Biomaterials

IIT-K REACH Symposium 2007

Theme: Materials of Tomorrow

Dhirendra S. Katti

Dept. of Biological Sciences and Bioengineering (BSBE)

IIT-Kanpur

What is Biomaterial Science ?

"**Biomaterial Science**" is the physical and biological study of materials and their interactions with the biological environment.

What are Biomaterials ?

- A **biomaterial** is a nonviable material used in a medical device, intended to interact with biological systems (Williams, 1987)
- If the words "**nonviable**" (incapable of growing and developing independently) or "**medical**" are removed, the definition becomes broader and can encompass a wide range of applications

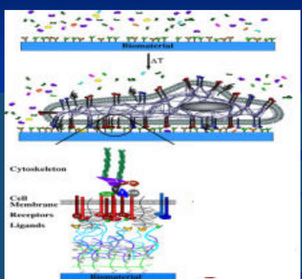
Williams, D.F., Proceedings of a Consensus Conference of the European Society for Biomaterials, Chester, England, March 3-5, 1987.

What is Biocompatibility ?

- **Biocompatibility** is the ability of a material to perform with an appropriate host response in a specific application (Williams, 1987)
- "**appropriate host response**"
  - resistance to blood clotting (eg. hemodialysis membrane – in contact with the patients blood for 3 hrs.),
  - resistance to bacterial colonization (eg. urinary catheter – may be inserted for a week or hip-joint replacement prosthesis – may be for the life of the patient), and
  - normal, uncomplicated healing (eg. tissue engineering applications).

Williams, D.F., Proceedings of a Consensus Conference of the European Society for Biomaterials, Chester, England, March 3-5, 1987.

Cell Biomaterial Interaction



Design Considerations

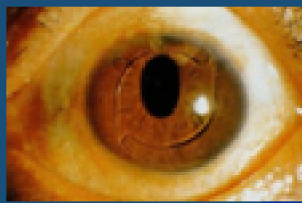
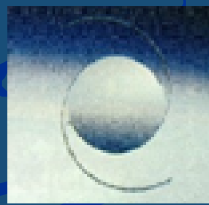
- The "**bulk**" and "**surface**" properties of biomaterials used for medical implants have been shown to directly influence, and in some cases, control the dynamic interactions that take place at the tissue-implant interface.
- These characteristics and the **changes in these characteristics** that may take place over time ***in vivo*** should be known for designing biomaterials for specific applications,
  eg. Cardiovascular (flowing blood contact), Orthopaedic (functional load bearing).

Some examples of "Biomaterials"

Intraocular Lens

Basic materials – PMMA (Acrylic), Silicone

Challenges – Combining long term biocompatibility with optical properties

Vascular Grafts

Basic Material: Polyurethane, Teflon & Dacron

Challenges: Maintenance of mechanical integrity

Long term blood compatibility (avoidance of blood clotting).

Artificial Hip Joints

Basic material: Stainless Steel, titanium and its alloys, and UHMWPE.

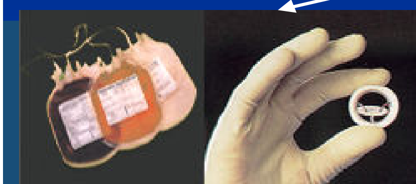
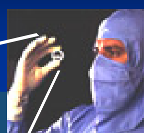
Challenges: Prevention of wear & loosening over extended periods (10-15 yrs.).

http://www.totaljoints.info/Hip.jpg

Substitute Heart Valves



Indian - Chitra Heart Valve

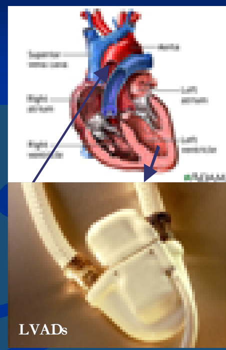



Chitra Heart Valve – What Material

- The disc which is tiltably mounted has to flutter more than **115,000 times per day** in a normal person having 72 to 80 beats per minute (translates to the disc opening and closing **40 million times a year** at an average), causing **tremendous strain** on the material. Therefore, the material used should be extremely durable in terms of **wear resistance and fatigue strength**.
- A valve may have to operate inside the human body up to 25 years or more which necessitates the material to have excellent **chemical and structural stability**.
- The **bio-compatibility** (both tissue compatibility and blood compatibility) of the material is also a major requirement.
- Finally the material should be **processable** to achieve the required surface finish and dimensional stability
- UHMWPE has all the advantageous properties such as durability, longevity, high stress resistance, wear resistance, tissue and blood compatibility, fatigue strength, and toughness

Ventricular Assist Device (VADs)

- VADs that can be considered as one half of a total artificial heart, have evolved from a daring experimental concept to a life-prolonging tool.
- They are now used to maintain a patient with a failing heart while waiting for a heart transplantation.
- **Challenges**:
  - maintain proper electro-mechanical functioning
  - prevention of infection and clotting of blood



http://www.worldheart.com/products/novacor_lvas.cfm

BIOMATERIALS

METALS | POLYMERS | CERAMICS

COMBINATIONS both
WITHIN A CLASS & BETWEEN CLASSES

BASIC SCIENCES

ENGINEERING SCIENCES

Biomaterials
A multidisciplinary science

MEDICAL SCIENCES

From IDEA → To → PATIENT !!

ACTION	FACILITATOR
Identify a need	Clinician / Researcher / Inventor
Device design	Clinician / Engineer
Material synthesis	Materials Scientist
Materials testing	Materials Scientist / Bioengineer / Veterinarian
Fabrication	Engineer / Machinist
Device testing	Bioengineer / Clinician / Regulatory Agency
Clinical Use	Clinician
Explant analysis	Pathologist / Bioengineer

Personal Research

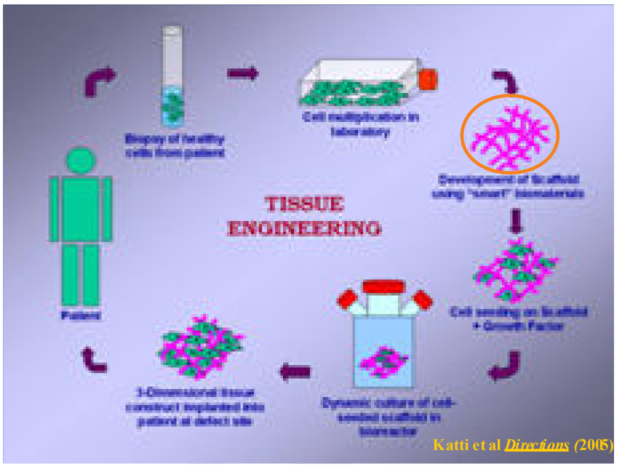
Biomaterials

- Tissue Engineering Applications
- Drug Delivery Applications

Tissue Engineering

Tissue engineering is an interdisciplinary field that applies the **principles** of **engineering** and **life sciences** toward the development of **biological substitutes** that restore, maintain or improve tissue function.

Langer et al., *Science*, 260 (1993)



Katti et al *Directions* (2005)

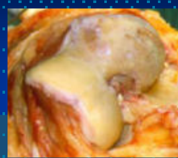
Our Approach

Development of a Nanofiberous scaffold for cartilage tissue engineering

Major unmet medical need

Cartilage damage

Age
Weight
Genetics
Trauma



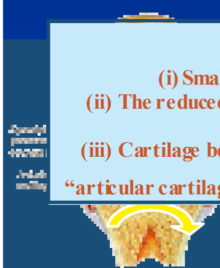
Osteoarthritis

- More than **43 million** people have some form of arthritis.
- OA affecting over 10% of the USA population
- OA will inflict 70-100 million Indians (~ 10% of population)
- **No effective treatment today** !!!!

www.boneandjointdecade.org

Articular Cartilage Biology

Dense connective tissue that forms the load bearing surfaces of synovial joints



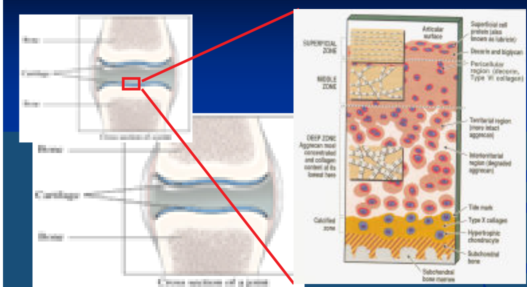
Because of

(i) Small quantity of chondrocyte
(ii) The reduced availability of progenitor cells in the local environment
(iii) Cartilage being a avascular and alymphatic tissue

"articular cartilage has limited capacity to regenerate"

Brighton CT edt. *Clinical orthopaedics and related research*, 2001

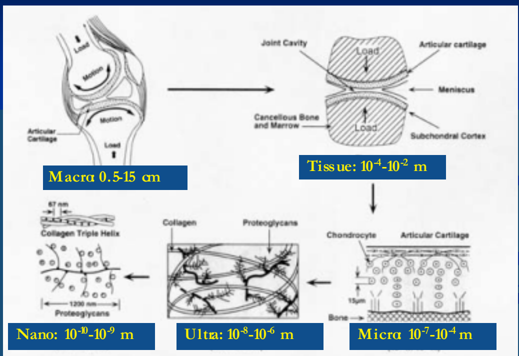
Articular Cartilage



- A tough, elastic, fibrous connective tissue
- Avascular, Aneural, alymphatic tissue

Brighton CT edt. *Clinical Orthopaedics and Related Research*, 2001

Hierarchical Structure of Cartilage: Collagen fibers have nanometer dimensions



Molecular and fibrillar structure of collagen

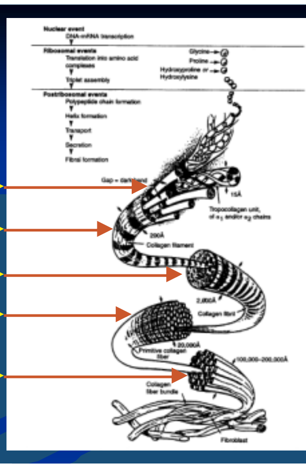
15 °A = 1.5 nm

Filament 200 °A = 20 nm

Fibril 2,000 °A = 200 nm

Primitive Fiber 20,000 °A = 2000 nm or 2 µm

Fiber bundle 100,000 - 200,000 °A = 10-20 µm

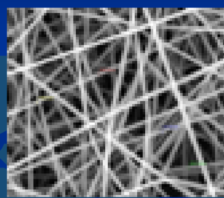


Hypothesis

We hypothesize that **fibers** made from biodegradable and biocompatible polymers such as poly(lactide-co-glycolide) (PLAGA) **that have nanometer dimensions will mimic the collagen fibrils present in native human tissue** and that these polymeric nanofibers **can be engineered into porous three-dimensional (3-D) scaffolds** that are appropriate for tissue engineering.

Development of Nanofiberous scaffold for cartilage tissue engineering

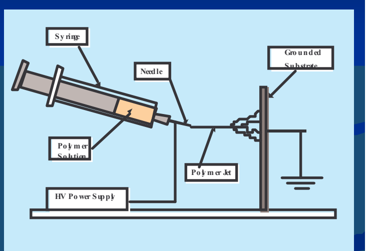
- Mimics natural ECM composition
- High porosity
- Higher surface area for cell adhesion
- Better mechanical strength
- **Synthesis of Nanofiber: Electrospinning**
- Biomaterials: Poly (l-lactic acid), poly (lactide-co-glycolide), chitosan.



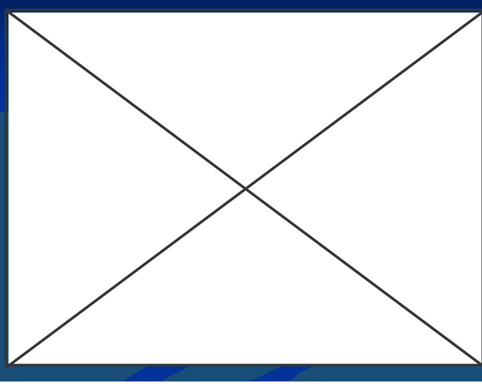
Nanofiber Fabrication

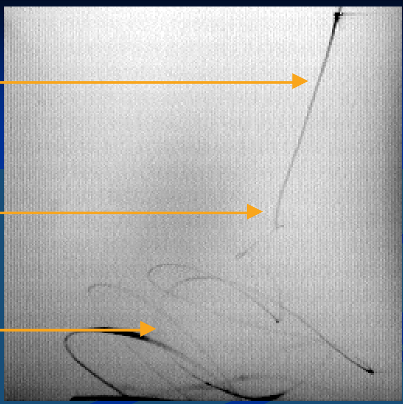
Electrospinning

High electrical potential applied to a polymer solution to cause jet formation that progressively thins to form nanofibers

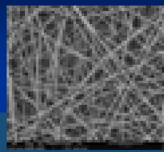


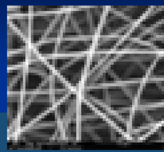
Electrospinning



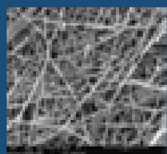


Examples of Nanofibers


Poly(lactic acid)


Poly(styrene)

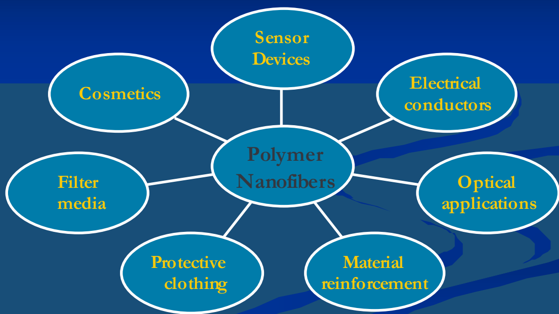

Poly(lactide-co-glycolide)


Poly(lactide-co-glycolide) & Poly(vinyl alcohol)


Poly(styrene) – Aligned


Poly(styrene) – Aligned

Possibilities



Personal Research

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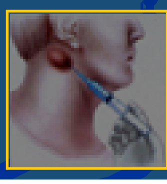
Biomaterials

Tissue Engineering Applications

Drug Delivery Applications

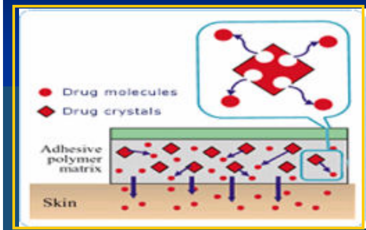
Drug Delivery Systems

- Formulation or device that delivers therapeutic agent(s) to desired body location(s) and/or provides timely release of therapeutic agent(s).
- The system, on its own, is not a therapy, but improves the efficacy and/or safety of the therapeutic agent(s) that it carries.



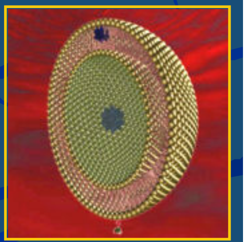
http://www.drugdel.com/

Drug Delivery Systems



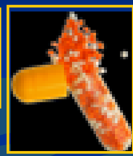
Transdermal Drug Delivery

Liposomes



Conventional Approaches of drug administration

- Oral (pills, tablets)



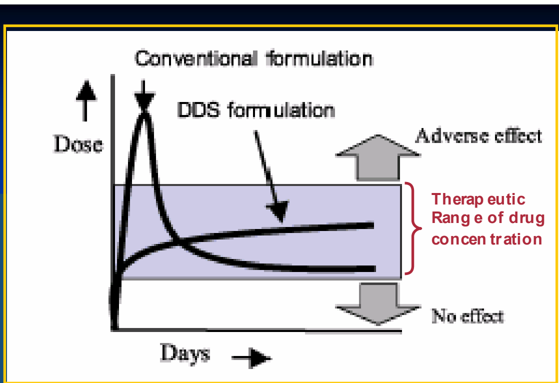
- Injection of solublized drug (intravenous/intramuscular/subcutaneous)

Disadvantages

- Rapid breakdown of the drug *in vivo*.
- Hydrophobic drugs may precipitate in aqueous media.
- Unfavorable pharmacokinetics.
- Poor biodistribution – dose limiting side effects.
- Lack of selectivity for target tissues.

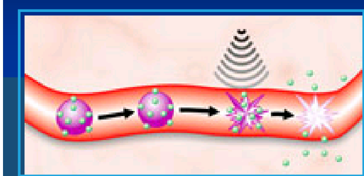
Possible Solution

- Drug delivery systems
  - Maintenance of optimum therapeutic drug concentration (Improved bioavailability).
  - Predetermined release rates for extended periods of time.
  - Elimination of side effects and frequent dosing– hence providing optimized therapy.
  - Better patient compliance.



Drug release kinetics

Drug Delivery Systems

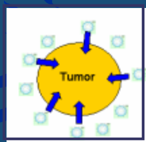


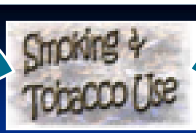
Target Specific

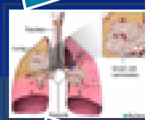
Duration specific

Our Research

Development of intratumoral drug delivery system for the treatment of lung cancer







Lung cancer is the leading cause for cancer related deaths not only in India, but in rest of the world too!!

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Disadvantages of Systemic Chemotherapy

- Low bioavailability at target site
- Side effects
- High Cost

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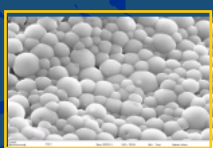
Intratumoral Chemotherapy

- Enhances antitumor activity by focusing therapy at the tumor site.

Proposed Intratumoral Chemotherapy: Polymer based, micro/nanoparticle

Importance of nanocarriers

- Blood vessels and cells have diameter in range of 500nm- 20µm.
- Nanoscale carriers offer advantage of easy cell and tissue uptake.
- High surface area to volume ratio.



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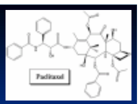
http://www.csir.co.za/websource/ptl0002/ima ges/m&mtek/cpt/nano particles

Combination Chemotherapy

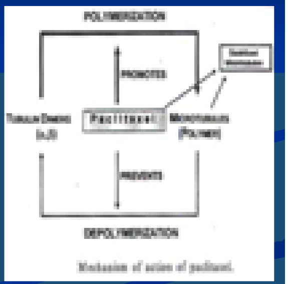
- Tumor cell death in a heterogenous tumor cell population can be achieved in a more effective way when drugs working on different principles

Proposed Combination Chemotherapy – Paclitaxel and Topotecan

Paclitaxel



- Paclitaxel is a microtubule interfering agent which antagonizes the disassembly of β-tubulin.
- Mitotic arrest follow in G2M phase of cell cycle.
- A portion of these arrested cells undergo apoptosis, remainder portion of non-lethally injured cells move forward in the cell-cycle after a period of latency.



Topotecan

- A camptothecin analog
- Topotecan binds to the topoisomerase I-DNA complex and prevents re-ligation of these single strand breaks.
- The cytotoxicity of topotecan is due to irreversible double strand DNA damage produced during DNA synthesis.

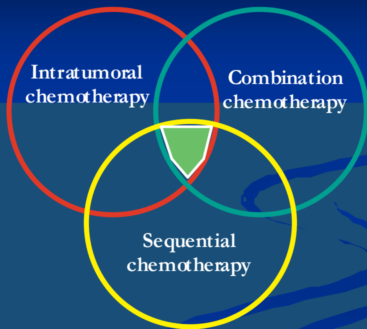
Sequential Chemotherapy

- In many cases of combination chemotherapy,

Proposed Sequential Chemotherapy:

- Paclitaxel : 3-5 hours
- Drug free incubation period : 17-19 hours
- Topotecan : 5 days
  - Cost-effective treatment

Our Approach



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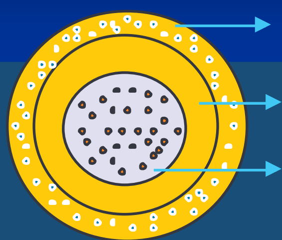
Hypothesis

- We hypothesize that *sequential delivery* of paclitaxel and topotecan using a *polymeric particulate delivery system* when administered *intratumorally* will lead to better permeability into the tumor, higher local concentration of the drugs and better toxicity profile.
- We further hypothesize that this delivery system will eventually provide for *improved loco-regional control* and hence *increased survival rates* of lung cancer patients.

Schematic of proposed model of sequential drug delivery system



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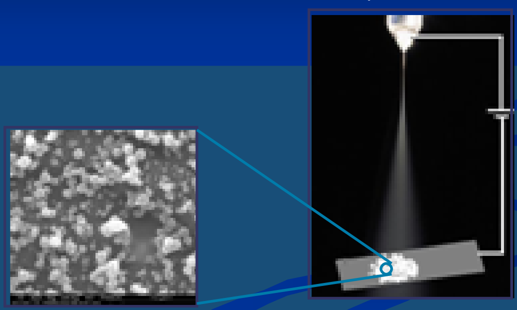
Electrospraying



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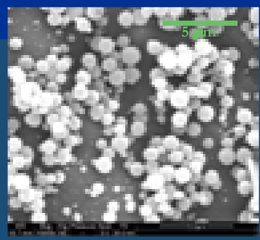
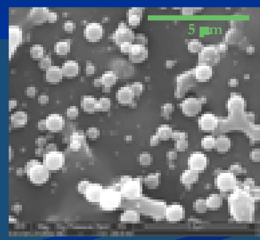
Synthesis of chitosan micro/nanospheres by electrospraying.





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Possibilities

- **Diagnostic** – Micro/nanoparticles tagged with antibodies that can detect specific antigens in body fluids such as urine and blood as well as in cell culture.
  - **Portable, simple, fast, specific and quantitative.**
- **Magnetic** – Contrast vehicle for MRI
- **Thermal** - Improve efficiency of coolants by suspending metallic nanoparticles in the heat transfer fluids.
- **Electronic** – Langmuir-Blodgett films of nanoparticles.

http://www.malvern.co.uk; 1. Kelly *et al.* J. Phys. Chem (2003); 2. Mulder *et al.* NMR Biomed (2006); 3. Choi *et al.* (1996); 4. Paul *et al.* Nano Lett (2003).

Future of Biomaterials

- An appropriate combination of **engineers**, **clinicians** and **basic science researchers** will pave the way for the development of better **biomaterials** and hence (medical) devices that will help improve the quality of life of humans.

Thanks to

- Rajesh Vasita
- Neha Arya

Thank you for your attention !!

Department of Biological Sciences & Bioengineering,
Indian Institute of Technology - Kanpur

Some Commonly used Biomaterials

Material	Applications
Silicone rubber	Catheters, tubing
Dacron	Vascular grafts
Cellulose	Dialysis membranes
Poly(methyl methacrylate)	Intraocular lenses, bone cement
Polyurethanes	Catheters, pacemaker leads
Hydogels	Opthalmological devices, Drug Delivery
Stainless steel	Orthopedic devices, stents
Titanium	Orthopedic and dental devices
Alumina	Orthopedic and dental devices
Hydroxyapatite	Orthopedic and dental devices
Collagen (reprocessed)	Opthalmologic applications, wound dressings

Application	Types of materials
Skeletal system	
Joint replacements (hip, knee)	Titanium, Ti–Al–V alloy, stainless steel, polyethylene
Bone plate for fracture fixation	Stainless steel, cobalt–chromium alloy
Bone cement	Poly(methyl methacrylate)
Bony defect repair	Hydroxylapatite
Artificial tendon and ligament	Teflon, Dacron
Dental implant for tooth fixation	Titanium, Ti–Al–V alloy, stainless steel, polyethylene; Titanium, alumina, calcium phosphate
Cardiovascular system	
Blood vessel prosthesis	Dacron, Teflon, polyurethane
Heart valve	Reprocessed tissue, stainless steel, carbon
Catheter	Silicone rubber, Teflon, polyurethane
Organs	
Artificial heart	Polyurethane
Skin repair template	Silicone–collagen composite
Artificial kidney (hemodialyzer)	Cellulose, polyacrylonitrile
Heart–lung machine	Silicone rubber
Senses	
Cochlear replacement	Platinum electrodes
Intraocular lens	Poly(methyl methacrylate), silicone rubber, hydrogel
Contact lens	Silicone-acrylate, hydrogel
Corneal bandage	Collagen, hydrogel

Application	Types of materials
Skeletal system	
Joint replacements (hip, knee)	Titanium, Ti–Al–V alloy, stainless steel, polyethylene
Bone plate for fracture fixation	Stainless steel, cobalt–chromium alloy
Bone cement	Poly(methyl methacrylate)
Bony defect repair	Hydroxylapatite
Artificial tendon and ligament	Teflon, Dacron
Dental implant for tooth fixation	Titanium, Ti–Al–V alloy, stainless steel, polyethylene; Titanium, alumina, calcium phosphate

Cardiovascular system	
Blood vessel prosthesis	Dacron, Teflon, polyurethane
Heart valve	Reprocessed tissue, stainless steel, carbon
Catheter	Silicone rubber, Teflon, polyurethane
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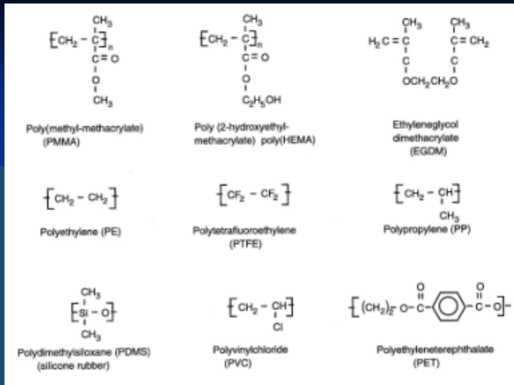
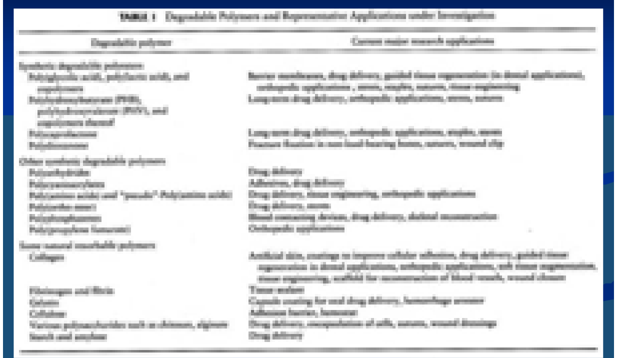
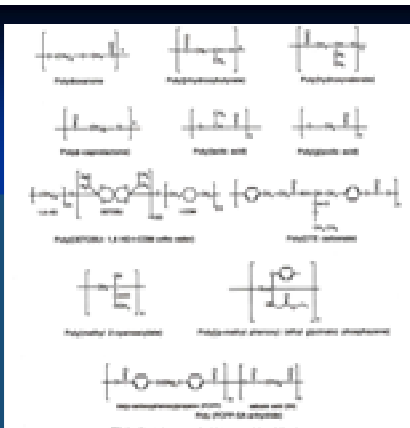


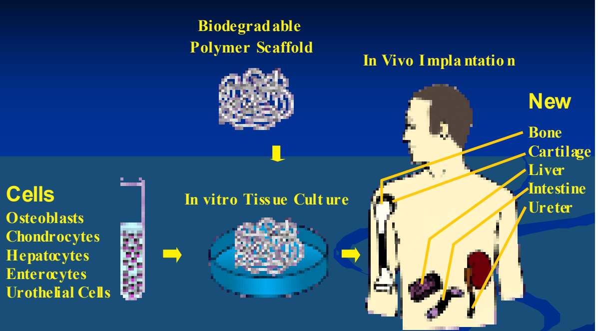
Nondegradable Homopolymers used as biomaterials

Degradable Homopolymers used as biomaterials





Degradable Homopolymers used as biomaterials



Paclitaxel and Topotecan- Sequence in action!