Bioengineering Soft Tissue with Ceramics

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Biomaterial Challenges

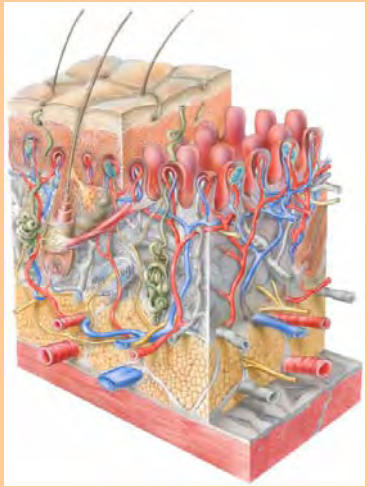
- Promoting tissue growth into “large scaffolds” for bone regeneration
- Materials that stimulate more than bone regeneration
  - Composition and microstructure, hemostasis
  - Blood vessels, nerves, skin, muscle
- Lower cost options
- Decreased or minimal scarring (internal and external)
  - physical appearance and nerve regeneration

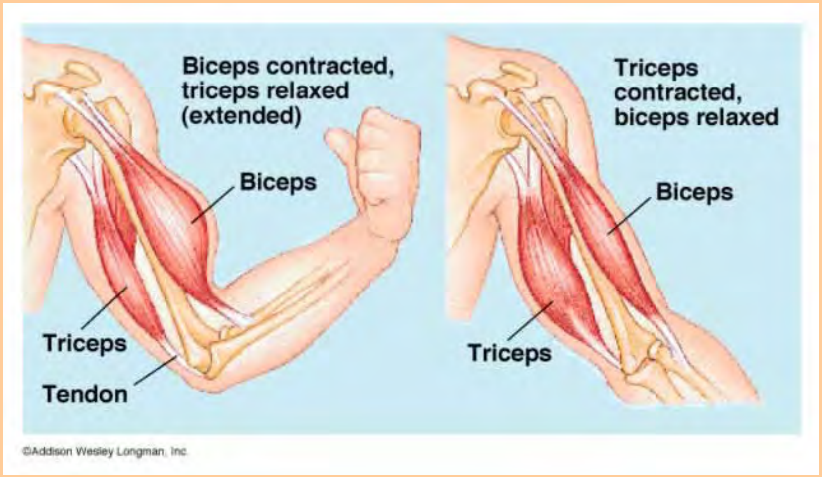
Outline

- Connective tissue and what that means to a materials engineer
- Biomaterial microstructure, what are the important parameters?
- Improving the properties in bioactive/biocompatible glasses
- New treatments and how this can change the future of medicine

Key Points

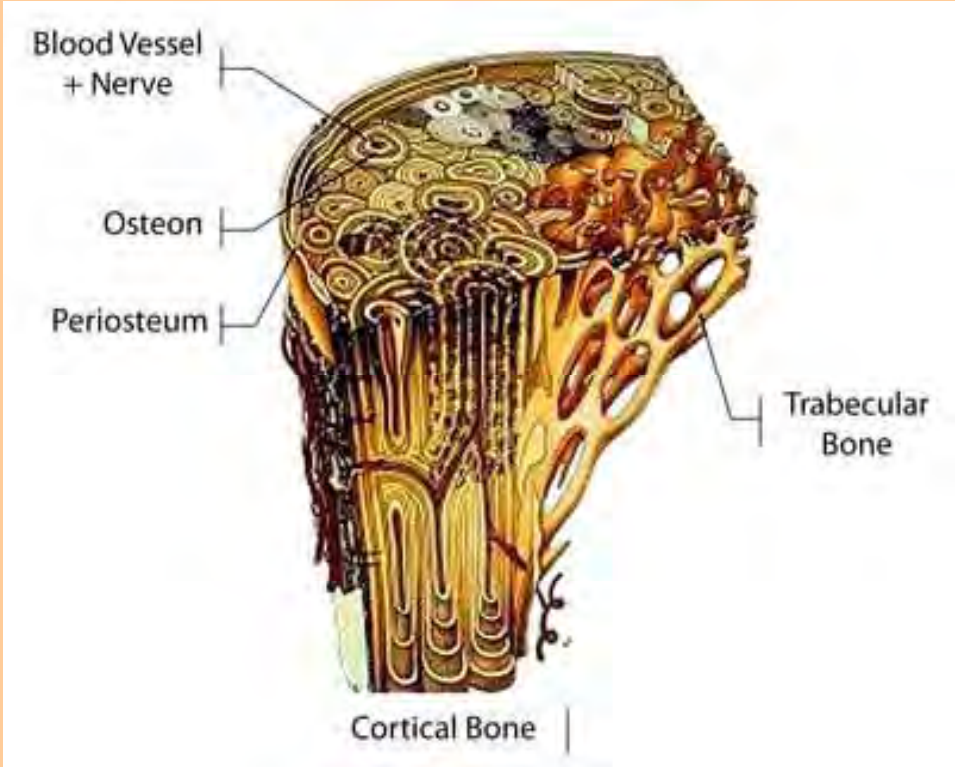
- Soft tissues (skin and muscle) and hard tissues (bone) are all connective tissues
- Connective tissues heal by the same basic mechanisms
- Bioactive glasses can be used to effectively stimulate connective tissue regeneration
- Microstructure of scaffolds and implants is important
- New areas of ceramic based treatments are under exploration as we speak





Biomaterial Parameters

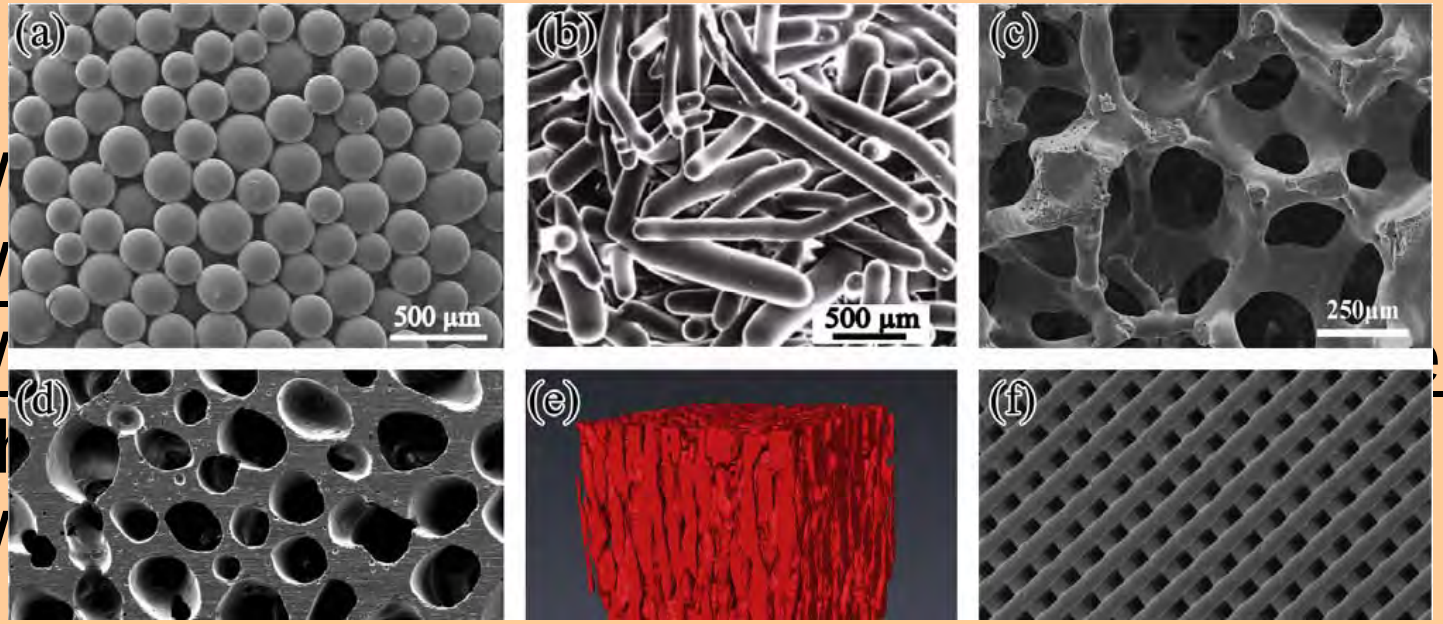
- Biocompatibility (in-vivo)
- Open Porosity
- Pore Size (100 to 400µm)
- Pore Orientation
- Mechanical Strength (0.2 to 170MPa for bone)
- Material Reaction Rates (inert to very reactive)
- Surface Texture
- Particle Size/ Fiber Diameter
- Hemostasis
- Antimicrobial/ Antifungal
- Angiogenic
- Degradable
- Ease of Use
- Others?



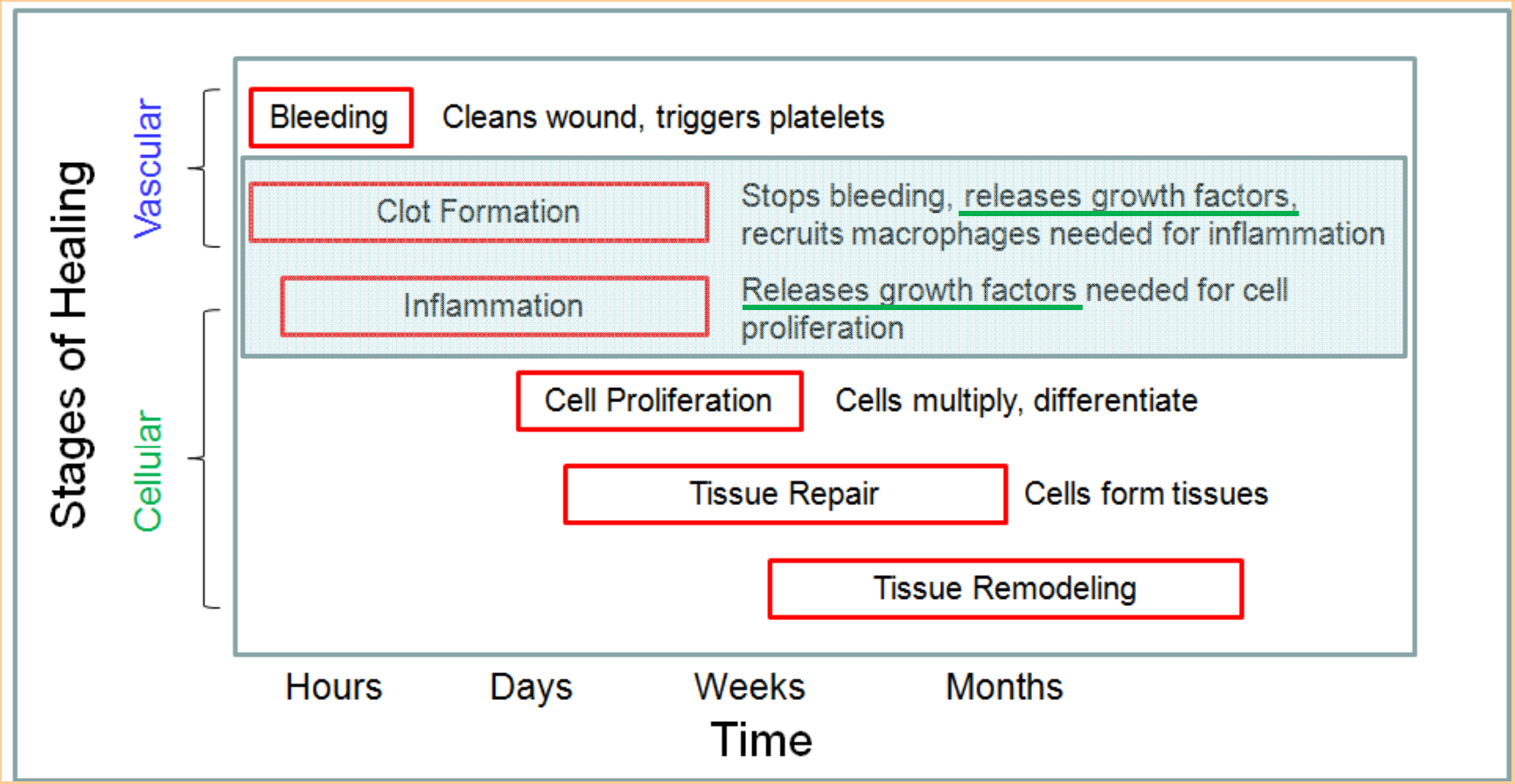
Look to the Body for Answers

- Typically, the scaffold designs in the literature represent the <u>final desired shape</u>
  - i.e. (cancellous and cortical bone)

1. W
2. W
3. W lf
   wh
4. W



Stages of Healing



Treatment with Growth Factors

- Area of great risk and reward
- If harnessed correctly, powerful tools
- If improperly used, potential consequences
  - i.e. Medtronic's InFuse (~85% off label use), FDA review
- Growth factors are most useful when released:
  - at the correct concentrations
  - in the correct order and/or combination
  - at the correct time and duration

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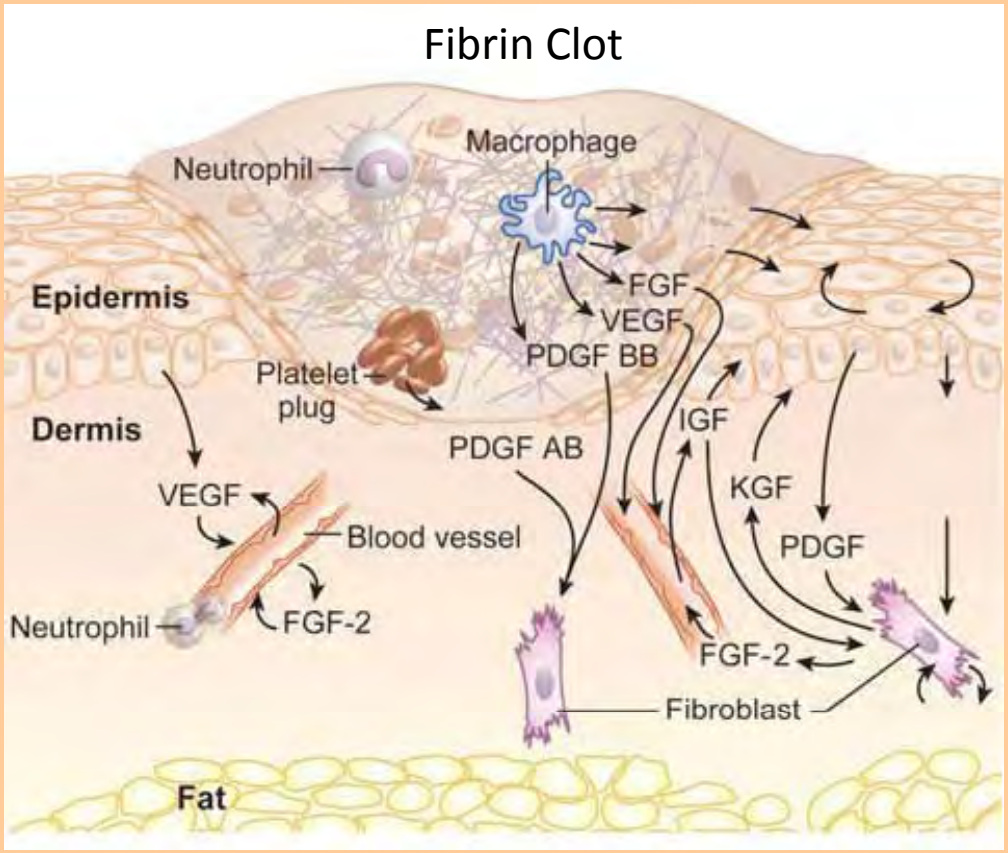
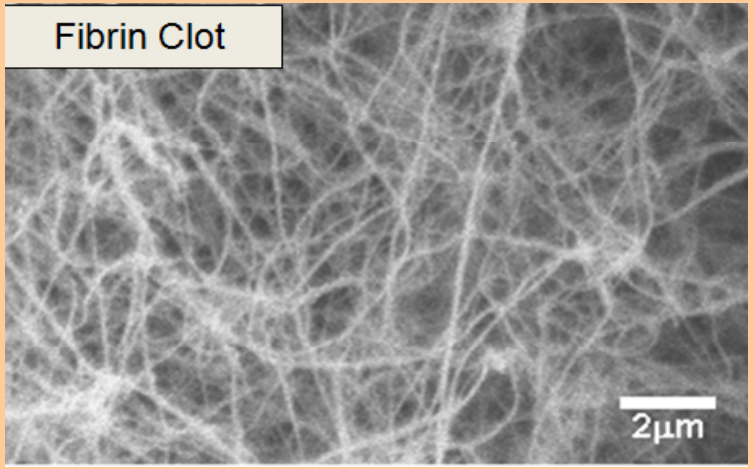
Connective Tissue Healing (skin)





- Fibrinogen and thrombin react to form cross-linked fibrin matrix
- Fiber mediated healing
- Basic mechanism for all connective tissue healing
- **This is Natures Way of Healing!**

Clark et al. Tissue Engineering for Cutaneous Wounds
Journal of Investigative Dermatology (2007) 127, 1018–1029. doi:10.1038/sj.jid.5700715

Growth factors Required: PDGF – Platelet Derived Growth Factor, **VEGF** – Vascular Endothelial Growth Factor, **IGF** – Insulin Derived Growth factor, **KGF** – Kerotinocyte Derived Growth Factor, **FGF** – Fibroblast Derived Growth Factor, **BMP** – Bone Morphogenic Proteins (not shown)

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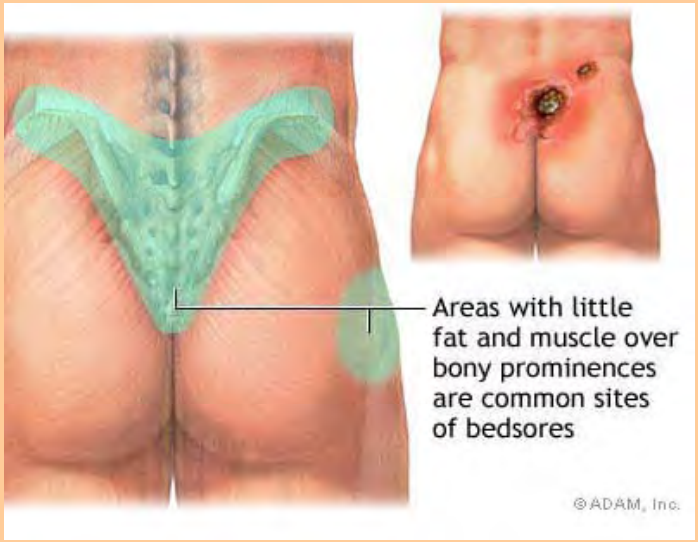
The Need for Better Wound Healing Materials

Chronic Skin Ulcer
Caused by Pressure



graphics8.nytimes.com/.../thumbnails/19091t.jpg

6.5 million people suffer from chronic skin ulcers annually in U.S.

- •Pressure (bed ridden, usually backside)
- •Venous Stasis (poor circulation, usually in legs)
- •Diabetes (extremities)

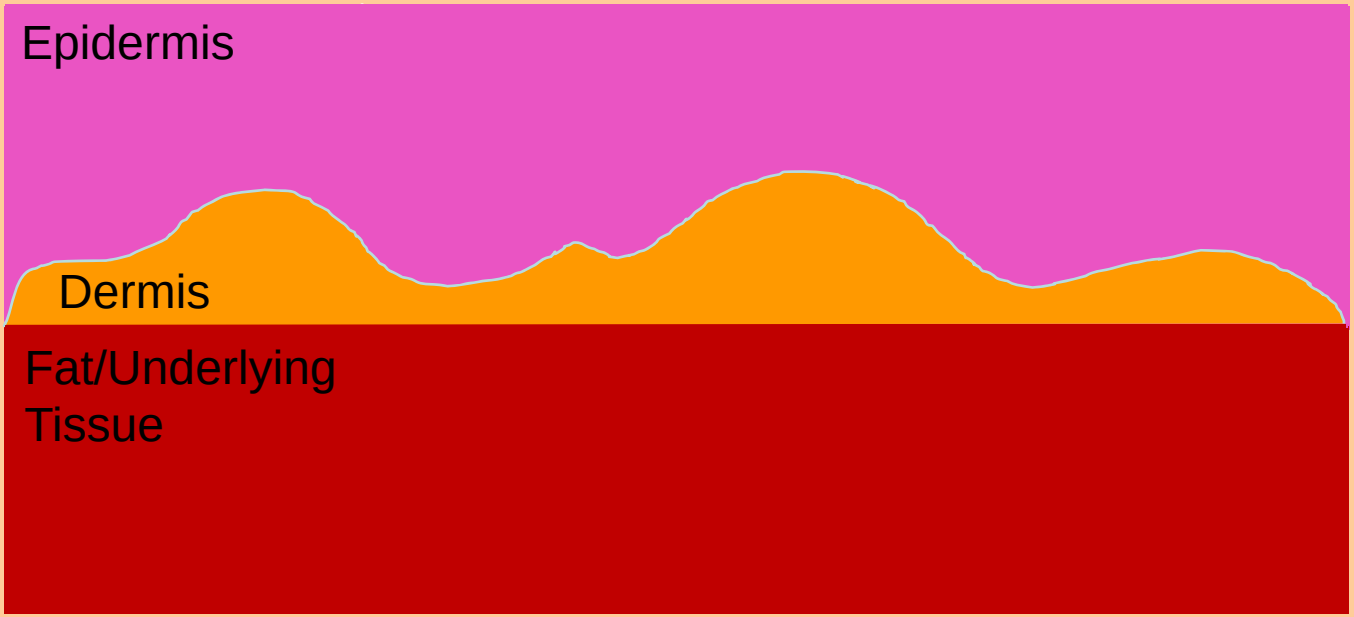
Diabetic Ulcer

www.skinpatientalliance

Venous Leg Ulcer Caused by Poor Circulation

www.skinpatientalliance

Bioactive Glasses Have Potential To Help Regenerate Damaged or Non-Healing Soft Tissue



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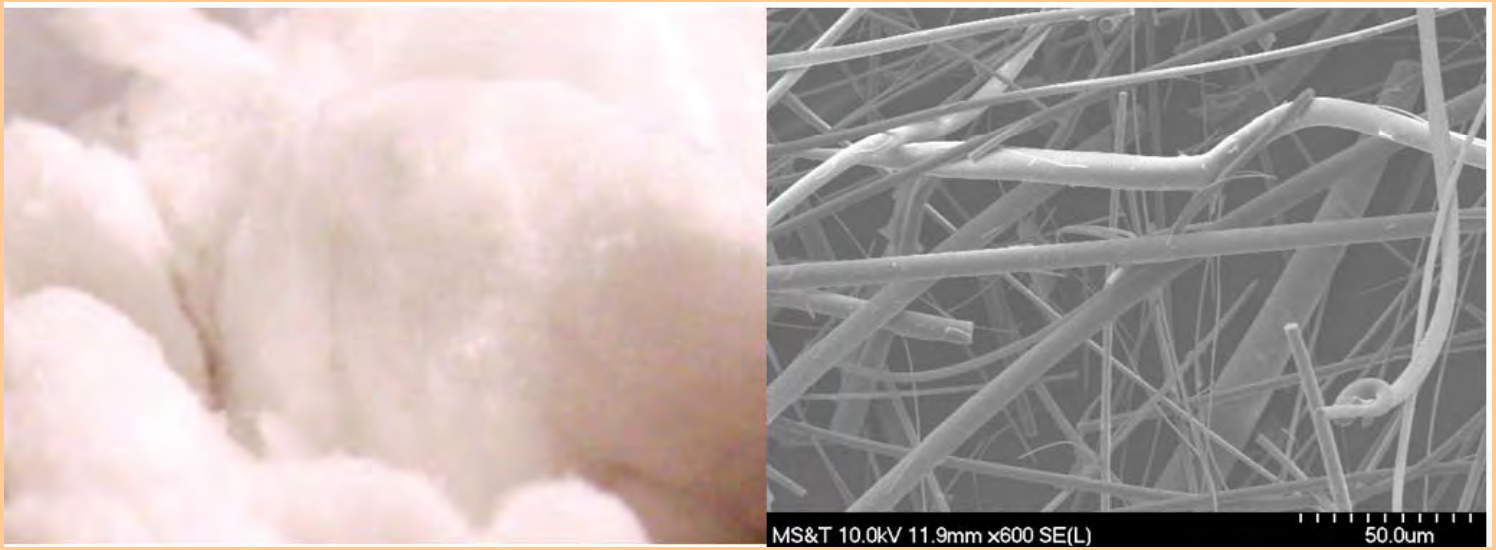
Fiber Mediated Healing



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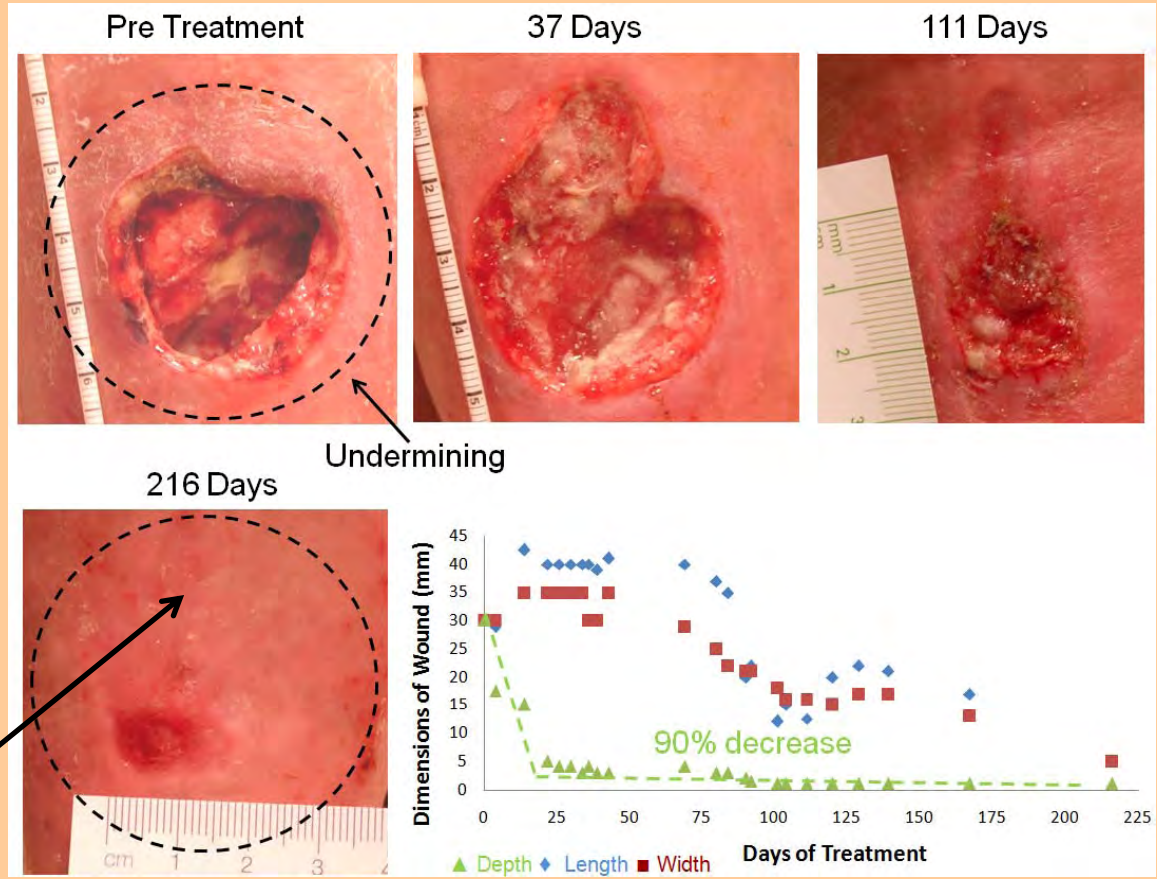
Patient Profile
70yr old F with Venous Stasis Ulcer on Lower Leg, Non-smoker
Age of wound: ~4 months, started from a small bruise from falling
Chronic health problems: Diabetes, PVD, PAD, neuropathy; Charcot foot; previous chronic wounds; previous recurring leg infections; venous insufficiency

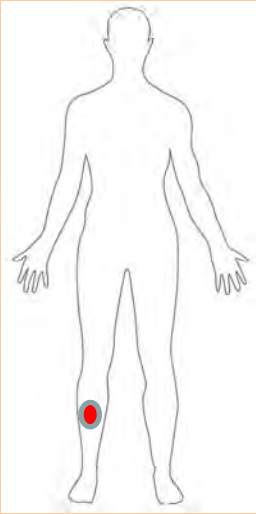
Initial wound w/ undermining was approx. golf ball sized

*Vascular deficiency inhibits the healing process

**Hydrostatic pressure in lower leg further complicates healing

***Notice minimal scarring





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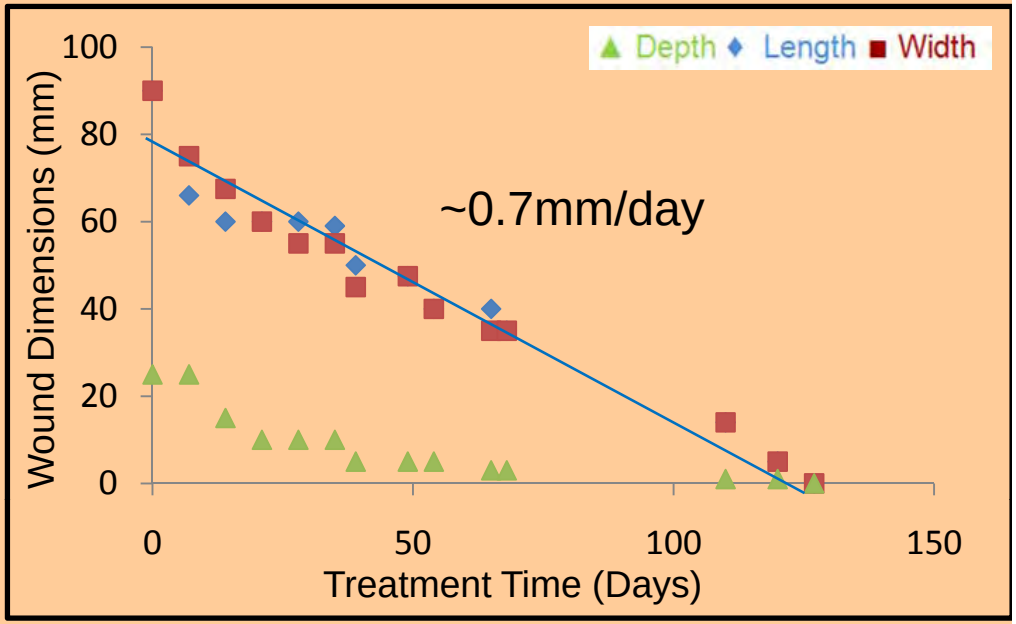
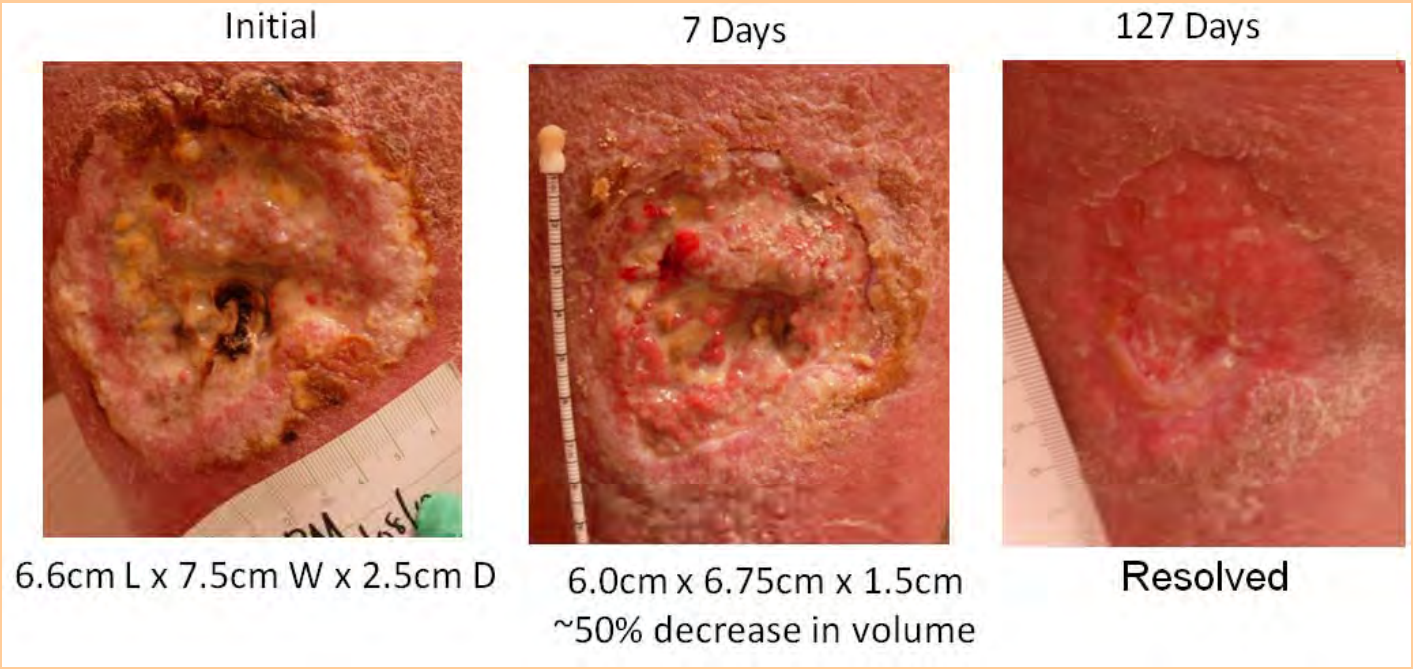
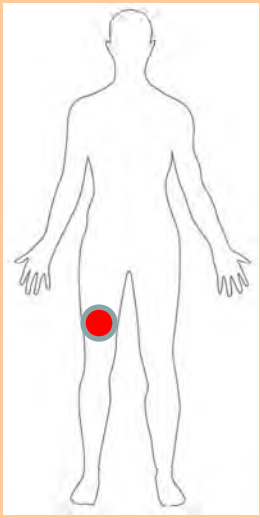
Patient Profile
F (mid 40's) with hypertension, hypothyroidism; denies other health concerns
Age of wound: several months (no known initial date)
Etiology: Venous Stasis Ulcer







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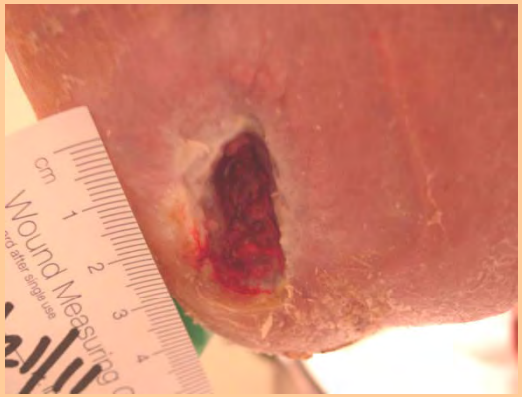
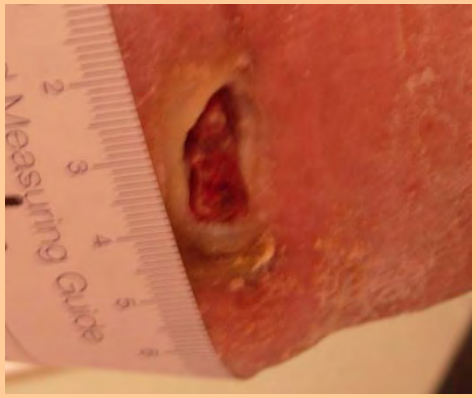
Patient Profile - Male
Age of wound: ~2 years (no known initial date)
Etiology: Pressure wound on heel
Chronic health problems: Diabetes - insulin dependent, with peripheral neuropathy; hypertension, renal failure with dialysis 3 x weekly; chronic pain with degenerative disk disease of the lumbar spine; and chronic foot wounds

Initial

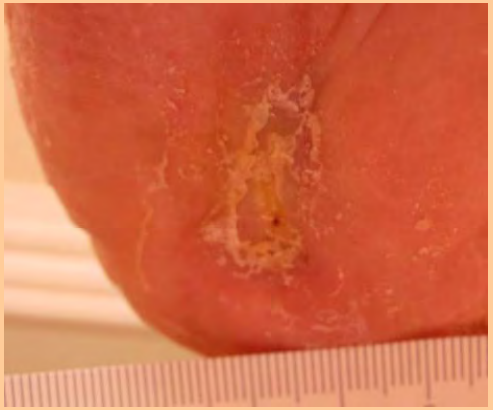


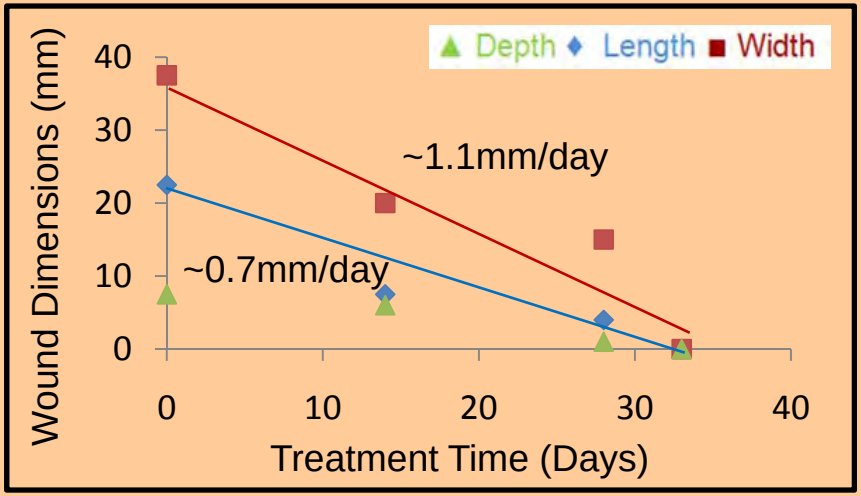
7 Days

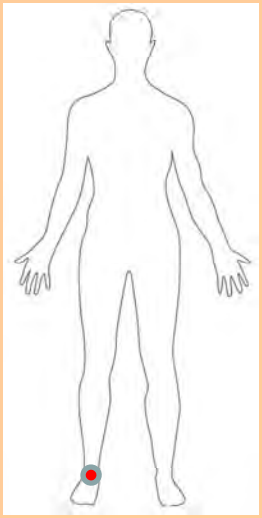


28 Days

33 Days







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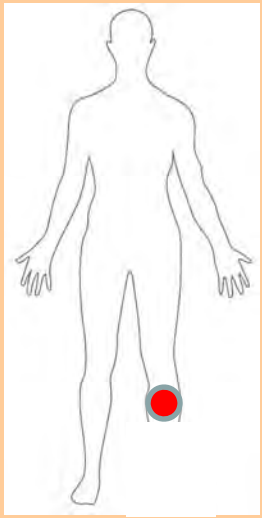
Patient Profile
M amputee requiring stump revision
Age of wound: ~1 to 2 months
Etiology: Stump revision (below knee)
Diabetic with vascular deficiency



Initial

Resolved (32 Days)

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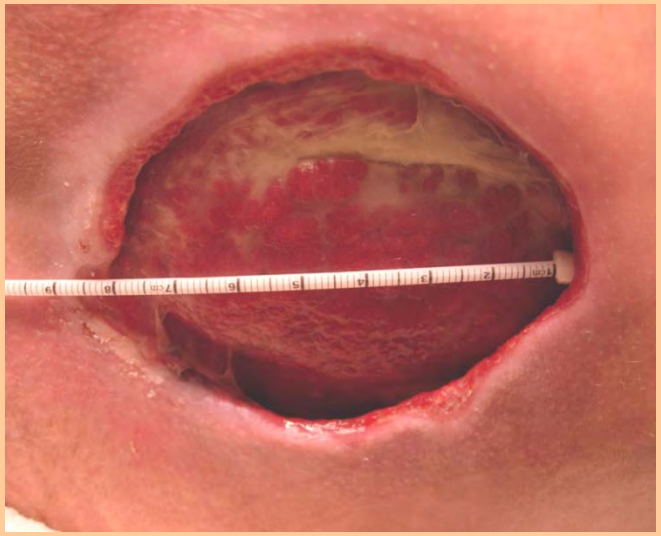
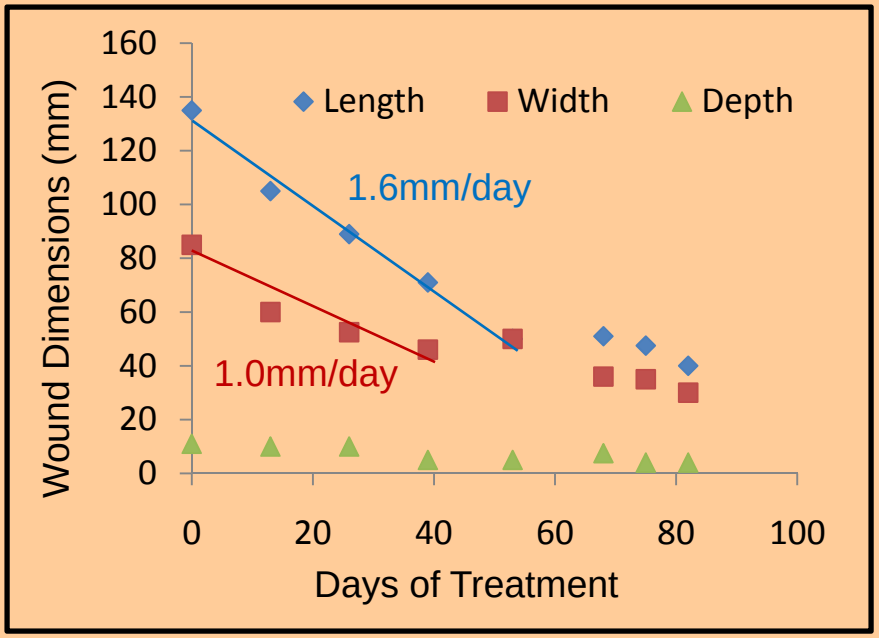
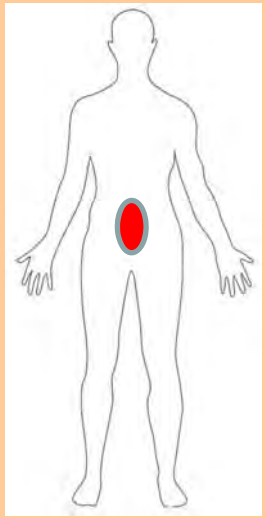
Initial



Day 82

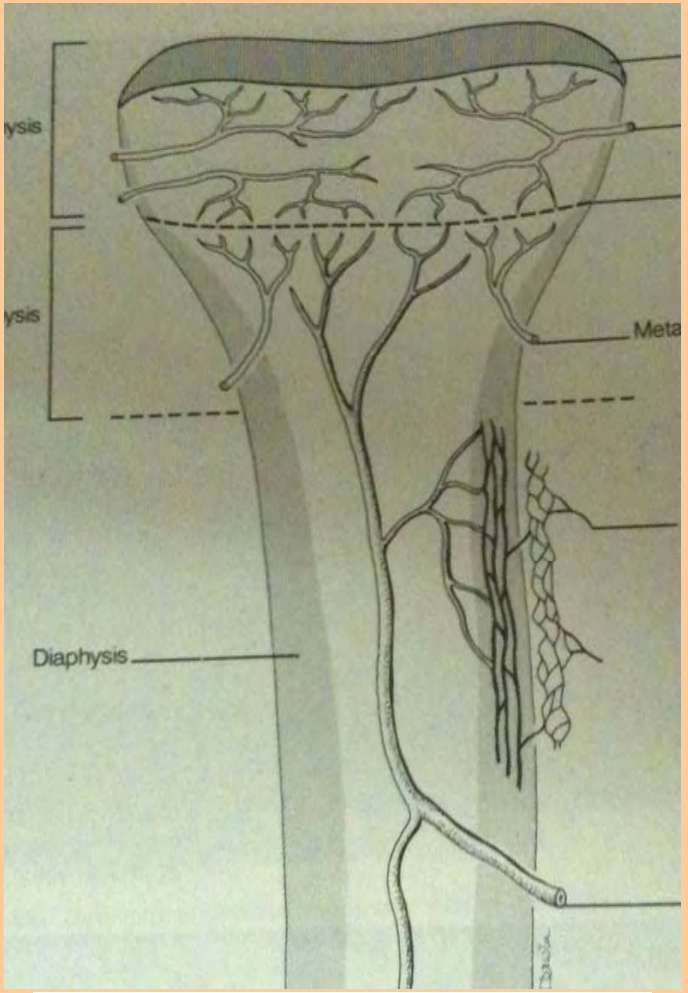
Patient Profile
39 yr old M paraplegic (motorcycle accident)
Age of wound unknown
Etiology: Sacral ulcer over bony prominence (lower back, tail bone)
Drainage noted
'Killer Wound'





The Need for Angiogenic Ceramics

- Bioactive glasses contain calcium needed to form HA and bond to bone
- Reports on angiogenic properties of silicate based bioactive glasses have been mixed
- Angiogenesis is key to improving in-growth in large scaffolds (segmental defects)
- Osteocytes must to be within 100 to 200µm of a capillary
- Blood vessels are the conduit for oxygen, nutrients, growth factors, and waste removal



Mature Long Bone (Tibia)

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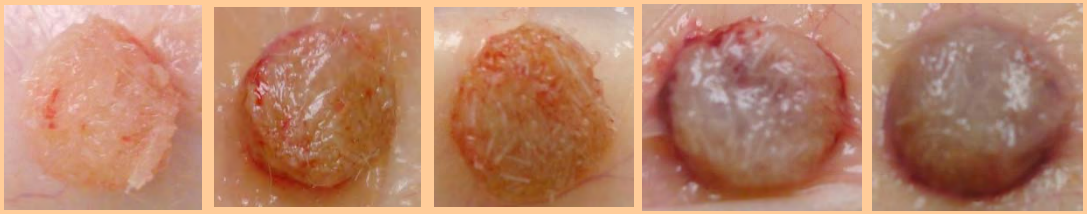
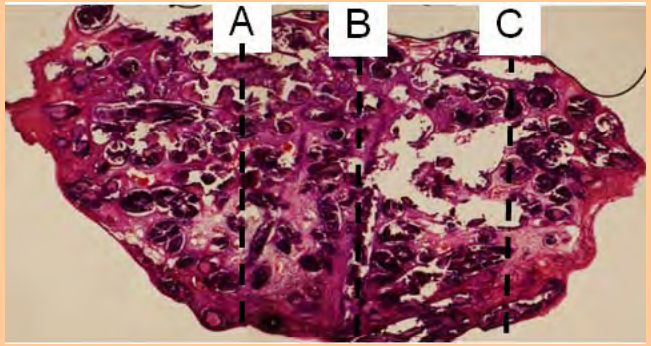
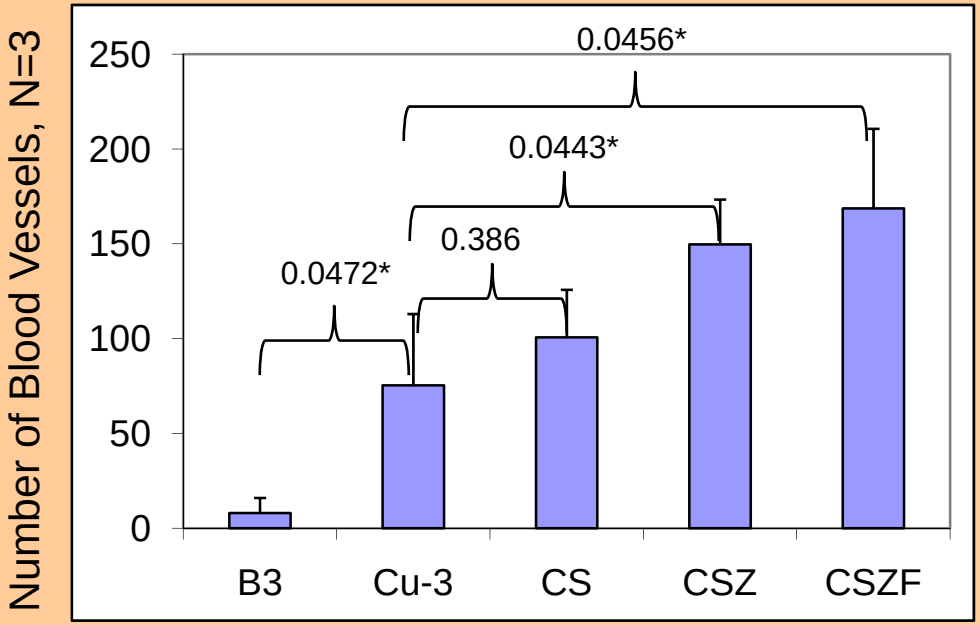
Multifunctional Bioactive Ceramics

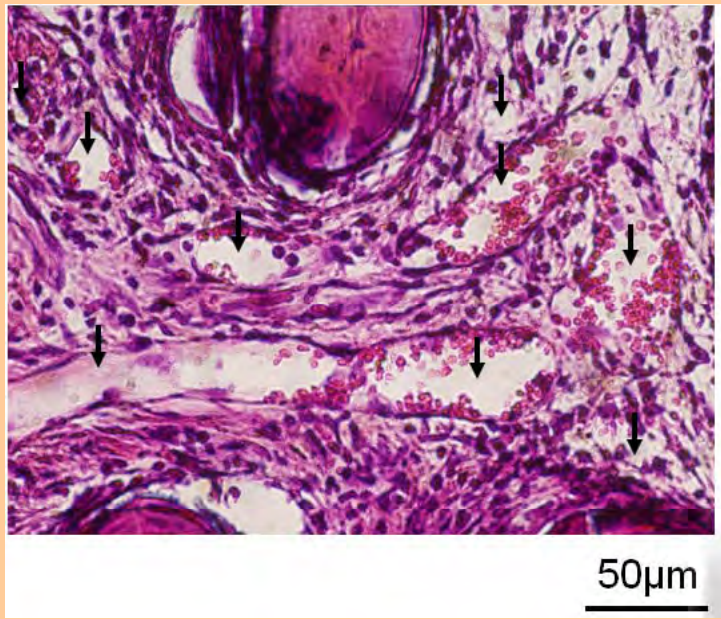
Blood Vessel Analysis of B3, Cu-3, CS, CSZ, and CSZF random fiber scaffolds after 6 Weeks *In-Vivo*





Assessment of Angiogenesis

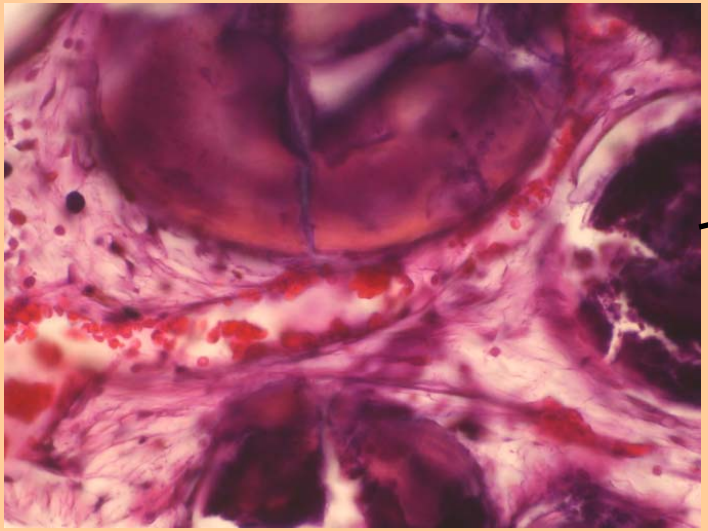


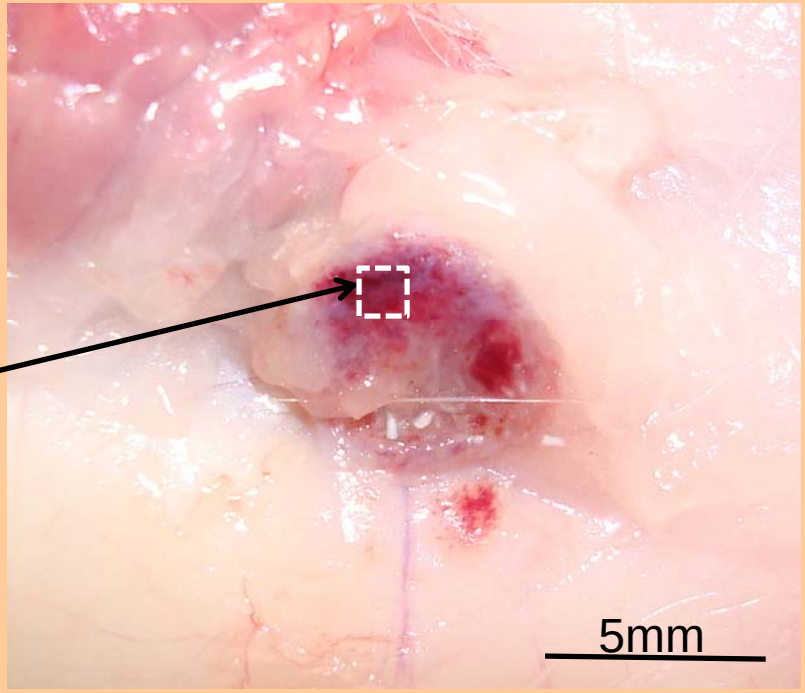


C or *Cu* – Copper, *S* – Strontium, *Z* – Zinc, *F* – Iron

Angiogenic Bioactive Glasses

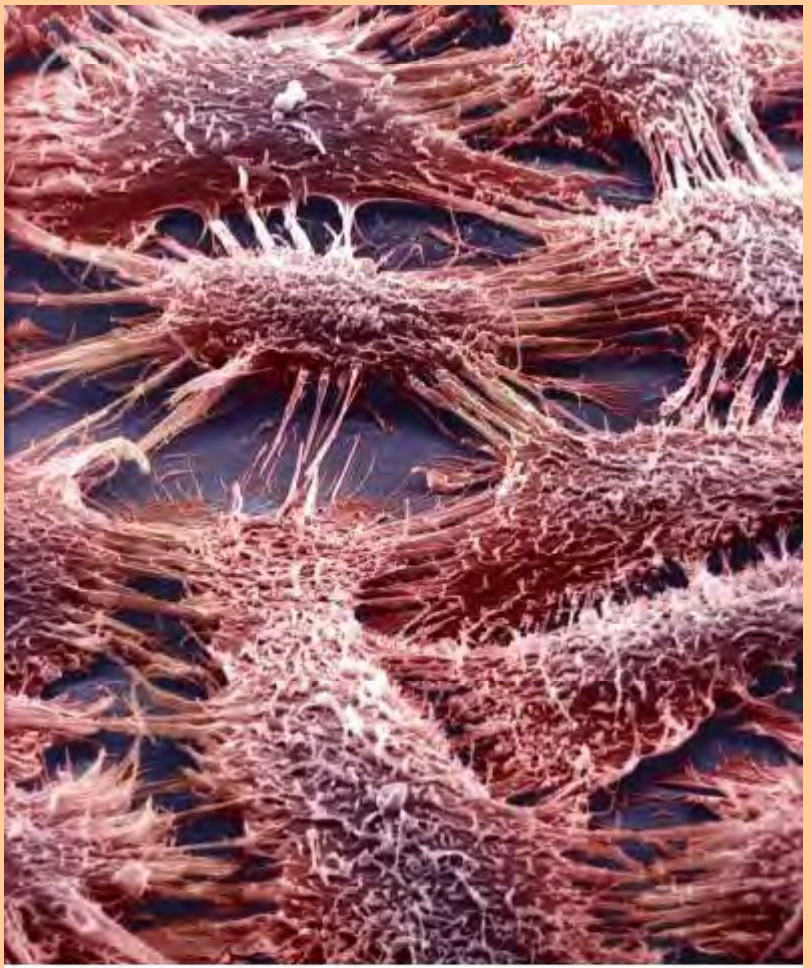
- Glass in general can be doped with most elements (excellent delivery vehicle)
- Glasses can be tailored to degrade in minutes to years
- Degradation rate can be modeled and is reliable
- Bioactive glasses are biocompatible and resorbable
- No growth factors required
- Site specific treatment





Conclusions

- Connective tissues heal by the same basic biological mechanisms
- Biomaterial microstructure is important
- Multifunctional bioactive glasses and ceramics are new important tools in the biomaterial toolbox
- Healing from a biological perspective is improving biomaterial design and function



Thank you

Questions?