Biomaterials in Bone Tissue Engineering

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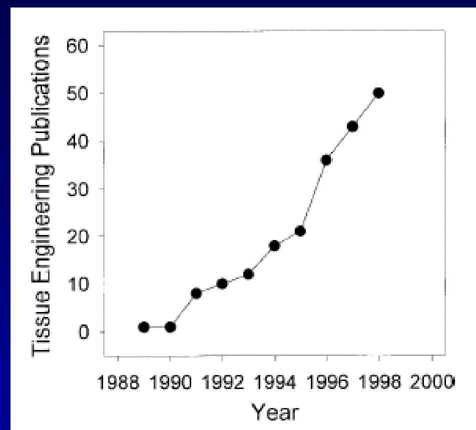
Outline

- Background in tissue engineering
- Structure and function of bone
- Motivation and background in bone tissue engineering
- Biomaterials in bone tissue engineering

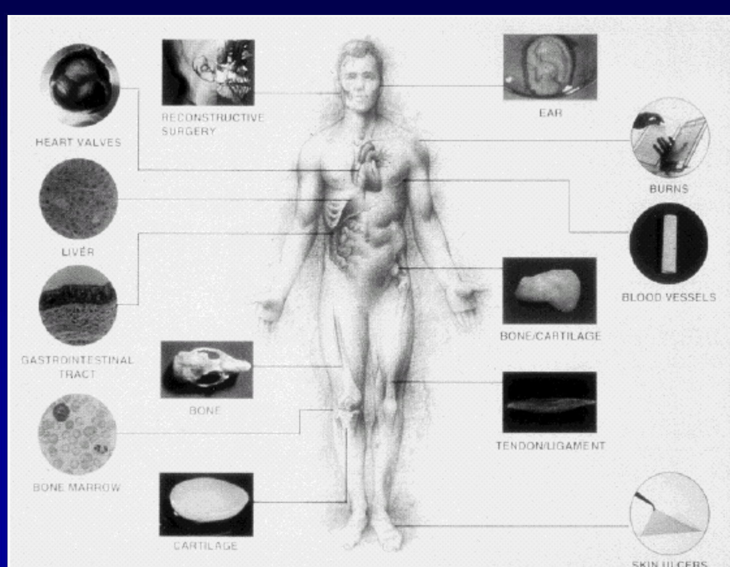
History of Tissue Engineering

- ~ 25 years
- Yannnas et al: artificial skin from collagen and glycosaminoglycan (1980)
  Cima et al: chondrocytes from PLGA (1991)
- Langer and Vacanti (1993) defined "tissue engineering"

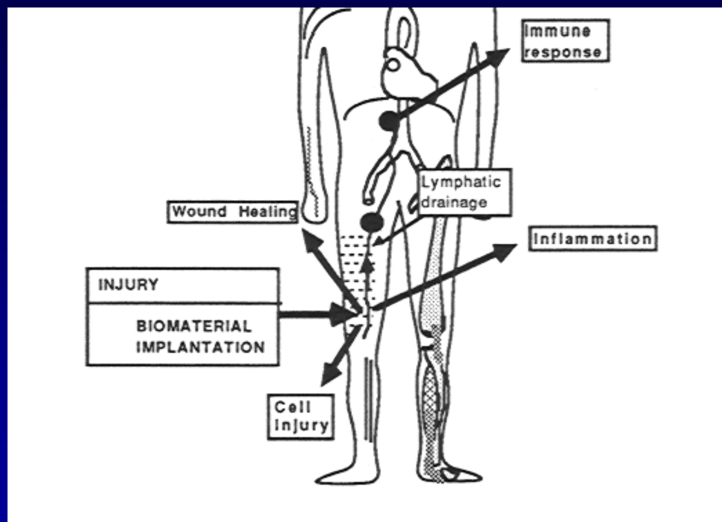


L. Bonassar, CA Vacanti, Journal of Cellular Biochemistry Supplements, 30/31:297-303 (1998)

Possible Tissue-Engineered Devices



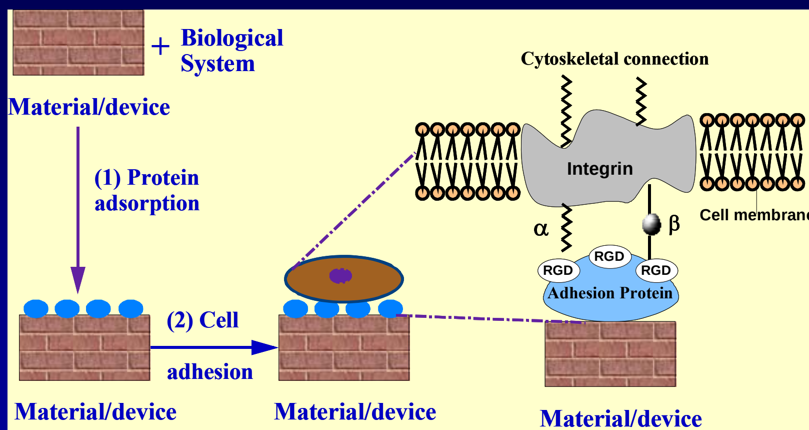
Host Response



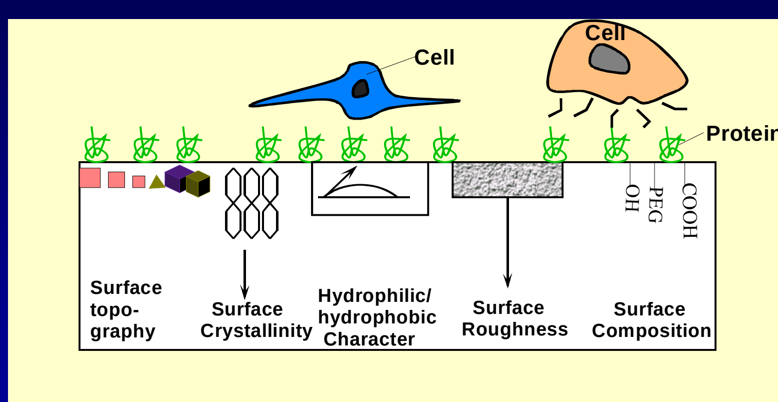
Material Response

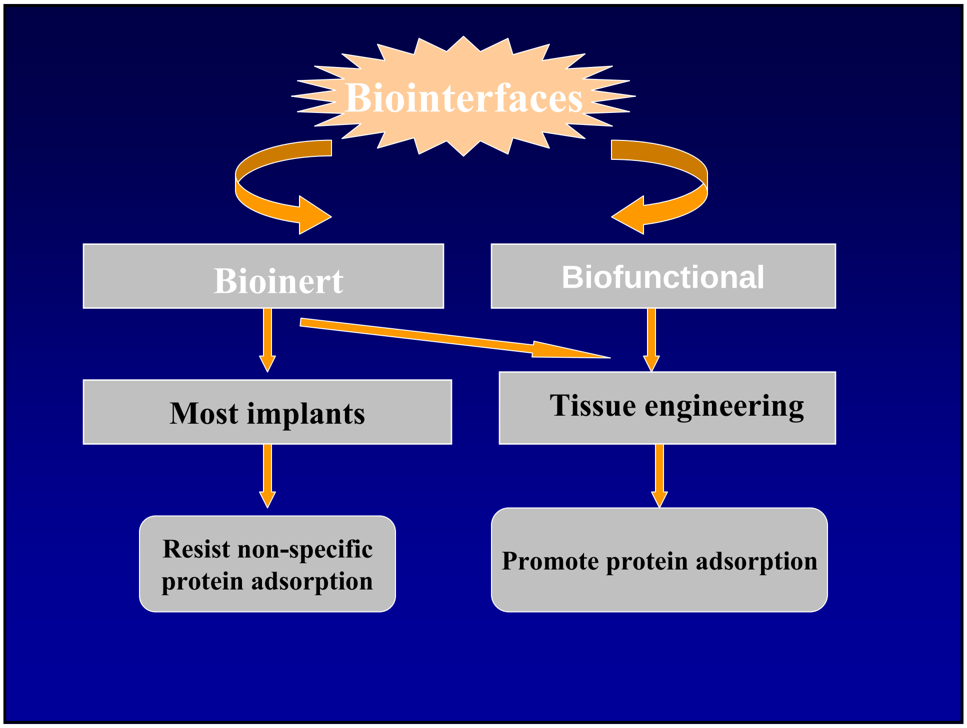
- Swelling and leaching
- Corrosion
- Particulates
- Deformation and failure

Material/device-Living System Interaction



Effects of Surface Properties on Living Systems





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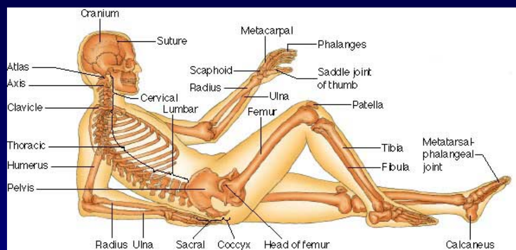
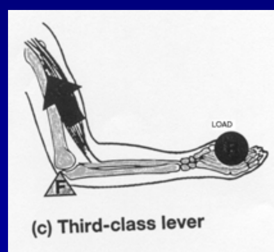
Function of Bone

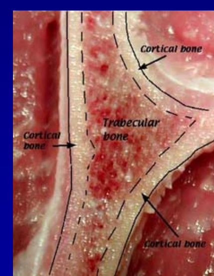


Support

Protection

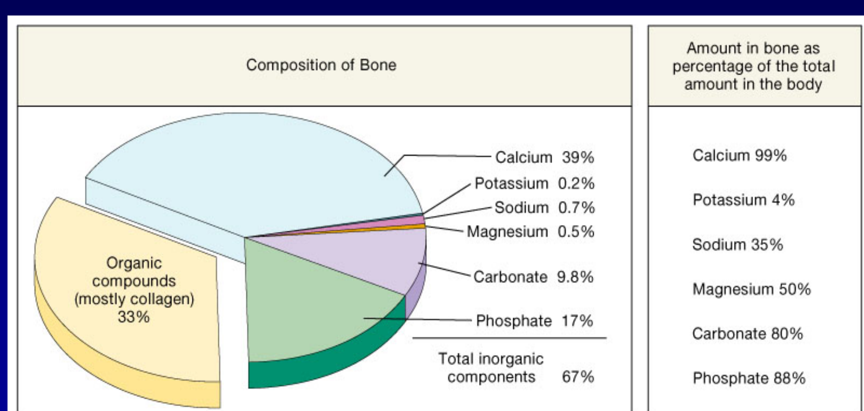


Leverage



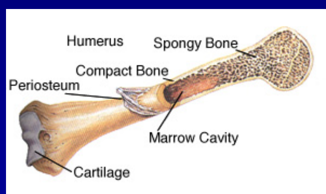
Storage and production

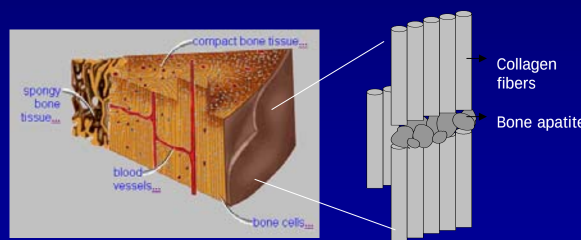
Composition of Bone



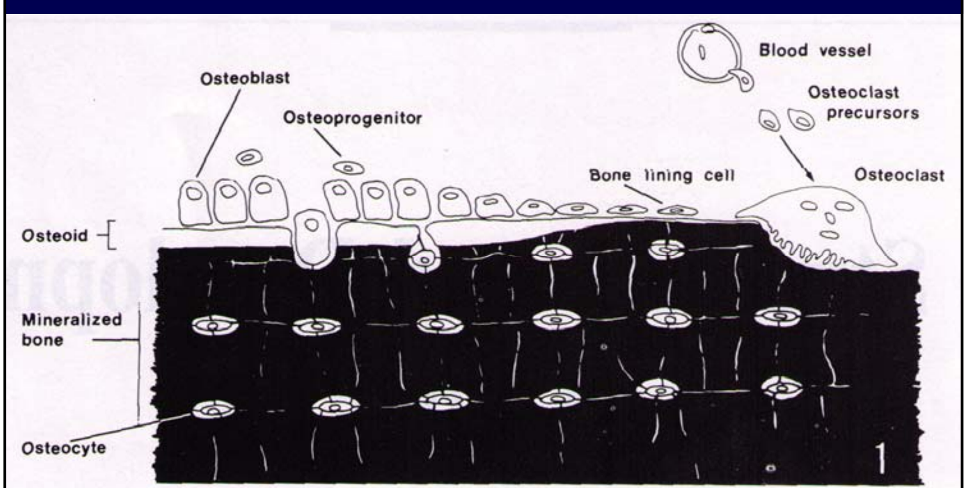
The Structure of Bone

- **Bone organic composition**: 95% type I collagen, and 5% of proteoglycans and noncollagenous proteins
- **Bone:** cortical (compact) and cancellous (spongy)

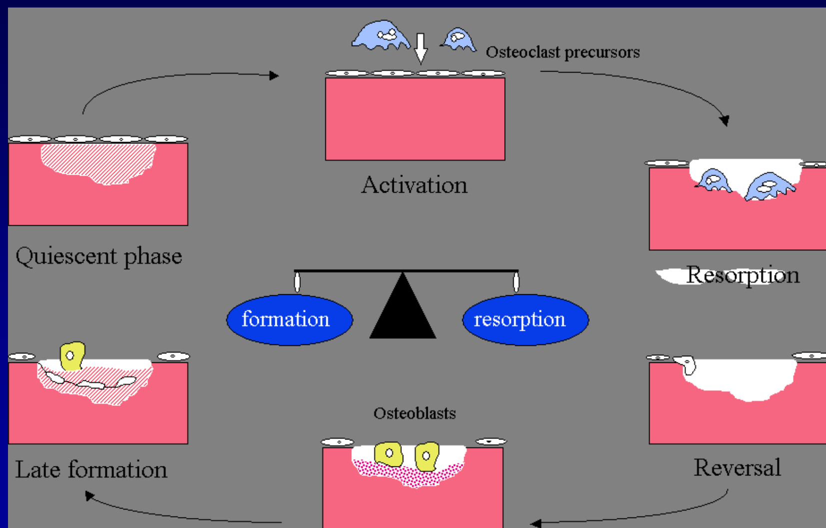




The Types and Locations of Bone Cells



Bone Remodeling



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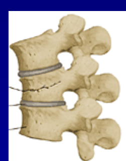
Causes of Bone Defects

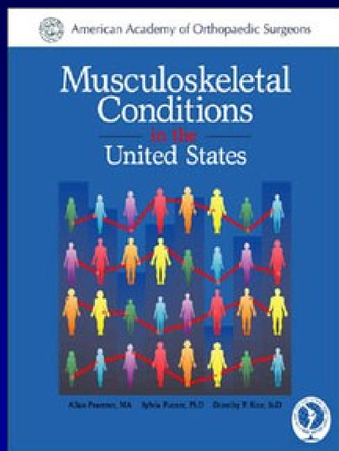
Trauma, tumors, aging, osteoporosis ….



Bone Defects – Affect Everyone

- Osteoposis: 15% of those 50-59; 70% of those over 89
- Spine disorders: 80% of population

Musculoskeletal Conditions are Worsening!!!



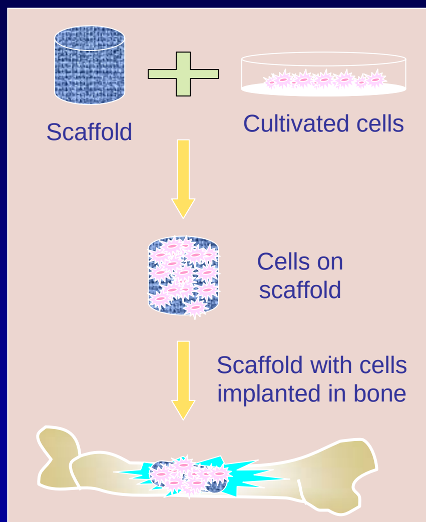
- 1 out of 7 Americans have musculoskeletal impairments. 36.9 million Americans incur injuries every year.
- 1 out of 2 women and 1 out of 4 men over 50 suffer an osteoporosis-related fracture
- $300 billion every year

Data from AAOS, NIH, NOF and http://www.usbjd.org

Treatments of Bone Defects

- **Autograft** — Patient
  1. Patient pain
  2. Infection
  3. High cost
- **Allograft** — Other patient
  1. Donor shortage
  2. Infection
  3. Pathogens
  4. Immune Rejection
- **Xenograft** — Animal
  1. Immune rejection
  2. Pathogens
- **Material substitutes** — Biomaterial
  - Metals polymers bioceramics do not have good properties
- **Tissue engineering** — Promising therapy
  - See next slide

Bone Tissue Engineering



- Scaffolds gradually degraded and eventually eliminated
- Patient-derived bone cells onto a macroporous man-made scaffolds to create completely natural new tissues
- Common cells: osteoblast, mesenchymal stem cells

Criteria for Scaffold Materials

- Excellent mechanical strength
  Cancerous bone (compressive stress 0.5-10 MPa)
- Three dimensional (3D) interconnected macroporous microstructures
- Controllable biodegradation and bioresorption
- Suitable surface chemistry
- Malleable
- Good biocompatibility and biofunctionality

Biocompatibility of Porous Materials for Bone Tissue Engineering

Bioinert — Resist non-specific protein adsorption

Biofunctional

- Bioactive: form bond between tissues and materials
- Osteoconduction: stimulate cell attachment and migration
- Osteoinduction: stimulate proliferation and differentiation of stem cells
- Osteogenesis: produce bone independently

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  - Porous ceramic scaffolds for load bearing bone
  - Polymeric materials for non-load bearing bone

I. Porous Scaffolds for load-bearing Bone Tissue Engineering (hard tissue)

Background: Existing Porous Scaffolds

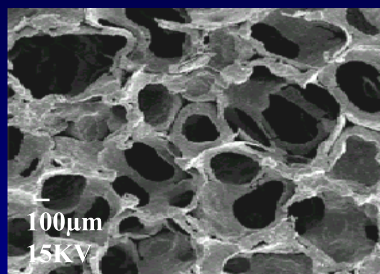
Metals → **Stainless Steel, Titanium**
- High mechanical strength
- Not bioactive and osteoconductive
- need surface coatings

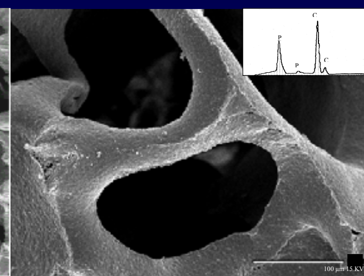
Ceramics → **HA & β-TCP**
- Composition similar to bone
- β-TCP > HA in degradation
- bioactive, osteoconductive
- ~ 2MPa

Coral → **Can be converted into HA**
- High mechanical strength ~ 14 MPa
- limited resources, expensive
- uncontrollable microstructures

- Hydroxyapatite (HA), tricalcium phosphate (TCP)

HA Scaffolds by a Gel-Polymer Method

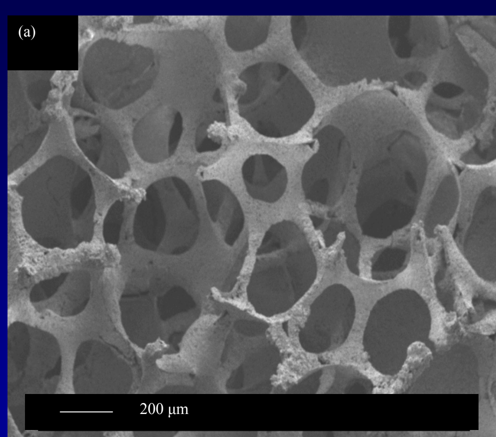


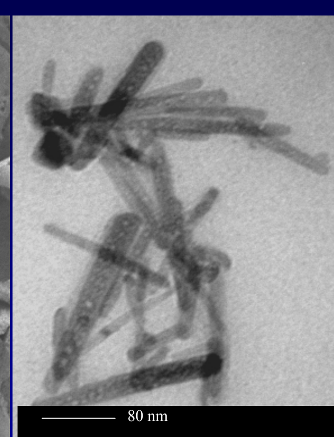


Compressive yield stress: 5 MPa
Compressive elastic modulus: 7 GPa

H. Ramay and M. Zhang, Biomaterials 24 (19), 2003

β-TCP and HA Nanofiber Nanocomposite Scaffolds





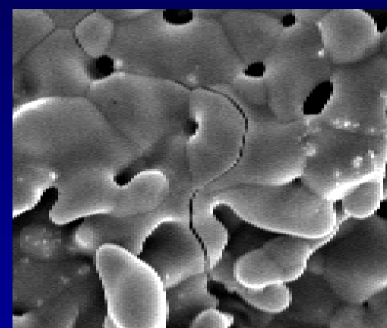
Compressive stress 9.8 MPa – Human cancellous bone 2-10MPa

H. Ramay and M. Zhang, *Biomaterials*, 25 (21), 5171-5180 (2004). Filed US patent.

Mechanisms for Increased Toughness

Wavy fracture surface
- Area of crack surface is increased

Clinching at crack tip
- Clinching reduces the applied stress intensity factor



10 μm

UWEB

II. Porous polymeric scaffolds for non-load bearing bone

Polymeric Porous Scaffolds

Synthetic polymers → Polyglycolic acid (PGA) Polylactic acid (PLA) Poly- lactic-co-glycolic (PLGA) →

- Hydrophobic
- Acidic degradation products

Chitosan

Natural polymer

→

More biocompatible
Minimal foreign body reaction
Hydrophilic
Suitable surface chemistry

Why Chitosan-alginate Scaffolds?

Chitosan →

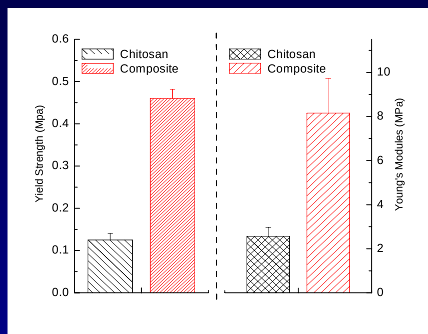
Weak
Swelling
Soluble in strong acid
Difficult to incorporate drug

Chitosan + Alginate →

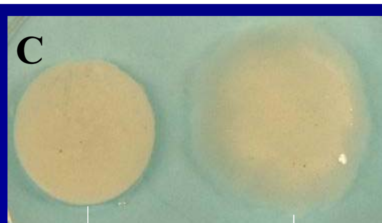
Strong
Strong ironic bonding
No swelling
Neutral pH: easy to incorporate drugs

Natural polymer

Mechanical and Swelling Properties



3~4 times increase in mechanical strength and compressive modulus



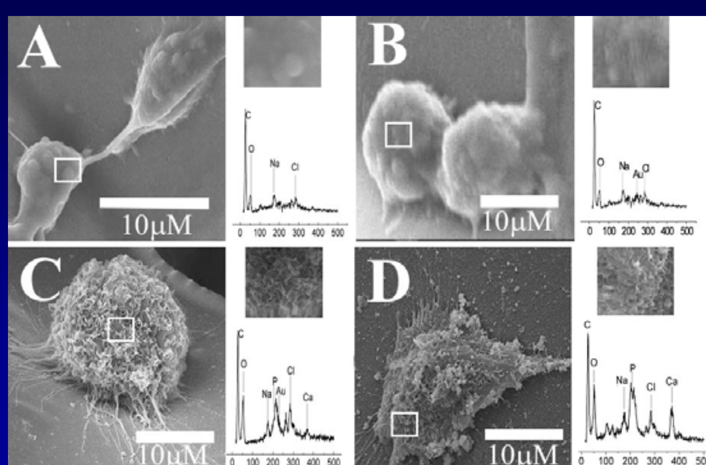
Chitosan hybrid   Chitosan

Chitosan composite scaffolds

- Do not swell in PBS solution
- Stable in neutral solution
- Incorporation of proteins without denaturization

In vitro Study of Bone Mineralization

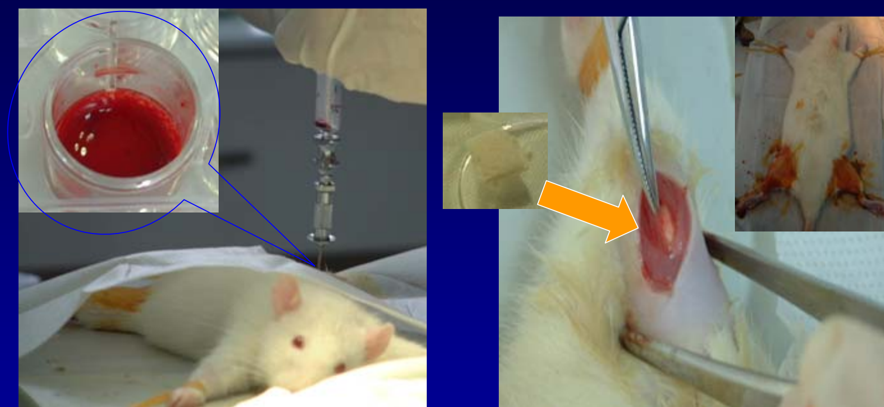
3 days



7 days

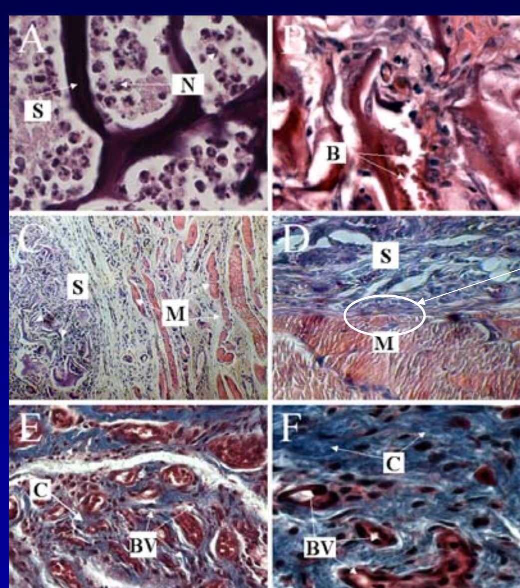
A large amount of minerals was formed on chitosan-alginate scaffold

In vivo Ectopic Animal Model



Z. Li, H. Ramay, K. Hauch, D. Xiao, and M. Zhang, *Biomaterials*, 26 (18), 3919-3928 (2005).

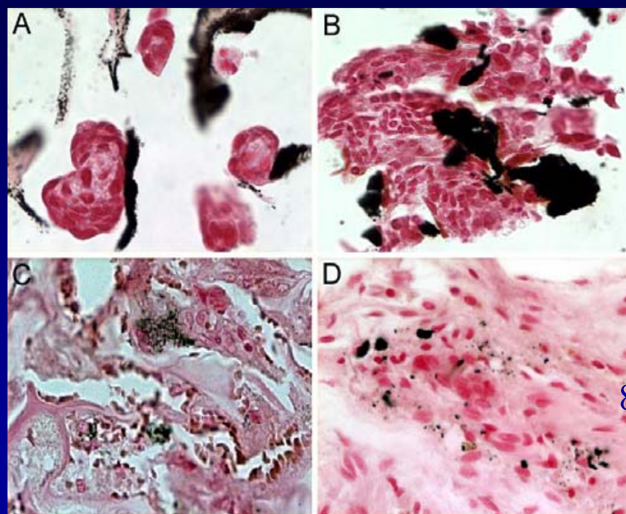
Compatibility of Chitosan-alginate Scaffolds



No fibrotic layer

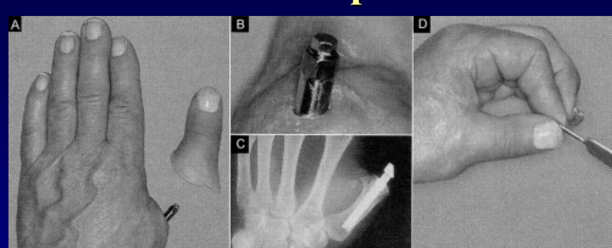
Blood vessel formation

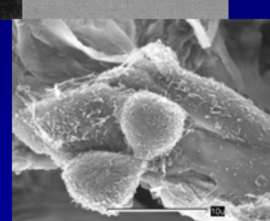
In vivo Study of Mineral Formation



Black stain indicates bone formation

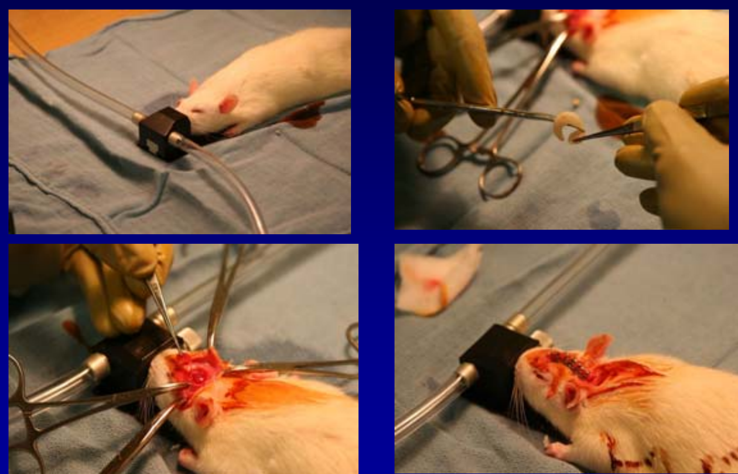
In vivo Orthotopic Animal Model: Digit Bone Defect Repair





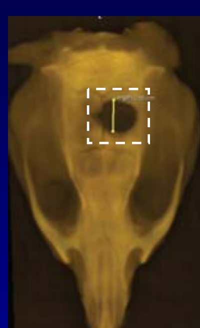
Chris Allan (MD, UW Orthopedics) (bone)
Buddy Ratner (UW Bioengineering)
Miqin Zhang (UW Materials Science and Engineering)

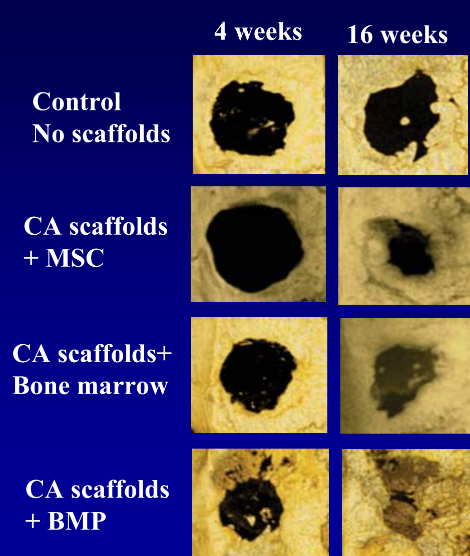
In vivo Orthotopic Animal Model: Cranial defects



Richard Hopper (MD, Children Hospital)
Miqin Zhang (UW Materials Science and Engineering)

Micro CT results





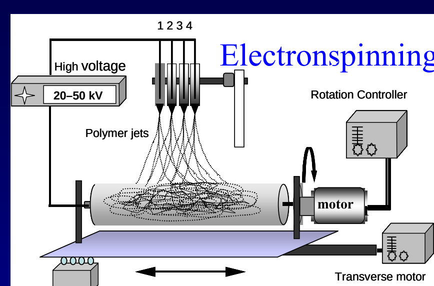
- All samples show defect closure
- The CA scaffolds with BMP-2 have the best result on bone formation

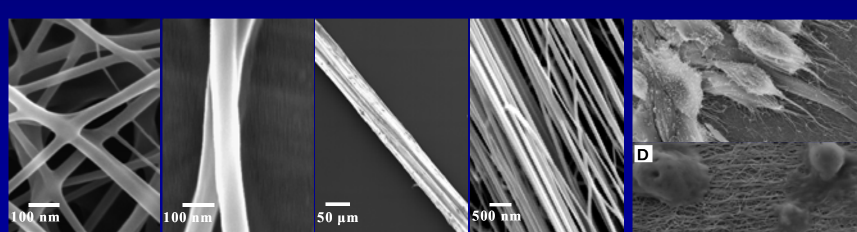
III. Other novel biomaterials

for bone tissue engineering

Biomimic Extracellular Matrix

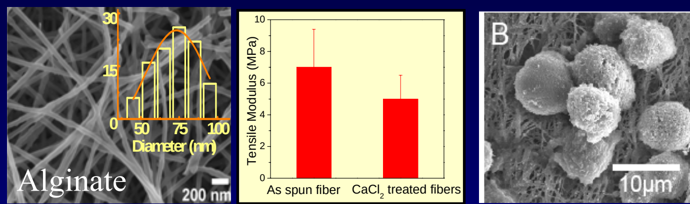
Extracellular matrix: proteoglycans and fibrous proteins with fiber diameters in the range of 50 to 150 nm



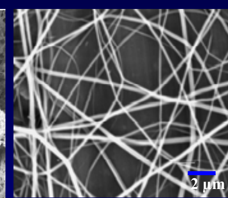


N. Bhattarai, D. Edmondson, O. Veiseh, F. A. Matsen, and M. Zhang, Biomaterials, **26** (31), 6176-6184 (2005) 2006.

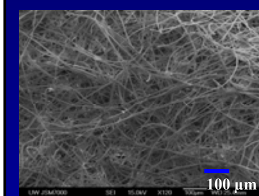
Various Electronspun Nanofibers



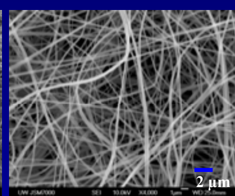
N. Bhattarai, C. Li, D. Edmondson, M. Zhang, Advanced Material, 2006



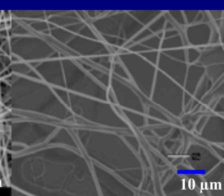
Silk fibroin



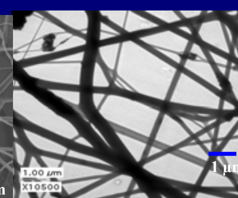
Gelatin



Polylactide (PLLA)

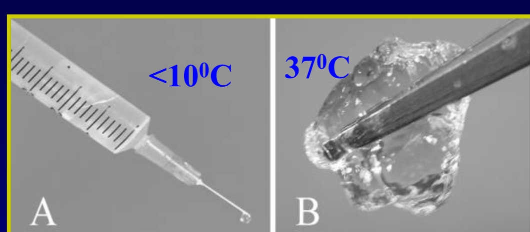


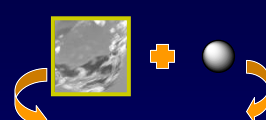
Polycaprolactone



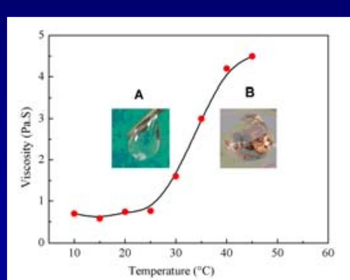
TEM image of PLLA/Iron oxide nanoparticle

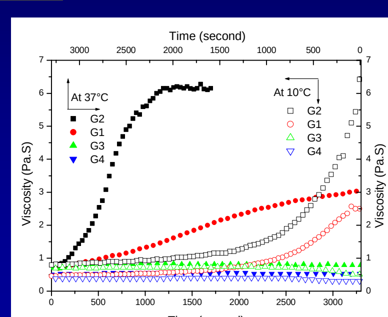
Thermoreversible Hydrogel





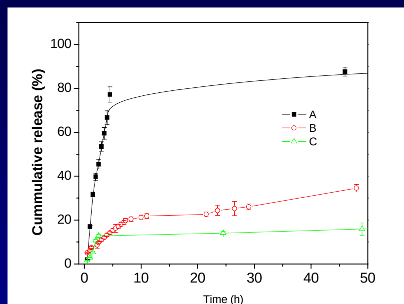
Gel + nanoparticles prolonged drug release for months

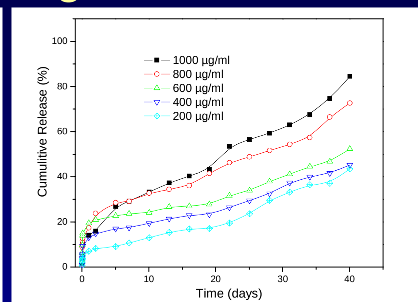




N. Bhattarai, F. A. Matsen, and M. Zhang*, *Macromolecular Bioscience*, 5, 107-111 (2005).

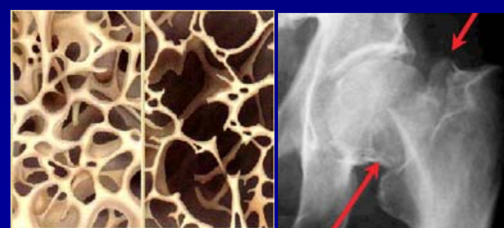
Thermoreversible Hydrogel for Controlled Drug release





N. Bhattarai, H. R. Ramay, J. Gunn, F. A. Matsen, and M. Zhang, *Journal of Controlled Release*, 103,

609-624 (2005).



Treatment of osteoporosis