Bioceramics

426620 Advanced Ceramic Materials
Asst. Prof. Dr. Sirirat T. Rattanachan
Outline

• Fundamentals and types of bioceramics (1 h.)
• Clinical applications of bioceramics (1 h.)
• Testing of Biomaterials (1h.)
Bone

- Classic hierarchical structure
  - Mineral + collagen
  - Fibrils
  - Fibres
  - Lamellar & woven bone
  - Fibrolamellar & Haversian bone
  - Compact & cancellous bone
  - Whole bones
Bone is composed of

- support cells (osteoblasts and osteocytes)
- remodeling cells (osteoclasts)
- nonmineral matrix of collagen and noncollagenous proteins (osteoid)
- inorganic mineral salts deposited within the matrix
Bone cells

- **Osteoblast**: These cells are derived from mesenchymal stem cells and are responsible for bone matrix synthesis and its subsequent mineralization. In the adult skeleton, the majority of bone surfaces that are undergoing neither formation nor resorption (i.e., not being remodeled) are lined by bone lining cells (the inactive form of the osteoblast).

- **Osteocytes**: These cells are osteoblasts that become incorporated within the newly formed osteoid which eventually becomes calcified bone. Osteocytes situated deep in bone matrix maintain contact with newly incorporated osteocytes in osteoid, and with osteoblasts and bone lining cells on the bone surfaces, through an extensive network of cell processes (canaliculi). They are thought to be ideally situated to respond to changes in physical forces upon bone and to transduce messages to the osteoblastic cells on the bone surface, directing them to initiate resorption or formation responses.

- **Osteoclasts**: These cells are large multinucleated cells, like macrophages, derived from the hematopoietic lineage. Osteoclasts function in resorption of mineralized tissue and are found attached to the bone surface at sites of active bone resorption. Their characteristic feature is a ruffled edge where active resorption takes place with the secretion of bone-resorbing enzymes, which digest bone matrix.
The main morphological features of bone

- Woven bone -> fibrils 0.1-0.3 µm wide, arranged in a felt
- Parallel-fibred bone -> Intermediate
- Lamellar bone -> Fibrils 2-3µ wide in sheets (lamellae), 2- 10µm thick
- Connected to each other and, indirectly, to blood channels by cell processes in canaliculi 0.2-0.3µm wide. About 50-100 canaliculi per cell.
FIG. 4 Hierarchical structure in human compact bone; individual size scales adapted from refs 28–31. Fibrous, laminar, particulate and porous structure is present at different size scales.

Bone tissue is different from bones:
- **bones are organs** made up of bone tissue as well as marrow, blood vessels, epithelium and nerves
- **bone tissue** refers to the mineral matrix ("mineralized tissue") that forms the rigid sections of the organ.
BONE FORMATION

Crystals of bone mineral form within and between collagen fibrils in a process called “bone mineralization”. The crystals are carbonated hydroxyapatite $[\text{Ca}_5(\text{PO}_4)_3\text{OH}]$ HCA”. The crystals are aligned along the axis of the collagen fibrils and reinforce the collagen matrix to provide a very strong and tough composite.
Two Major Types of Bone Tissue:

1. Cancellous bone (or “trabecular bone”)
   - spongy: made up of individual trabeculae
   - Elastic Modulus = 0.1-4.5 GPa

2. Cortical bone (or “compact bone”)
   - represents nearly 80% of the skeletal mass
   - Elastic Modulus = 17-24 GPa
BONE TISSUE COMPOSITION:

(1) Living cells
- **osteoblasts**: bone-forming cells; produce mineralized collagen matrix
- **osteocytes**: osteoblasts become osteocytes when entrapped in matrix (maintenance)
- **osteoclasts**: bone-adsorbing cells; remove mineralized matrix (“bone resorption”)

Osteoblasts deposit a **matrix of collagen** and release **calcium, magnesium, and phosphate ions**, which chemically combine and harden within the matrix into **carbonated hydroxyapatite** \( \text{[Ca}_5\text{(PO}_4\text{)}_3\text{OH]} \): mineralized connective tissue.

(2) Extracellular Matrix (ECM)
* A **structural component of tissues that is not part of the cell.**
- **collagen fibers** (Type I):
  - **a fibrous structural protein**
  - ~25%
- **carbonated hydroxyapatite**
- **proteoglycans***
- **water** ~20%

*FYI:* - **Proteoglycans**: composed of a protein backbone to which is attached long side chains of negatively charged glycosaminoglycan (GAGs)- long, unbranched polysaccharide units; e.g. GAGs: hyaluronan, chondroitin sulfate, keratan sulfate, heparin, etc
### BONE TISSUE MECHANICAL PROPERTIES

**Tensile Strength (MPa) and % elongation at break of cortical bone from the human femur as a function of age**

<table>
<thead>
<tr>
<th>Property</th>
<th>10 - 20</th>
<th>20 - 30</th>
<th>30 - 40</th>
<th>40 - 50</th>
<th>50 - 60</th>
<th>60 - 70</th>
<th>70 - 80</th>
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<tbody>
<tr>
<td><strong>Ultimate strength (MPa)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension</td>
<td>114</td>
<td>123</td>
<td>120</td>
<td>112</td>
<td>93</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>Compression</td>
<td>-</td>
<td>167</td>
<td>167</td>
<td>161</td>
<td>155</td>
<td>145</td>
<td>-</td>
</tr>
<tr>
<td>Bending</td>
<td>151</td>
<td>173</td>
<td>173</td>
<td>162</td>
<td>154</td>
<td>139</td>
<td>139</td>
</tr>
<tr>
<td>Torsion</td>
<td>-</td>
<td>57</td>
<td>57</td>
<td>52</td>
<td>52</td>
<td>49</td>
<td>49</td>
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<tr>
<td><strong>Ultimate strain (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Compression</td>
<td>-</td>
<td>1.9</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>-</td>
</tr>
<tr>
<td>Torsion</td>
<td>-</td>
<td>2.8</td>
<td>2.8</td>
<td>2.5</td>
<td>2.5</td>
<td>2.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Bone tissue is stronger in **compression** vs. in **tension** (anisotropic)
LONG BONE REPAIR

Long bones
- Are longer than they are wide
- Ends covered with articular cartilage
- Examples: femurs, tibias, fibulas (leg); humeri, radii, ulnas (arm); phalanges and toes
LONG BONE REPAIR

• Bone tissue undergoes spontaneous regeneration and remodeling.

• Accomplished via balance between ostegenic (bone forming) and osteoclastic (bone removing) processes which respond to mechanical environment.

• **Wolff’s Law of Bone Remodeling:**
  - More stress applied → equilibrium shifted to **osteogenic** activity.
  - Less stress applied → equilibrium shifted to **osteoclastic** activity.

• **Goal of long bone fracture treatment:**
  - Stabilize fracture (prevent excessive motion between bone fragments) and allow bone regeneration/remodeling.
LONG BONE REPAIR

Types of Treatments

1. **Non-surgical**: cast

2. **Surgical**
   a. **external fracture fixation**:
      - do not open fracture site
      - bone fragments held together by pins through skin onto skeleton and structurally supported by external bars.
   b. **internal fracture fixation**:
      - open fracture site
      - bone fragments held together by wires, screws, plates, and/or intramedullary devices
INTERNAL FIXATION DEVICES

Bone Plates

Nails/Rods

Pins

Screws
# METALLIC BIOMATERIALS FOR INTERNAL FIXATION DEVICES

<table>
<thead>
<tr>
<th>Material</th>
<th>Properties</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS 316L</td>
<td>Low cost</td>
<td>Surgical wire, pin, plates, screws, IM nails</td>
</tr>
<tr>
<td>Ti Alloy</td>
<td>High cost, Low density and modulus</td>
<td>Surgical wire, plate, screws, IM nails</td>
</tr>
<tr>
<td>Co-Cr Alloys (Wrought)</td>
<td>High cost, High density and modulus</td>
<td>Surgical wire, IM nails</td>
</tr>
</tbody>
</table>
“Osteopenia (reduced bone mass) as a result of removal of normal stress from the bone by an implant”

- Metal fixation device carries too large of a portion of bones load

- Mechanical mis-match (modulus) of metal fixation devices and bone (see Table)

- May be eliminated by use of lower-modulus materials: cp-Ti and Ti-alloys, polymers
<table>
<thead>
<tr>
<th>Material</th>
<th>Density (g/cm³)</th>
<th>Elastic modulus (GPa)*</th>
<th>Yield strength (MPa)</th>
<th>Tensile Strength (MPa)</th>
<th>% Elongation at break</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS 316L 30% cold worked</td>
<td>7.9</td>
<td>190</td>
<td>690</td>
<td>860</td>
<td>12%</td>
</tr>
<tr>
<td>Ti-6Al-4V or ASTM F136 annealed</td>
<td>4.5</td>
<td>114</td>
<td>830</td>
<td>900</td>
<td>14 %</td>
</tr>
<tr>
<td>PLLA</td>
<td>1.3</td>
<td>2.7</td>
<td></td>
<td>50</td>
<td>5 -10%</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>~2</td>
<td>17 - 24</td>
<td>100-230</td>
<td>90-130</td>
<td>1-3%</td>
</tr>
<tr>
<td>Cancellous Bone</td>
<td>~1</td>
<td>0.1 - 4.5</td>
<td>2-12</td>
<td>10-20</td>
<td>5-7%</td>
</tr>
</tbody>
</table>

1 GPa = 10³ MPa = 10⁹ N/m² = 145,038 psi

Hench and Jones, Biomaterials, artificial organs, and TE

*In tension
TOTAL JOINT REPLACEMENT

Why joint replacement?

Joint degeneration is caused by loss/destruction of articular cartilage
- disease (osteoarthritis)
- severe injury/wear

Loss of articular (hyaline) cartilage:
- severe pain, loss of motion, and sometimes angular deformity of the extremity
- Unlike bone, cartilage has very limited capacity for repair

Articular/hyaline cartilage: covers the ends of bones to form the smooth articular surface of joints).
# TOTAL JOINT REPLACEMENT

## Types of Total Joint Replacement

<table>
<thead>
<tr>
<th>Joint</th>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>Ball &amp; socket, “resurfacing”</td>
</tr>
<tr>
<td>Knee</td>
<td>Hinged, semiconstrained, surface replacement</td>
</tr>
<tr>
<td></td>
<td>(Fig. 9.9)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>Ball &amp; socket</td>
</tr>
<tr>
<td>Ankle</td>
<td>Surface replacement</td>
</tr>
<tr>
<td>Elbow</td>
<td>Hinged, semiconstrained, surface replacement</td>
</tr>
<tr>
<td>Wrist</td>
<td>Ball and socket, space filler</td>
</tr>
<tr>
<td>Finger</td>
<td>Hinged, space filler</td>
</tr>
</tbody>
</table>
The hip joint is the largest load-bearing joint. A hip joint is lined with **articular cartilage**: a layer of tissue that provides low-friction and shock-absorbing properties. Arthritis and injury can damage this protective layer of cartilage, causing extreme pain for a patient performing even simple activities.
Hip resurfacing (Birmingham hip resurfacing; BHR)

A relatively new kind of hip replacement in which the ball of the femur is "resurfaced" with a metal shell rather than being removed and replaced. This preserves more of the patient’s own bone and produces a more anatomical load bearing on the femur. The socket is replaced as in a traditional hip replacement procedure, without cement.

An X-ray showing the Birmingham hip in situ

The Birmingham hip resurfacing prosthesis by Midland Medical Technologies
Knee Replacement: Total and Partial
Types of Biomaterials for Total Hip Replacement

**Femoral Stem**
- Ti-alloy (ASTM F136)
- Co-Cr Alloys
- 316L no longer used

**Femoral Ball**
- Co-Cr Alloys
- Alumina
- Zirconia

**Acetabular Cup (Liner)**
- UHMWPE
- Co-Cr Alloys
- Alumina

**Acetabular Cup (Backign)**
- Co-Cr Alloy or none

**Securing or Fixation of Stem and Cup Backing**
- Cementless or Press fit: Ti porous coating allows for bone integration
- Bone cement: PMMA + bioactive glass
Types of Biomaterials for Knee Replacement

**Femoral Component**  
Ti-alloy (ASTM F136)  
Co-Cr Alloys

**Tibial Component**  
Ti-alloy (ASTM F136)  
Co-Cr Alloys

**Patellar Component**  
UHMWPE

**Securing or Fixation of Stem and Cup Backing**  
Cementless or Press fit: Ti porous coating allows for bone integration  
Bone cement: PMMA + bioactive glass
<table>
<thead>
<tr>
<th>Materials Used for Total Joint Replacement</th>
<th>Density (g/cm³)</th>
<th>Hardness, Mohs</th>
<th>Elastic modulus (GPa)</th>
<th>Flexural Strength (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alumina (ASTM F603-78)</strong></td>
<td>3.8-3.9</td>
<td>9</td>
<td>380</td>
<td>&gt; 400</td>
</tr>
<tr>
<td>Stabilized with 3 mol% Y₂O₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grain size = 4 micron</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zirconia</strong></td>
<td>5.95</td>
<td>6.5</td>
<td>190</td>
<td>1000</td>
</tr>
<tr>
<td>Stabilized with 3 mol% Y₂O₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grain size = 0.6 micron</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Haynes-Stellite 21 or ASTM F75</strong></td>
<td>8.3</td>
<td></td>
<td>210</td>
<td>655</td>
</tr>
<tr>
<td>Cast Co-Cr-Mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ASTM-F562 or MP35N</strong></td>
<td>~9.2</td>
<td></td>
<td>232</td>
<td>1210</td>
</tr>
<tr>
<td>Wrought Co-Ni-Cr-Mo-Ti, <em>Hot forged</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ASTM-F562 or MP35N</strong></td>
<td>~9.2</td>
<td></td>
<td>232</td>
<td>1800</td>
</tr>
<tr>
<td>Wrought Co-Ni-Cr-Mo-Ti, <em>Cold worked</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ti-6Al-4V or ASTM F136</strong></td>
<td>4.5</td>
<td>114</td>
<td>830</td>
<td>900</td>
</tr>
<tr>
<td>annealed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UHMWPE</strong></td>
<td>0.94</td>
<td></td>
<td>0.7</td>
<td>39-48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>350-525</td>
</tr>
<tr>
<td><strong>Cortical Bone</strong></td>
<td>--</td>
<td></td>
<td>17 - 24</td>
<td>90-130</td>
</tr>
<tr>
<td><strong>Cancellous Bone</strong></td>
<td>0.1 - 4.5</td>
<td></td>
<td>10-20</td>
<td></td>
</tr>
</tbody>
</table>

*18/08/53, 426620 A4*
Mohs Hardness:
Based on the scale on ten minerals that are all readily available. As the hardest known naturally occurring substance, diamond is at the top of the scale. The hardness of a material is measured against the scale by finding the hardest material that the given material can scratch, and/or the softest material that can scratch the given material. For example, if some material is scratched by apatite but not by fluorite, its hardness on the Mohs scale would fall between 4 and 5.
Osteolysis

- UHMWPE generates wear particles
  - billions to trillions wear particles produced (150,000 per step)
  - Wear rate = 0.1 mm/year
  - most are < 1 micron
  - Wear particles migrate to bone and cause osteolysis

- Osteolysis (rapid bone loss)
  - immune system response to wear particles
  - bone modeling balance upset
    - osteoclasts (bone resorption): increases
    - osteoblasts (bone building)
  - Causes loss of bone, implant loosening

(Courtesy of C. Schwartz, TAMU)
The healthy human knee joint is also lined with articular cartilage. Arthritis and injury can similarly damage this protective layer of cartilage causing extreme pain.
Sterilization of UHMWPE with gamma irradiation in an air-free environment leads to crosslinking and subsequent improved wear-resistance.

Graph demonstrating a **90 % reduction** in wear (measured by weight loss) at 5 million cycles (~5 years normal wear) based on hip simulator studies.

http://www.orthoassociates.com/Totalhip2.htm
Bone remodelling

- Remodeling is the replacement of old bone tissue by new bone tissue which mainly occurs in the adult skeleton to maintain bone mass. This process involves the coupling of bone formation and bone resorption and consists of five phases:
  - activation: preosteoclasts are stimulated and differentiate under the influence of cytokines and growth factors into mature active osteoclasts
  - resorption: osteoclasts digest mineral matrix (old bone)
  - reversal: end of resorption
  - formation: osteoblasts synthesize new bone matrix
  - quiescence: osteoblasts become resting bone lining cells on the newly formed bone surface
First Generation Implants

- “ad hoc” implants
- specified by physicians using common and borrowed materials
- most successes were accidental rather than by design

Examples — First Generation Implants

- gold fillings, wooden teeth, PMMA dental prosthesis
- steel, gold, ivory, etc., bone plates
- glass eyes and other body parts
- dacron and parachute cloth vascular implants
Intraocular Lens

3 basic materials - PMMA, acrylic, silicone
Vascular Grafts
Second generation implants

- engineered implants using common and borrowed materials
- developed through collaborations of physicians and engineers
- built on first generation experiences
- used advances in materials science (from other fields)

Examples — Second generation implants

- titanium alloy dental and orthopaedic implants
- cobalt-chromium-molybdenum orthopaedic implants
- UHMW polyethylene bearing surfaces for total joint replacements
- heart valves and pacemakers
Artificial Hip Joints

http://www.totaljoints.info/Hip.jpg
Third generation implants

- bioengineered implants using bioengineered materials
- few examples on the market
- some modified and new polymeric devices
- many under development

Example - Third generation implants

- tissue engineered implants designed to regrow rather than replace tissues
- Integra LifeSciences artificial skin
- Genzyme cartilage cell procedure
- some resorbable bone repair cements
- genetically engineered “biological” components (Genetics Institute and Creative Biomolecules BMPs)
Substitute Heart Valves
# Mechanical properties of bioceramics

<table>
<thead>
<tr>
<th>Bioceramics</th>
<th>Flexural strength (MPa)</th>
<th>Elastic modulus (GPa)</th>
<th>Hardness (GPa)</th>
<th>Fracture toughness (MPam$^{1/2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical bone</td>
<td>50-150</td>
<td>7-30</td>
<td>-</td>
<td>2-12</td>
</tr>
<tr>
<td>Human tooth enamel</td>
<td>8-35</td>
<td>9-90</td>
<td>3.2-4.4</td>
<td>0.52-1.3</td>
</tr>
<tr>
<td>Human tooth dentin</td>
<td>31-104</td>
<td>11-20</td>
<td>0.25-0.8</td>
<td>2.8-3.1</td>
</tr>
<tr>
<td>Sintered HA</td>
<td>115-120</td>
<td>80-110</td>
<td>500(HV)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sintered Zirconia</td>
<td>840</td>
<td>220</td>
<td>12</td>
<td>7.4</td>
</tr>
<tr>
<td>Glass-ceramic</td>
<td>-</td>
<td>70.5</td>
<td>4.15</td>
<td>1.04</td>
</tr>
<tr>
<td>Feldspathic porcelain</td>
<td>95</td>
<td>60</td>
<td>-</td>
<td>0.9</td>
</tr>
<tr>
<td>Alumina bioceramics</td>
<td>595</td>
<td>400</td>
<td>2300 (HV)</td>
<td>5-6</td>
</tr>
</tbody>
</table>
Evolution of Biomaterials

Structural

Soft Tissue Replacements

Functional Tissue Engineering Constructs
Compositions and shapes of bioceramics

- Calcium phosphate group
  - Hydroxyapatite (HAp or HA, Ca$_5$(PO$_4$)$_3$OH): sintered body, powder, coating, composite, fiber
  - $\beta$-tricalcium phosphate ($\beta$-TCP, Ca$_3$(PO$_4$)$_2$): sintered body and powder
  - Other powders -> DCPA (CaHPO$_4$), DCPD (CaPO$_4$.2H$_2$O), CPP (Ca$_2$P$_2$O$_7$), $\alpha$-TCP, TeCP (Ca$_4$(PO$_4$)$_2$O), OCP (Ca$_8$H$_2$(PO$_4$)$_6$.5H$_2$O), ACP (Ca$_3$(PO$_4$)$_2$nH$_2$O)
Types of bioceramics

- Alumina: Biolox, Biolox® Delta (alumina matrix composite), Biolox® Forte
- Zirconia: Y-TZP
- Bioactive glass
Processing of zirconia femoral head

Cold isostatic pressing
Of 3Y-TZP powder

Natural sintering

Low temp.
Hot isostatic pressing

Whitening

Grinding
Polishing

Drilling of the bore
chamfers

Laser marking
And
sterilisation
Clinical applications of bioceramics

- Maxillofacial, ear, nose and throat applications
- Vertebral body prosthesis
- Intervertebral spacer for the lumber spine

Bioactive glass granules and plates (BonAlive™) for Bone cavity filling and reconstruction. Copyright Vivoxid Ltd.

Bone substitutes of AW-GC in various shapes
Other bioceramics

- Yttria-stabilized tetragonal zirconia (Y-TZP): sintered body
- Alumina (Al₂O₃): sintered body
- Titania (TiO₂)
- Silicon nitride (Si₃N₄)
- Silicon carbide (SiC)
- Carbon fiber
- Bioactive glasses system: bulk
- Bioactive glass-ceramics system: bulk and fibers
Bioactive glasses system

- $\text{SiO}_2\cdot\text{P}_2\text{O}_5\cdot\text{Na}_2\text{O}\cdot\text{CaO}$
- $\text{SiO}_2\cdot\text{P}_2\text{O}_5\cdot\text{Na}_2\text{O}\cdot\text{K}_2\text{O}\cdot\text{CaO}\cdot\text{MgO}$
- $\text{SiO}_2\cdot\text{P}_2\text{O}_5\cdot\text{CaO}\cdot\text{Al}_2\text{O}_3$
Bioactive glass-ceramics system

- $\text{SiO}_2\cdot\text{P}_2\text{O}_5\cdot\text{CaO}\cdot\text{MgO}$ (A-W)
- $\text{SiO}_2\cdot\text{P}_2\text{O}_5\cdot\text{Na}_2\text{O}\cdot\text{K}_2\text{O}\cdot\text{CaO}\cdot\text{MgO}$ (Ceravital): fiber
AW-glass ceramics

Chemical composition (%wt)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MgO</td>
<td>4.6</td>
</tr>
<tr>
<td>CaO</td>
<td>44.9</td>
</tr>
<tr>
<td>SiO₂</td>
<td>34.2</td>
</tr>
<tr>
<td>P₂O₅</td>
<td>16.3</td>
</tr>
<tr>
<td>CaF₂</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 26.2 Mechanical properties of bone and ceramics

<table>
<thead>
<tr>
<th></th>
<th>Bending strength (MPa)</th>
<th>Compressive strength (MPa)</th>
<th>Elastic modules (GPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural bone</td>
<td>30–190</td>
<td>90–230</td>
<td>3.8–17</td>
</tr>
<tr>
<td>Synthesized hydroxyapatite</td>
<td>110–170</td>
<td>500–900</td>
<td>35–120</td>
</tr>
<tr>
<td>AW glass-ceramic</td>
<td>200–220</td>
<td>1000</td>
<td>120</td>
</tr>
<tr>
<td>Alumina polycrystal</td>
<td>300–400</td>
<td>2500–3000</td>
<td>350–380</td>
</tr>
</tbody>
</table>

Table 26.3 Apatite formation on the surface of bioactive ceramics soaked in simulated body fluid (SBF) (36.5°C)

<table>
<thead>
<tr>
<th>Ceramics</th>
<th>Apatite formation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioglass</td>
<td>1</td>
</tr>
<tr>
<td>AW-GC</td>
<td>5–7</td>
</tr>
<tr>
<td>KGS (Ceravital)</td>
<td>7</td>
</tr>
<tr>
<td>TCP</td>
<td>(14)</td>
</tr>
<tr>
<td>HA</td>
<td>28</td>
</tr>
</tbody>
</table>
Advances in Biomaterials Technology

• Cell matrices for 3-D growth and tissue reconstruction
• Biosensors, Biomimetic, and smart devices
• Controlled Drug Delivery/Targeted delivery
• Biohybrid organs and Cell immunoisolation
  – New biomaterials - bioactive, biodegradable, inorganic
  – New processing techniques
BIOMATERIALS

Polymers

Metals

Ceramics

Semiconductor Materials

Synthetic

Drug Delivery Devices

Orthopedic screws/fixation

Dental Implants

Implantable Microelectrodes

Biosensors

Skin/cartilage

Ocular implants

Bone replacements

Heart valves

Orthopedic screws/fixation

Dental Implants

Implantable Microelectrodes

Biosensors
Biomaterials for Tissue Replacements

- Bioresorbable vascular graft
- Biodegradable nerve guidance channel
- Skin Grafts
- Bone Replacements
SEM displaying the cross section of a composite disk, which had been seeded with cultured bone marrow stromal cells.
... in the shape of a nose (left) is "seeded" with cells called chondrocytes that replace the polymer with cartilage over time (right) to make a suitable implant.
Biomaterials - An Emerging Industry

• Next generation of medical implants and therapeutic modalities
• Interface of biotechnology and traditional engineering
• Significant industrial growth in the next 15 years -- potential of a multi-billion dollar industry
Biomaterials Companies

- **BioForma Research & Consulting, Inc.**, fibrinolytic systems, protein-material interactions
- **Baxter International** develops technologies related to the blood and circulatory system.
- **Biocompatibles Ltd.** develops commercial applications for technology in the field of biocompatibility.
- **Carmeda** makes a biologically active surface that interacts with and supports the body's own control mechanisms.
- **Collagen Aesthetics Inc.** bovine and human placental sourced collagens, recombinant collagens, and PEG-polymers.
- **Endura-Tec Systems Corp.** bio-mechanical endurance testing of stents, grafts, and cardiovascular materials.
- **Howmedica** develops and manufactures products in orthopaedics.
- **MATECH Biomedical Technologies**, development of biomaterials by chemical polymerization methods.
- **Medtronic, Inc.** is a medical technology company specializing in implantable and invasive therapies.
- **Molecular Geodesics Inc.**, biomimetic materials for biomedical, industrial, and military applications.
- **Polymer Technology Group** is involved in the synthesis, characterization, and manufacture of new polymer products.
- **SurModics**, offers PhotoLink(R) surface modification technology that can be used to immobilize biomolecules.
- **W.L. Gore Medical Products Division**, PTFE microstructures configured to exclude or accept tissue ingrowth.
- **Zimmer**, design, manufacture and distribution of orthopaedic implants and related equipment and supplies.
What are some of the Challenges?

• To more closely replicate complex tissue architecture and arrangement *in vitro*

• To better understand extracellular and intracellular modulators of cell function

• To develop novel materials and processing techniques that are compatible with biological interfaces

• To find better strategies for immune acceptance
Biological Responses and Biocompatibility
What happens when a foreign object enters the body?
normal tissue healing

foreign body removed/dissolved/digested

chronic inflammation

fibrous encapsulation

seconds-minutes

months-years

weeks
What determines the outcome?

- Whether the foreign body can be digested or degraded
- Foreign body size
  - Can it be phagocytosed?
- Surface chemistry
  - Different materials preferentially adsorb different proteins, or none at all (non-fouling)
  - Presence of bioactive molecules (bacterial cell wall, tissue engineering scaffold)
Fibrous encapsulation

- Granulation tissue formation
- Collagen fiber deposition
- Angiogenesis
  - < 1 day
  - 1-5 days
  - Weeks
  - 4-6 weeks
- Scar tissue remodeling
Example: Birdshot Left in the Body

Not digestible or degradable, so pellet stays in tissue

Too large to phagocytose, so no frustrated phagocytosis

Birdshot is walled off from the body by fibrous tissue
Chronic Inflammation

- < 1 day
- days-months
- months-years

Granuloma - mass of macrophages and FBGCs

Macrophages cannot clear material - frustrated phagocytosis

Foreign body giant cells form from merged macrophages and monocytes
Example: Wear-Mediated Osteolysis

- Wear particles
- Opsonization
- Phagocytosis
- Osteolysis
- Disrupted balance between osteoclasts/PMNs and osteoblasts: osteoclasts ↑, osteoblasts ↓

http://academic.brooklyn.cuny.edu/biology/bio4fv/page/aviruses/cellular-immune.html

Archibeck, MJ; Jacobs, JJ; Roebuck, KA; Glant, TT. Journal of Bone & Joint Surg, 2000
Biocompatibility

The ability of a material to perform with an appropriate host response in a specific application

Ratner, *Biomaterials Science*, 2004
## FDA Guidelines for Biocompatibility Testing of Permanent Implant Devices

<table>
<thead>
<tr>
<th></th>
<th>Tissue/bone</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytotoxicity (toxicity to cells)</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Sensitization (induced allergic response)</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Irritation or Intracutaneous Reactivity</strong></td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td><strong>Acute Systemic Toxicity</strong></td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td><strong>Sub-Chronic Toxicity (24 hours to 10% of lifespan)</strong></td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td><strong>Genotoxicity (exposure changes cells’ DNA)</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Implantation</strong></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Hemocompatibility</strong></td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>

X = ISO evaluation test  
O = additional tests may be applicable  

Cellular response to bioactive ceramics

- Dissolution from the ceramic
- Precipitation from solution onto the ceramic
- Ion exchange and structural rearrangement at the surface-tissue interface
- Interdiffusion from the surface boundary layer into the ceramic
- Solution-mediated effects on cellular activity
- Deposition of either the mineral phase or the organic phase (without integration into the ceramic surface)
- Chemotaxis to the ceramic surface
- Cell attachment and proliferation
- Cell differentiation
- Extracellular matrix formation
Imaging techniques for ceramics

- X-ray diffraction
- Auger electron spectroscopy (AES): elemental analysis -> reaction stages on the bioglass interface, CaP formation on the surface of bioglass
- X-ray photoelectron spectroscopy (XPS): chemical composition, chemical bonding states (or oxidation state), electronic structure of the surface
- Secondary ion mass spectroscopy (SIMS)
- TEM, SEM
- FT-IR: molecular analysis of bulk and surface of materials
- NMR: the structure change in the phase transition, formation or growth of crystalline phase from colloids, glass or gels.
Apatite layer formation

7.2 TEM picture of apatite layer formed at interface between sintered hydroxyapatite (HA) and tibial bone of rat, 10 weeks after implantation (Neo et al., 1992).

7.3 SEM picture of apatite layer formed on a CaO-SiO₂ glass after soaking in SBF for 20 days (Ebisawa et al., 1990).
What types of materials form apatite?

7.6 Apatite formation induced on various metal oxide gels in SBF (Li et al., 1992, 1994; Miyazaki et al., 2001a, 2001b; Uchida et al., 2001).
Mechanisms of apatite formation

7.7 Schematic representation of mechanism of apatite formation on the sintered hydroxyapatite in SBF (Kim et al., 2004).
Osteoconduction

• Bone graft healing process
• Graft incorporation by the host
• Apparent growth of bone tissue ‘along’ an implant’s surface
• Opposed to osteoinduction
Mechanism of osteoconduction

- Bone ingrowths into porous or tube-shaped implants.
- A population of migratory capillaries → fibrovascular tissues → osteogenic cells → new bone formation
- Osteogenic cells need matrix or scaffold and blood supply from the surrounding tissue → bone growth → bone conduction
Osteoconductivity of biomaterials

- Surface chemistry
- The surface topography (smooth/rough)
- Architectural geometry (porous 100-400 µm)
Monitoring osteoconduction

- Bone ingrowth and apposition
- Bone histomorphometric methods: optical microscope
- Incident-light fluorescence microscopy
- SEM

8.1 Histological observation of bone ingrowth using various methods. Optical microscope photographs (a and c), incident-light fluorescence microscopic photographs (b and d), and a BSE-SEM photograph (e) of histological slides of porous titanium implanted into rabbit femoral condyle for a period of 6 weeks. Here (a, b) = untreated porous titanium; (c, d, e) = chemically and thermally treated porous titanium. The scale bar = 1000μm. The stain used in a–d was Stevenel’s blue and von Gieson’s microfuchsin. The apparent growth of bone ‘along’ the implant surface (oste-conduction) can be seen in the chemically and thermally treated porous titanium (c, d, e), while it is less evident in the untreated porous titanium (a, b). A comparison of the optical microscopy (a, c), incident-light fluorescence microscopy (b, d), and BSE-SEM microscopy (e) is more accurate in evaluating bone-implant contact.
Approaches to encourage osteoconsuction

- Coat the implant surface with various calcium phosphate: plasma-sprayed HA coating
- Biomimetic coating
- Surface topography
Osteoinduction by BMPs (bone morphogenetic protein)

1. Mesenchymal stem cells
2. Chondroblasts and chondrocytes
3. Cartilage formation
4. Cartilage maturation and calcification
5. Osteoblasts and osteoclasts
6. Calcified cartilage resorption
7. Bone formation
8. Bone marrow
9. Bone remodelling

9.1 Sequence of events in endochondral bone formation.
Solid-shaped bioactive glass (S53P4) has been used in the treatment of facial injuries to replace the bone that supports the eye (BonAlive TM plate)

Copyright Vivoxid Ltd.
Large giant cell tumor

Large giant cell tumor developed in the right ilium of a 27-year-old female

Radiograph indicating a clear line between implanted HA and the pelvic bone (8 months after surgery)

(12 months after surgery)
Vertebral prosthesis

Radiographic changes around the AW-GC vertebral prosthesis which was used to replace a metastasis of alveolar soft part sarcoma developed in the third lumbar vertebra of a 13-year-old female.
Intervertebral spacer for the lumbar spine

26.13 Intervertebral spacer of AW-GC.

26.14 Isthmic spondylolisthesis developed between the third and fourth lumbar vertebra in a 40-year-old male.

26.15 AW-GC spacers fixed to the adjacent vertebral bodies above and below by the use of the spinal instruments in the case of Fig. 26.14.
Clinical application of HA

27.4 Bone growth on HA (100–300 μm) at 6 weeks. Spaces less than 20 μm are filled with new bone. Backscattered SEM.
Quantitative comparison of bone growth behavior into HA granule mass with other surface-bioactive ceramics

27.24 The bone ingrowth rate was calculated by the measurements of the area of new bony tissue in the implanted area. New bony tissue is shown as the White area on the figures on the right hand side.
Bioceramics as scaffolds for tissue engineering

- ‘culture bone’: continuous new bone formation after in vivo implantation → direct bone contact without fibrous tissue intervening between thus formed bone and ceramic surface.

30.1 Schematic representation of marrow cells or MSCs /hydroxyapatite ceramic composite. About 4 weeks after the subcutaneous implantation, de novo bone formation (arrows in right figure) on ceramic (asterisks) pore areas can be observed.

30.2 SEM of subcutaneous implantation of marrow/hydroxyapatite ceramic composite. Backscattered electron image which displays no intervening soft tissue (black area) between bone (gray area) and alumina ceramic (white area), indicating bone bonding to the ceramic surface. Reprinted from Biomaterials (1991), 12, 411–416 ‘Bonding osteogenesis in coralline hydroxyapatite combined with bone marrow cells’ by Okumura M., Ohgushi H. and Tamai S. with permission from Elsevier.
Mesenchymal stem cells (MSCs)

Stem cell transplant using a patient’s own cells

The patient’s stem cells are extracted from the patient.

The patient’s stem cells are used to grow compatible tissue in the lab.

The compatible tissue is re-transplanted into the patient restoring organ function.
Mesenchymal Stem cells
Tissue engineering approach

30.5 Schematic representation of *in vitro* bone formation (upper figure) and *in vivo* bone found in histological section (lower figure) of marrow/hydroxyapatite ceramic composite at subcutaneous sites.
Fabrication of tissue engineered alumina ceramic implants

In vitro cultured bone formation on alumina ceramics

30.10 Schematic representation of fabrication of tissue engineered alumina ceramic implants. After expansion of MSCs from patients fresh marrow (A to B), the culture expanded MSCs were seeded on alumina ceramics (C). The seeded MSCs could undergo in vitro osteogenic differentiation, resulted in cultured bone formation (D). Upper figure is reprinted from Biomaterials (2005), 26, 4654–4661 ‘Tissue engineered ceramic artificial joint’ by Ohgushi H. et al. with permission from Elsevier.
in vivo performance of in vitro fabricated cultured bone after its implantation in bone defect

30.11 Schematic representation of in vivo performance of in vitro fabricated cultured bone after its implantation in bone defect. Tissue engineered alumina implants (D; implants having culture bone) can show new bone formation after implantation (F). The new bone well integrates with bone from host origin, resulting in firm bone union (G). Upper figure is reprinted from Biomaterials (2005), 26, 4654–4661 ‘Tissue engineered ceramic artificial joint’ by Ohgushi H. et al. with permission from Elsevier.
FDA & ISO 10993

- FDA mandates tests based on length of contact (24 Hr, 1-30 Days, >30 days)
- See table for details
- ISO 10993 – required for European Union Certification – see flowchart for exemptions
- See Device Categories & examples
- Harmonization – in process…