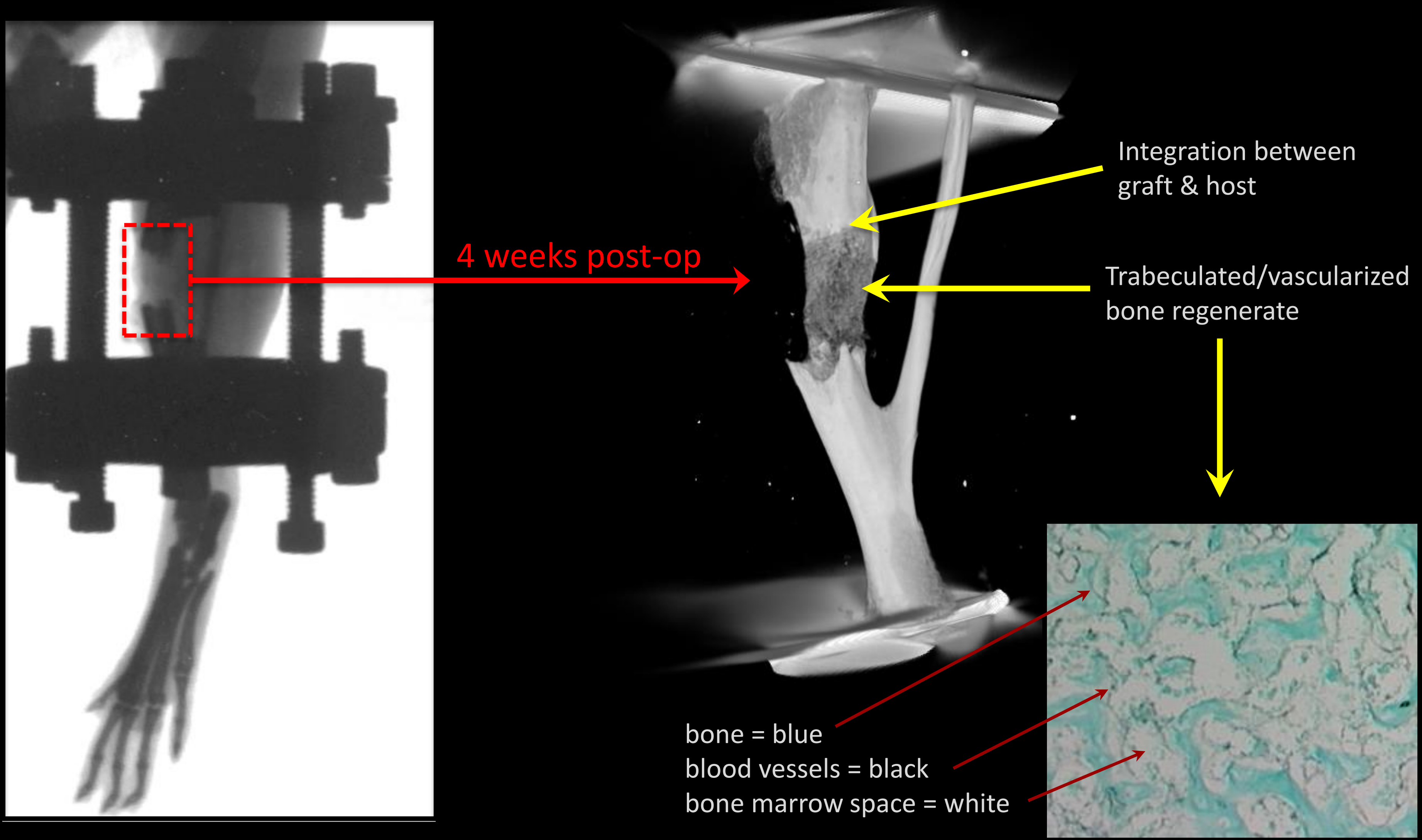
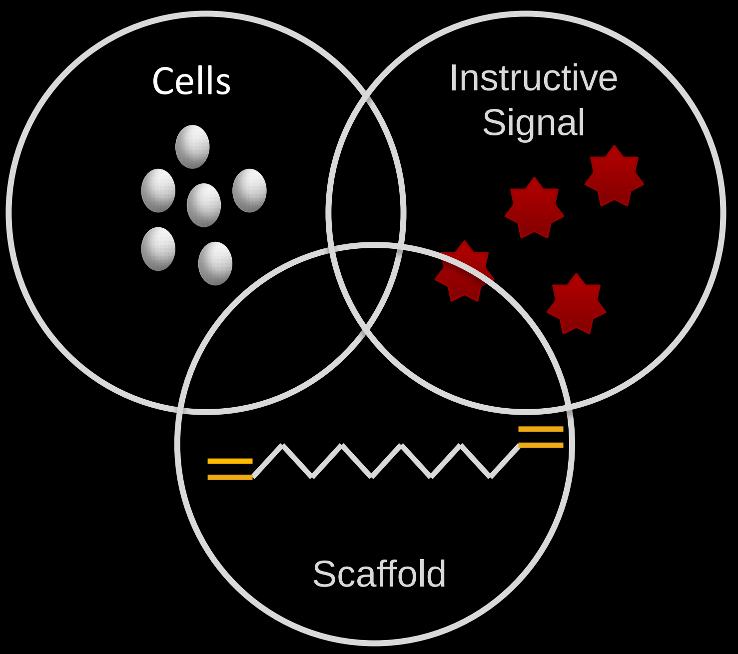
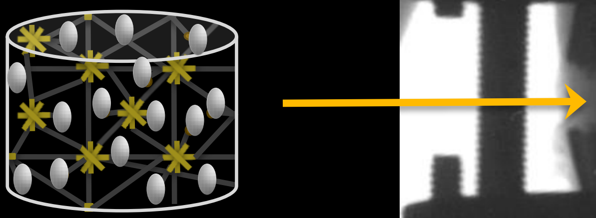
Cartilage graft heals the bone defect

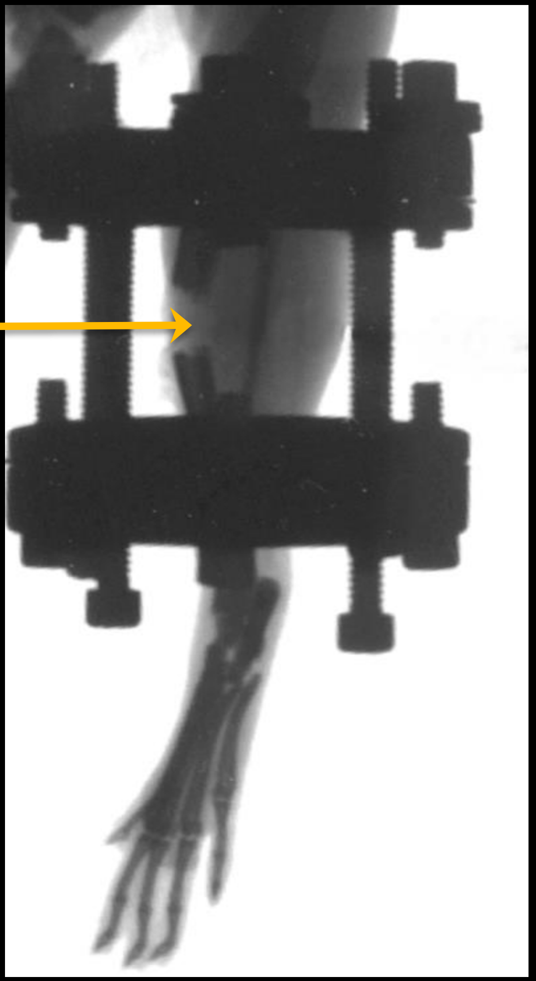


Tissue Engineering Endochondral Bone Regeneration

Tissue Engineering Strategy







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Components in Tissue Engineering

Repair damaged or diseased tissue with a regenerate that has metabolic and mechanical function of native tissue.

1. Three dimensional scaffold → housing
2. Bioactive factors → trigger healing
3. Cells → replace tissue

Unanswered questions in Tissue Engineering…

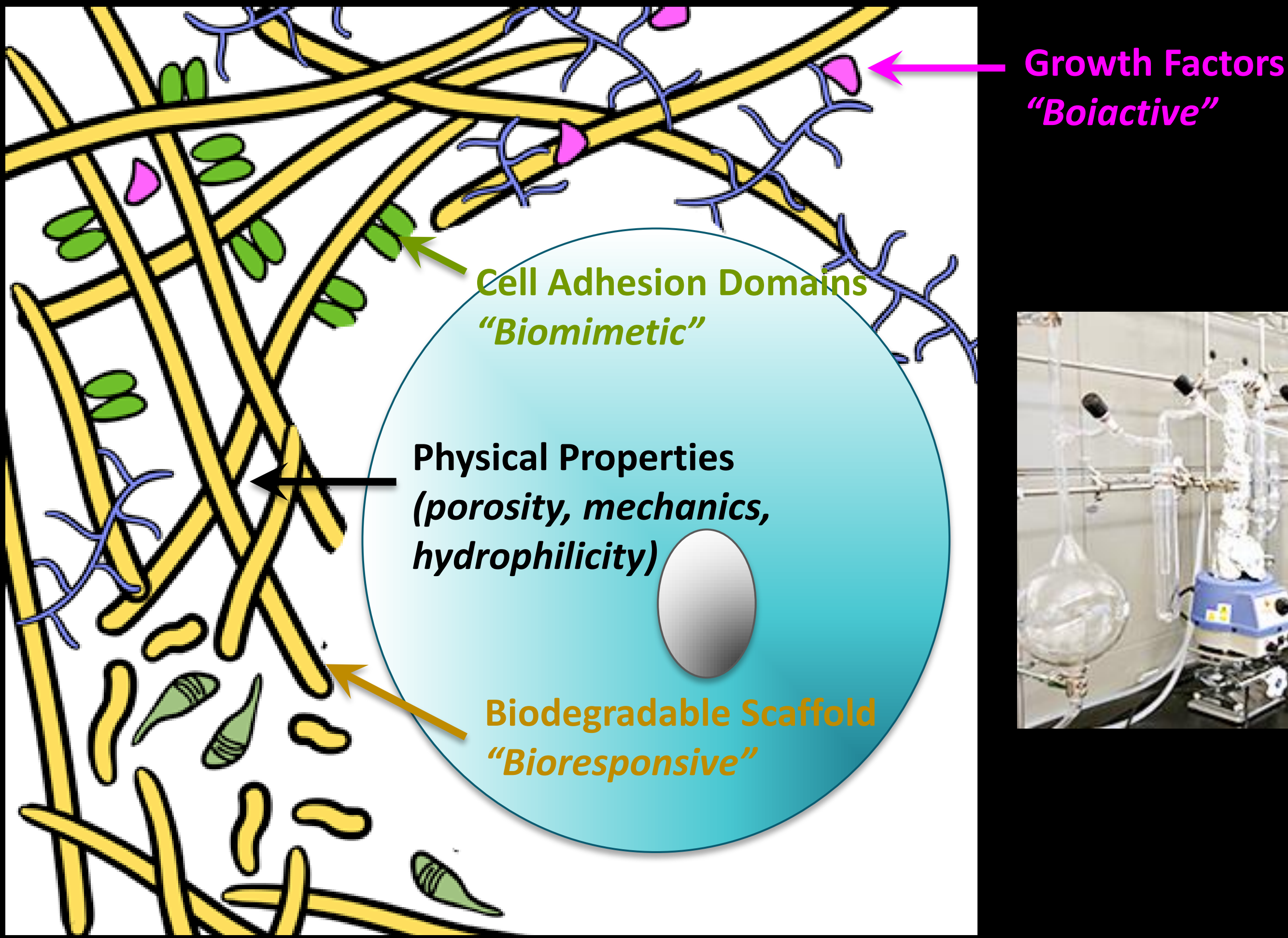
Scaffold: which material, microstructure, strength, method for synthesis??

Bioactive factors: what to deliver, how to deliver??

Cells: which cells, how to deliver??

Smart Scaffolds – The Next Generation of Tissue Engineering

Trying to re-engineer our native system with nanotechnology



Pollock, J., and Healy, K.E., "Biomimetic and Bio-responsive Materials in Regenerative Medicine: Intelligent Materials for Healing Living Tissues," In *Strategies in Regenerative Medicine, M. Santin (Ed.), Springer, 2009*

Types of Scaffolds for Tissue Engineering

	Natural	Synthetic
PROs:	✓ Biological Signal ✓ Biodegradable	✓ Easy to Control ○ Mechanical Strength ○ Degradation profile ○ Porosity
CONs:	✓ Weak Mechanical Strength ✓ Immunogenetic Response ✓ Hard to modify	✓ Inert ○ Low cell adhesion ○ Low cell response

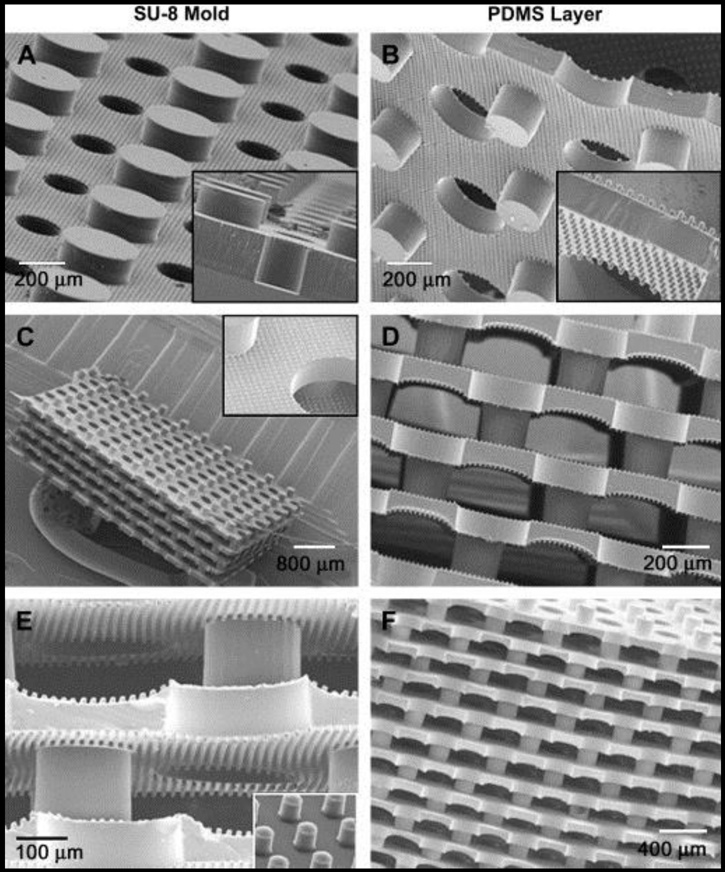
↓

Bio-synthetic Hybrid Scaffolds

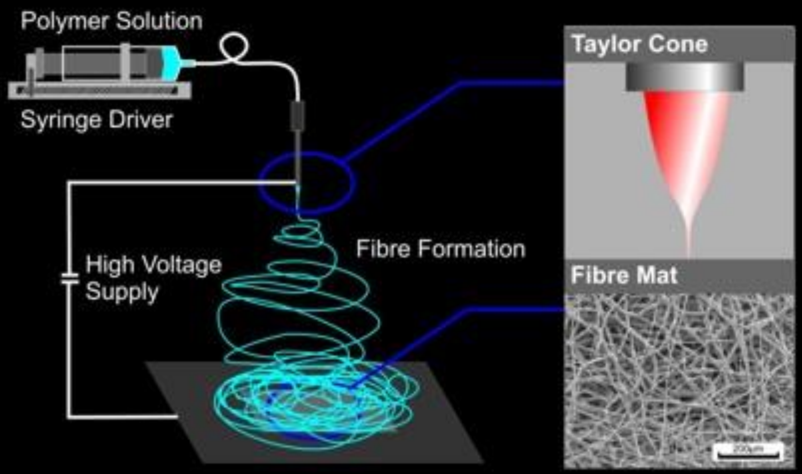
Adapted from: Hwang & Elisseeff. Controlled Differentiation of Stem Cells. (2009)

Emerging Technologies in Tissue Engineering

Photopatterning



Electrospinning



3D Bioprinting

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