BMED3201 INTRODUCTION TO BIOMATERIALS
SYLLABUS

Date: February 26, 2021

Semester : 2021 Spring
Course : BME302.01, Introduction to Biomaterials
Level of Course : Undergraduate
Year of Study : 3
Type of Course : BME
Language of Instruction : English

Instructor : Assist. Prof. Dr. Sakip ONDER

Instructor's office hours : ---
Instructor's office no/phone no/e-mail address : Room No. LMF 421, (0216) 5287019, sakip.onder@isikun.edu.tr

Class hours : BMED3201 / FFF 123
Prerequisite :
Corequisite :

Course description
The Nature of Matter and Materials, Classes of Materials Used in Medicine: Polymers, Metals, Ceramics, Glasses, Glass-Ceramics, composites, hydrogels, Non-fouling surfaces, Physicochemical surface modification and surface patterning, Cell-tissue and biomaterial interaction, Host Reaction to Biomaterials, Biological testing of biomaterials, Applications of biomaterials.
Recommended Textbook (s) :

1- Buddy D. Ratner, Allan S. Hoffman, Frederick J. Schoen and Jack E. Lemons, Biomaterials Science (Third Edition) An Introduction to Materials in Medicine, Elsevier Inc. (2013)

Tentative Schedule

Weeks	Topics
1	Introduction to Biomaterials
2	The Nature of Matter and Materials
3	Surface Characterization Techniques
4	Classes of Materials Used in Medicine: Polymers
5	Classes of Materials Used in Medicine: Metals
6	Classes of Materials Used in Medicine: Ceramics, Glasses, Glass-Ceramics
7	Midterm I
8	Classes of Materials Used in Medicine: composites, hydrogels and non-fouling surfaces
9	Physicochemical surface modification and surface patterning
10	Cell-tissue and biomaterial interaction
11	Host Reaction to Biomaterials
12	Biological testing of biomaterials
13	Applications of biomaterials (student presentations)
14	Applications of biomaterials (student presentations)

Grading Policy:
Final course grades will be computed according to the following:

Midterm I	20%
Student presentations	40%
Final	40%

Important Dates:

- Last date to add/drop from BMED 3201 : March 1, 2021

The Black-board will be the main source of information for the course. Homework and announcements will be posted. It is the student's responsibility to download and print the necessary documents needed in the course.

I N T R O D U C T I O N

BIOMATERIALS AND BIOMATERIALS SCIENCE

- Biomaterials science addresses both therapeutics and diagnostics. It encompasses basic sciences (biology, chemistry, physics), and engineering and medicine.

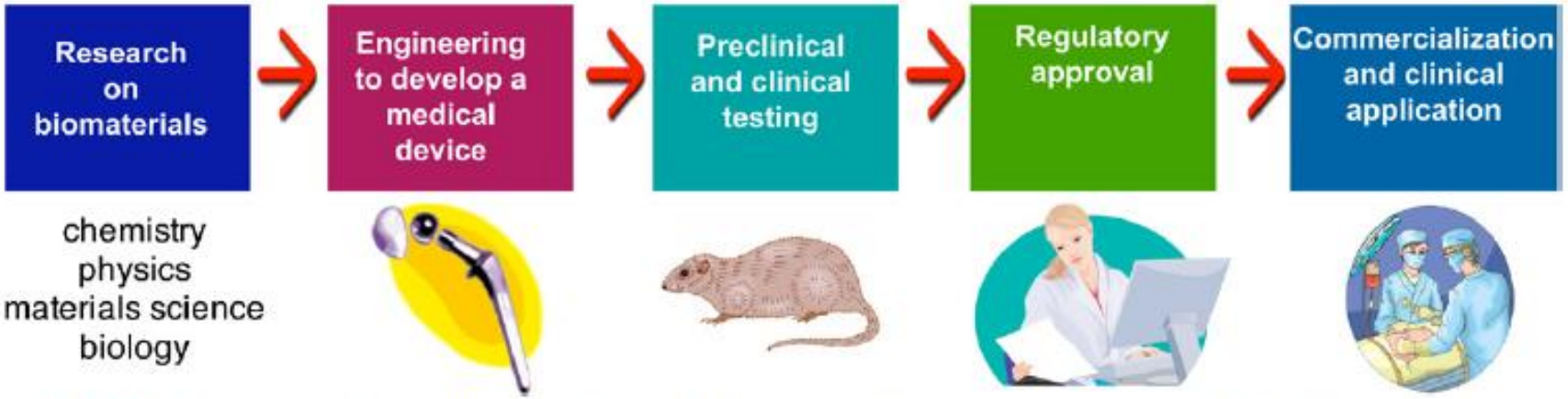

FIGURE 1 The path from the basic science of biomaterials, to a medical device, to clinical application.

KEY DEFINITIONS

Biomaterial : *A biomaterial is a nonviable material used in a medical device, intended to interact with biological systems.*
Williams, 1987

Biomaterials science : the study (from the physical and/or biological perspective) of materials with the biological environment.

Biocompatibility : *"Biocompatibility" is the ability of a material to perform with an appropriate host response in a specific application.*
Williams, 1987

Examples of appropriate host responses : resistance to blood clotting, resistance to bacterial colonization, and normal, uncomplicated healing.
Examples of specific applications: a hemodialysis membrane, a urinary catheter or a hip joint replacement prosthesis.

- a few applications for synthetic and natural materials in the body.

TABLE 1 Key Applications of Synthetic Materials and Modified Natural Materials in Medicine*

Application	Biomaterials Used	Number/Year – World (or World Market in US$)
Skeletal system		
Joint replacements (hip, knee, shoulder)	Titanium, stainless steel, polyethylene	2,500,000
Bone fixation plates and screws	Metals, poly(lactic acid) (PLA)	1,500,000
Spine disks and fusion hardware		800,000
Bone cement	Poly(methyl methacrylate)	($600M)
Bone defect repair	Calcium phosphates	–
Artificial tendon or ligament	Polyester fibers	–
Dental implant-tooth fixation	Titanium	($4B)
Cardiovascular system		
Blood vessel prosthesis	Dacron, expanded Teflon	200,000
Heart valve	Dacron, carbon, metal, treated natural tissue	400,000
Pacemaker	Titanium, polyurethane	600,000
Implantable defibrillator	Titanium, polyurethane	300,000
Stent	Stainless steel, other metals, PLA	1,500,000
Catheter	Teflon, silicone, polyurethane	1B ($20B)
Organs		
Heart assist device	Polyurethane, titanium, stainless steel	4000
Hemodialysis	Polysulfone, silicone	1,800,000 patients ($70B)
Blood oxygenator	silicone	1,000,000
Skin substitute	Collagen, cadaver skin, nylon, silicone	($1B)
Ophthalmologic		
Contact lens	Acrylate/methacrylate/silicone polymers	150,000,000
Intraocular lens	Acrylate/methacrylate polymers	7,000,000
Corneal bandage lens	hydrogel	–
Glaucoma drain	Silicone, polypropylene	($200M)
Other		
Cochlear prosthesis	Platinum, platinum-iridium, silicone	250,000 total users
Breast implant	Silicone	700,000
Hernia mesh	Silicone, polypropylene, Teflon	200,000 ($4B)
Sutures	PLA, polydioxanone, polypropylene, stainless steel	($2B)
Blood bags	Poly(vinyl chloride)	–
Ear tubes (Tympanostomy)	Silicone, Teflon	1,500,000
Intrauterine device (IUD)	Silicone, copper	1,000,000

*Data compiled from many sources – these numbers should be considered rough estimates that are changing with growing markets and new technologies. Where only US numbers are available, world usage is estimated at approximately 2.5× of US usage.
NOTE: M = millions, B = billions.

- It includes many classes of materials such as metals, ceramics, polymers, glasses, carbons, and composite materials.
- Such materials are used as molded or machined parts, coatings, fibers, films, membranes, foams, fabrics, and nanoparticles.

- the size of the commercial market for biomaterials and medical devices, is impressive .

TABLE 2 The Biomaterials and Healthcare Market: Facts and Figures (Per Year)

Total US healthcare expenditures (1990)	$714 billion
Total US healthcare expenditures (2009)	$2.5 trillion
Total US health research and development expenditure (2009)	$139 billion
Number of medical device companies in the US	12,000
Jobs in the US medical device industry (2008)	425,000
Sales by US medical device industry (2008)	$136 billion
World medical device market forecast for 2013*	$286 billion

*Source: Medical Market Fact Book 2008.

THE EVOLUTION OF THE BIOMATERIALS FIELD

① first generation biomaterials was to achieve a suitable combination of functional properties to adequately match those of the replaced tissue without deleterious response by the host.

- they were *bioinert* (i.e., they elicited minimal response from the host tissues), and therefore they were considered *biocompatible*

② Second generation biomaterials evolved from those early biomaterials, and were intended to elicit a controlled reaction with the tissues into which they were implanted in order to induce a desired therapeutic effect.

- delivery of drugs, active proteins, and other macromolecules localized to the site where the drug is needed.
- controlled drug delivery is now capable of targeting a wide range of drugs to tumors, to diseased blood vessels, to the pulmonary alveoli, etc.

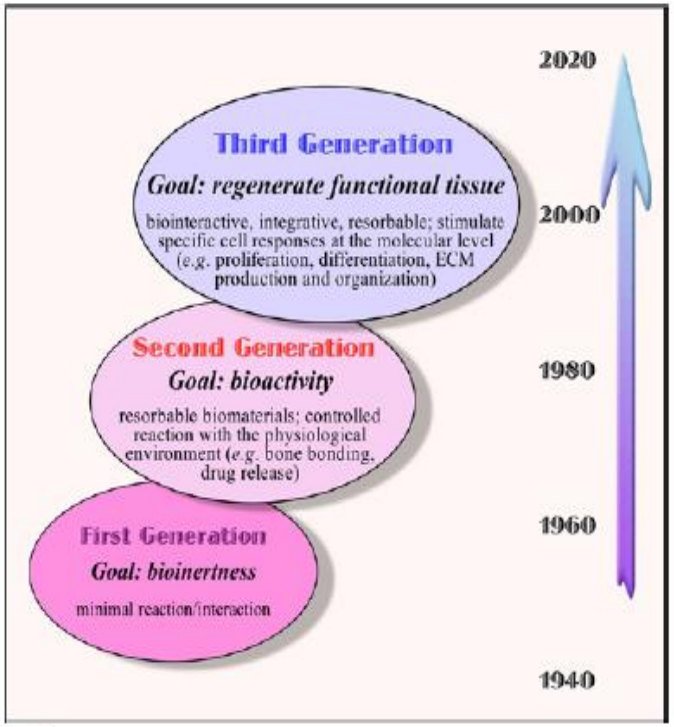

FIGURE 2 Evolution of biomaterials science and technology. (Based upon Rabkin, E. & Schoen, F. J. (2002). Cardiovascular tissue engineering. Cardiovasc Pathol, 11: 305.)

③ The third generation of biomaterials has <u>the goal of supporting and stimulating the regeneration of functional tissue.</u>

- it seems that true replacement with living tissue will be possible.
- Tissue engineering uses living cells (or attract endogenous cells) to aid tissue formation or regeneration.
- Tissue engineering has led to the replacement in humans of damaged bladders, trachea, skin, corneal epithelium, and cartilage.

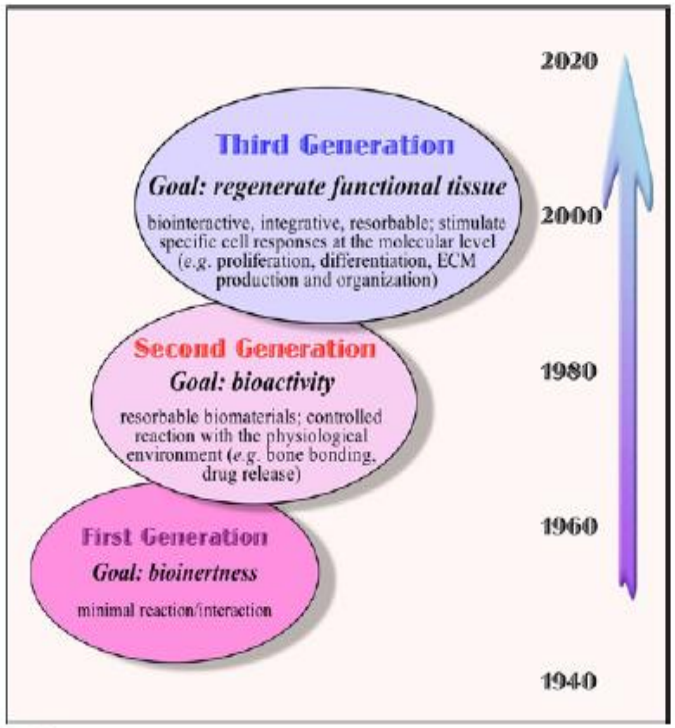

FIGURE 2 Evolution of biomaterials science and technology. (Based upon Rabkin, E. & Schoen, F. J. (2002). Cardiovascular tissue engineering. Cardiovasc Pathol, 11: 305.)

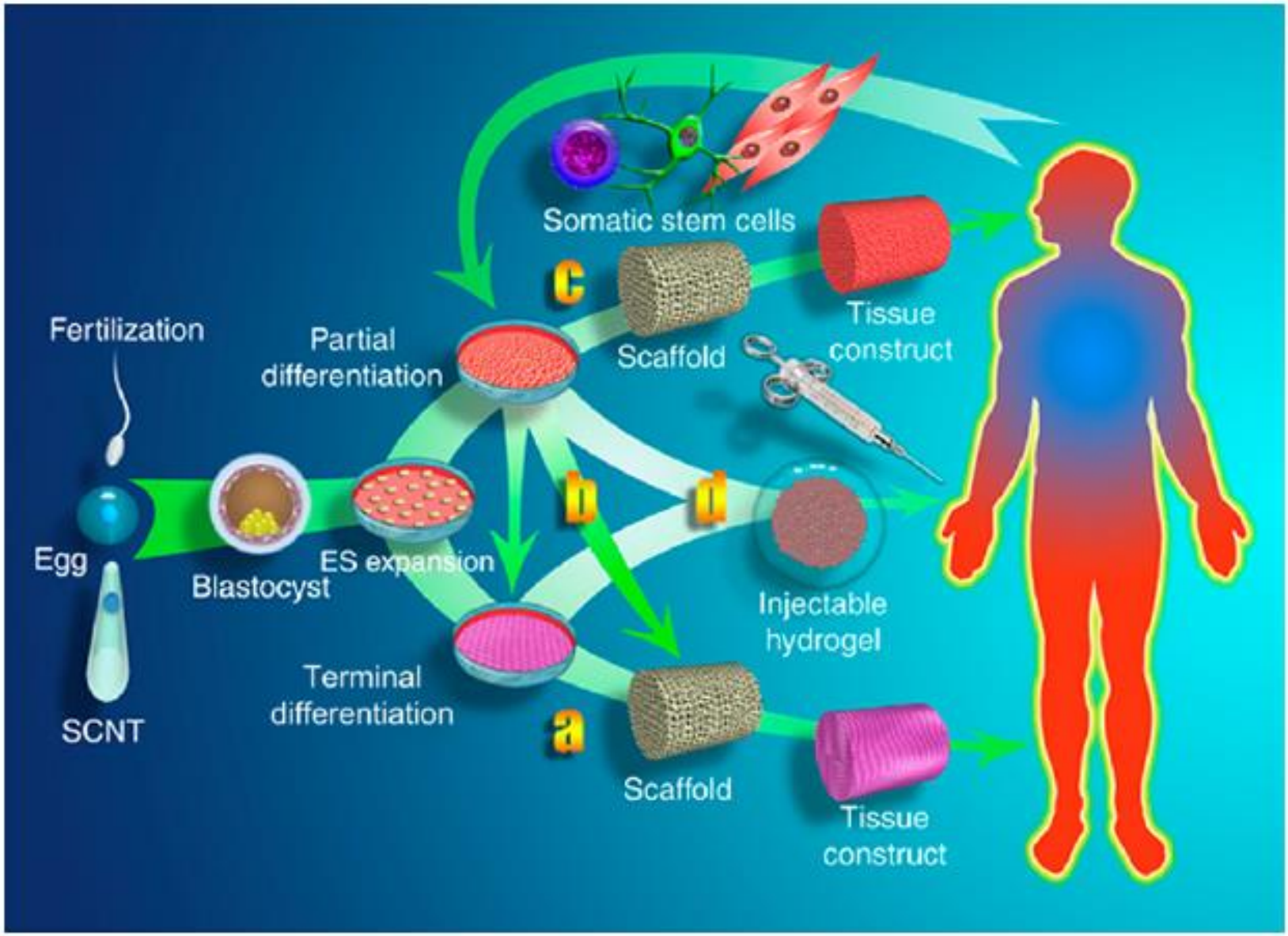

FIGURE 3 The tissue engineering paradigm – various cell types are seeded on porous scaffolds, possibly proliferated in a bioreactor, and finally implanted in various tissue sites to restore or regenerate damaged or missing tissue. (nature.com.)

EXAMPLES OF TODAY'S BIOMATERIALS APPLICATIONS

➢ Heart Valve Prostheses

- Diseases and degeneration of the heart valves often make surgical repair or replacement necessary.
- Approximately 250,000 replacement valves are implanted each year worldwide, because of acquired damage to the natural valve and congenital heart anomalies.
- There are many types of heart valve prostheses, and they are fabricated from carbons, metals, elastomers, plastics and animal or human tissues chemically pretreated to reduce their immunologic reactivity, and to enhance durability.

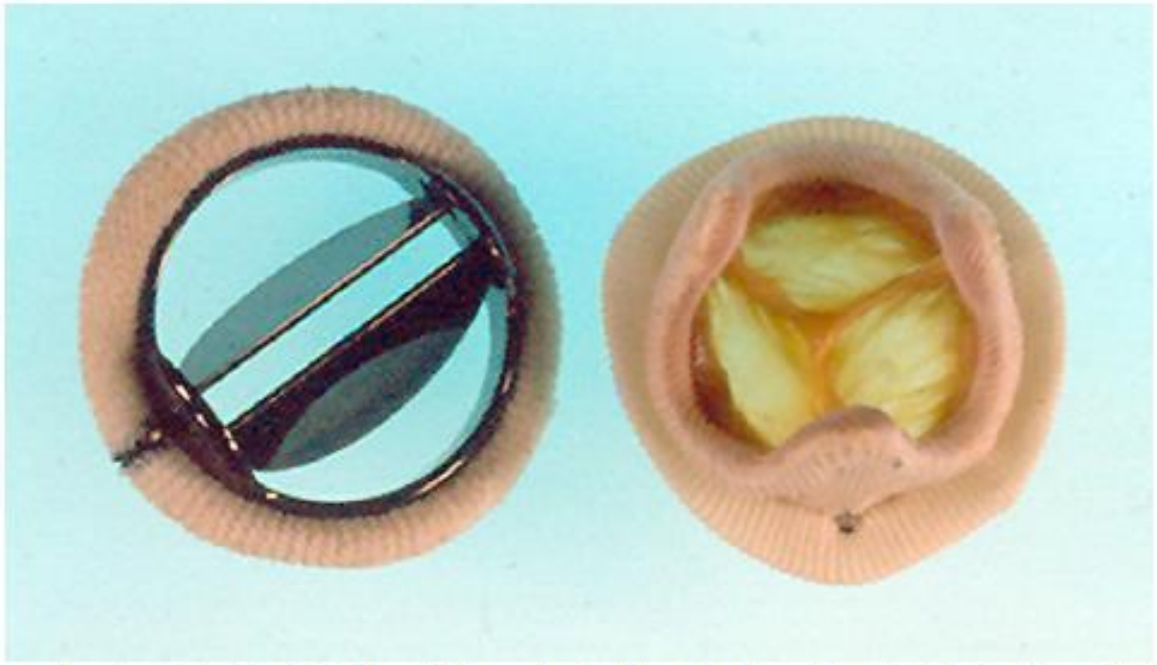

FIGURE 4 Prosthetic heart valves. Left: A bileaflet tilting disk mechanical heart valve. (St. Jude Medical Inc., St. Paul, MN.) Right: A bioprosthetic (xenograft) tissue heart valve (Hancock® valve, Medtronic Inc., MN.)

➢ Total Hip Replacement Prostheses

- The human hip joint is subjected to high levels of mechanical stress.
- after 50 or more years of cyclic mechanical stress or because of degenerative or rheumatoid disease, the natural joint wears out, leading to loss of mobility.
- Hip joint prostheses are fabricated from a variety of materials, including titanium, stainless steel, special high-strength alloys, ceramics, composites, and ultrahigh molecular weight polyethylene (UHMWPE).

- Replacement hip joints are implanted in more than 200,000 humans each year in the United States alone.
- After 10–15 years, many of these implants fail by loosening, which usually necessitates another operation (a revision procedure).

FIGURE 5 A hip prosthesis. Microplasty® titanium alloy femoral stem, Biolox® alumina-zirconia ceramic femoral head, ultra-high molecular weight polyethylene acetabular cup infused with vitamin E antioxidant. (Image courtesy of Biomet, Inc.)

➢ Dental Implants

- The development of root form designs of titanium implants revolutionized dental implantology.
- These devices form an implanted artificial tooth anchor upon which a crown is affixed, and are implanted in 2,000,000 people each year in the US alone, according to the American Dental Association.
- the tooth is connected to the jaw by the periodontal ligament, and is not directly attached to the jawbone.
- Titanium based implants are commonly used in dental applications because of their excellent osteointegrasyon properties with the bone of the jaw.

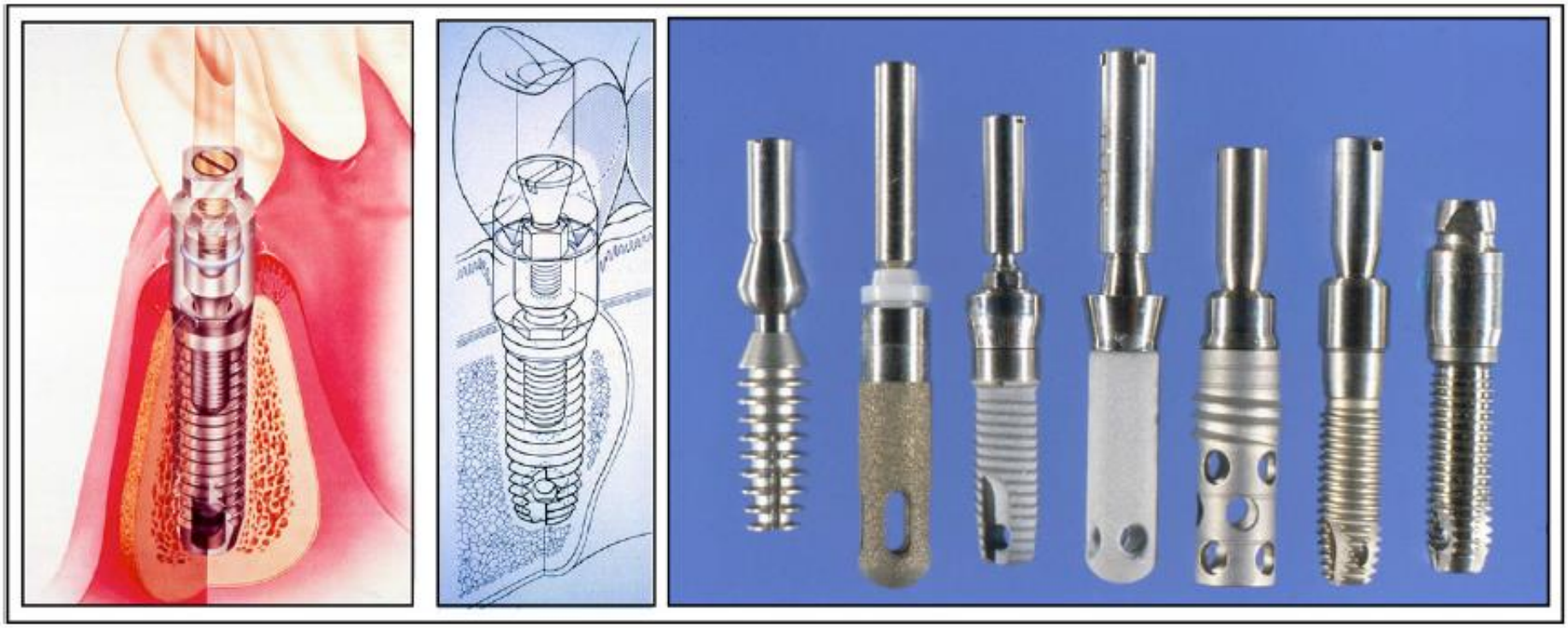

FIGURE 6 Schematic images of early dental root form implants and a photograph of several designs used in clinical practice.

➢ Intraocular Lenses

- Implants to replace lenses in the eye that have clouded due to cataracts are called intraocular lenses (IOLs).
- They have been fabricated from a variety of transparent materials including poly(methyl methacrylate), silicone elastomer, soft acrylic polymers, and hydrogels.
- By the age of 75, more than 50% of the population suffers from cataracts
- More than three million implantations in the US alone each year, and more than double that number worldwide.

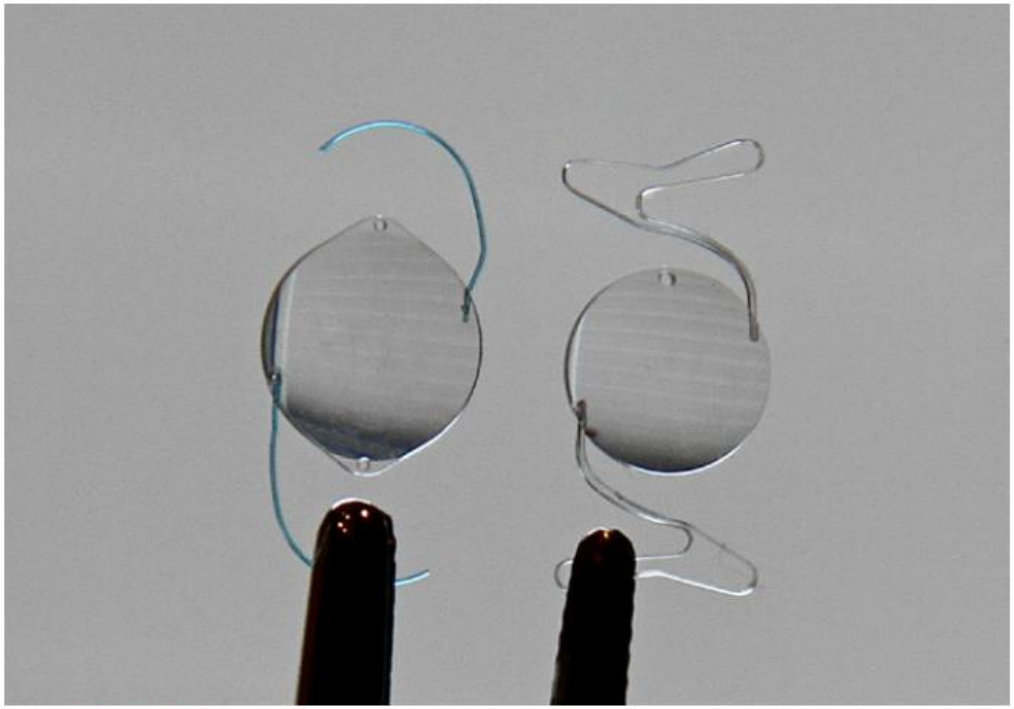

FIGURE 7 Two styles of multipiece intraocular lenses.

➢ Left Ventricular Assist Devices

- Nearly 5,000,000 Americans are living with seriously failing hearts (congestive heart failure), and 300,000 individuals will die each year from this disease.
- According to the American Heart Association, 50,000–100,000 of these individuals might benefit from cardiac transplantation or mechanical assist.
- LVADs are used to maintain a patient with a failing heart while the patient awaits the availability of a transplant heart.
- LVAD recipients can have considerable mobility and freedom while cardiac support is provided by the device. Patients have lived on LVAD support for more than four years

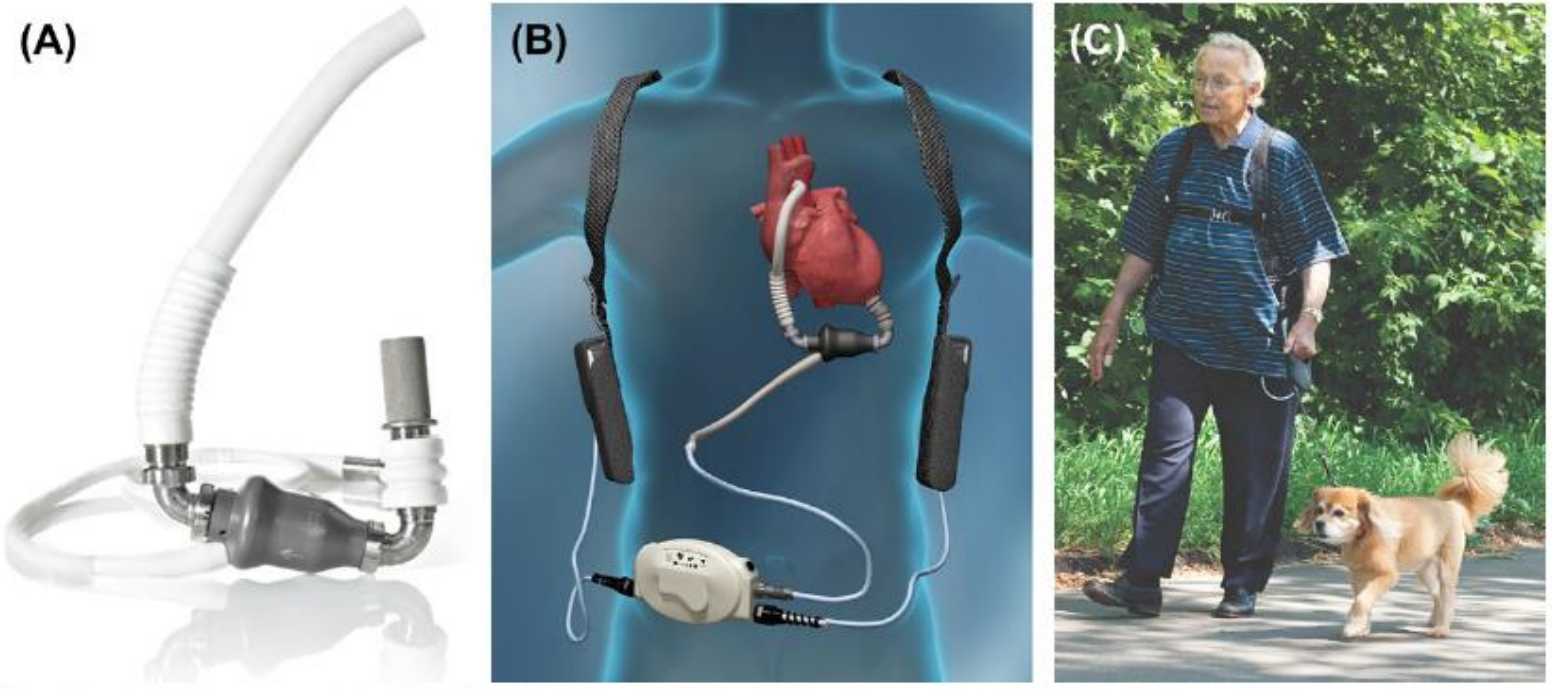

FIGURE 8 Left ventricular assist device (LVAD). (A) Continuous flow pump with associated inflow/outflow grafts and electrical drive line (Heartmate II® device). (B) Schematic of LVAD implanted as a left ventricular assist device with associated external power source. (C) Patient (human) implanted with this LVAD device illustrating freedom of activity. (Reprinted with the permission of Thoratec Corporation, Pleasantville, CA.)

CHARACTERISTICS OF BIOMATERIALS SCIENCE

➢ Multidisciplinary

- biomaterials science brings together teams of researchers from diverse academic and industrial backgrounds, who must clearly communicate and integrate complex concepts and data

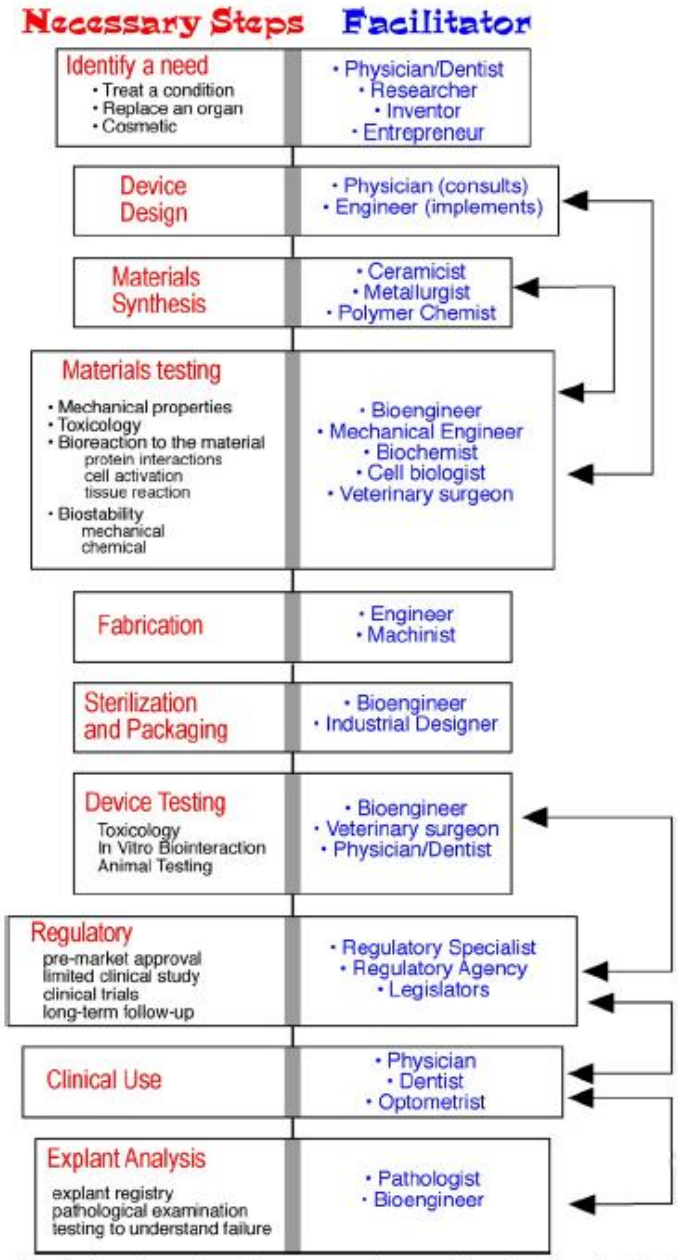

FIGURE 9 The path from an identified need to a clinical product, and some of the disciplines that facilitate this development process.

➢ Diverse Materials are Used

- The biomaterials scientist use different types of in medical applications including polymers, metals, ceramics, glasses, composites.

- There is a tendency to group biomaterials and researchers into the “hard tissue replacement”, typically represented by those involved in orthopedic and dental materials, and the “soft tissue replacement”, frequently associated with cardiovascular implants and general plastic surgery materials.

- Hard tissue biomaterials researchers are thought to focus on metals and ceramics, while soft tissue biomaterials researchers are considered polymer experts.

- In practice, this division is artificial: a heart valve may be fabricated from polymers, metals, and carbons. A hip joint will also be composed of metals and polymers (and sometimes ceramics), and will be interfaced to the body via a polymeric bone cement.

➢ Magnitude of the Field & Company

- The magnitude of the medical device field expresses both the magnitude of the need and a sizeable commercial market

- The process of biomaterial/medical device innovation is driven by clinical need: a patient or a physician defines a need and then initiates an invention.

- However, someone must test and manufacture the device, and shepherd it though the complex, expensive regulatory process. This "someone" is a company, and a company exists (by law) to return value to its shareholders.

➢ Success and Failure

- All manufactured devices have a failure rate.

- all humans are different, with differing ethnicities, ages, genetics, gender, body chemistries, living environments, and degrees of physical activity.

- physicians implant or use these devices with varying degrees of skill.

- The other side to the medical device success story is that there are problems, compromises, complications, and unintended consequences that often occur with medical devices.

- Central issues for the biomaterials scientist, manufacturer, patient, physician are:

① Is the design competent and optimal?
② who should be responsible when devices perform “with an inappropriate host response”?
③ what are the cost:risk or cost:benefit ratios for the implant or therapy?

SUBJECTS INTEGRAL TO BIOMATERIALS SCIENCE

➢ Toxicology.

- A biomaterial should not be toxic, unless it is specifically engineered for such requirements (e.g., a “smart” drug delivery system that targets cancer cells with a toxic drug and destroys them).

➢ Biocompatibility.

- biocompatibility is defined in terms of performance or success at a specific task.

➢ Inflammation and Healing.

- Specialized biological mechanisms are triggered when a material or device interfaces with the body. Injury to tissue will stimulate the well-defined inflammatory reaction sequence that ultimately leads to healing.
- Healing can be normal (physiological) or abnormal (pathological). Where a foreign body (e.g., an implant) is present in the wound site (the surgical incision), the reaction sequence is referred to as the “foreign-body reaction”

➢ Functional Tissue Structure and Pathobiology.

- Biomaterials-based medical devices are implanted into almost all tissues and organs.

- Tissues and organs vary widely in cell composition, morphological organization, vascularization, and innervation.

- Implantation of a biomaterial into bone, liver, or heart will have special physiological consequences.

- Therefore,

    - key principles governing the structure of normal (and abnormal) cells, tissues, and organs are important to biomaterials researchers,
    - techniques by which the structure and function of normal and abnormal tissue are studied must be mastered,
    - fundamental mechanisms leading to abnormal cell, tissue, and organ structures (i.e., diseases and other pathologies) are critical considerations to biomaterials researchers .

➢ Dependence on Specific Anatomical Sites of Implantation.

- Consideration of the anatomical site of an implant is essential.
- An intraocular lens may be implanted into the lens capsule or the anterior chamber of the eye.
- A hip joint may be implanted in bone across an articulating joint space.
- A prosthetic heart valve will be sutured into cardiac muscle, and will contact both soft tissue and blood.
- A catheter may be placed in an artery, a vein or the urinary tract.
- Each of these sites challenges the biomedical device designer with special requirements for anatomy, physiology, geometry, size, mechanical properties, and bioresponses.

➢ Mechanical Requirements and Physical Performance Requirements

- Each biomaterial and device has mechanical and performance requirements originating from the need to perform a physiological function.
    - A hip prosthesis must be strong and rigid
    - A bone plate may fulfill its function in six months or longer
    - The dialysis membrane has a specified permeability,
    - the acetabular cup of the hip joint must have high lubricity
    - the intraocular lens has transparency and refraction requirements

➢ Industrial Involvement

- A significant basic research effort is now under way, primarily at universities, to understand how biomaterials function and how to optimize them.

- At the same time, companies are producing implants for use in humans and, appropriate to the mission of a company, earning profits on the sale of medical devices.

- A risk–benefit analysis must be considered in developing new devices and improving existing devices.

➢ Ethics

- A wide range of ethical considerations impact biomaterials science. Some key ethical questions in biomaterials science are summarized

TABLE 3	Ethical Concerns Relevant to Biomaterials Science
Animals	Is the animal model relevant to human physiology? Specifically, is the experiment well-designed and outcome sufficiently important so that the data obtained will justify the suffering and sacrifice of the life of a living creature?
Human Subjects	How should human subject research be conducted to minimize negative outcomes to the patient and offer a reasonable risk-to-benefit ratio? How can we best ensure informed consent?
Industrial Involvement	Companies fund much biomaterials research and also own proprietary biomaterials. How can the needs of the patient be best balanced with the financial goals of a company? Consider that someone must manufacture devices – these would not be available if a company did not choose to manufacture them.
Researchers	Since researchers often stand to benefit financially from a successful biomedical device, and sometimes even have devices named after them, how can investigator bias be minimized in biomaterials research?
Patients	For life-sustaining devices, what is the trade-off between sustaining life and the quality of life with the device for the patient? Should the patient be permitted to "pull the plug" if the quality of life is not satisfactory?
Regulatory Agencies	With so many unanswered questions about the basic science of biomaterials, do government regulatory agencies have sufficient information to define adequate tests for materials and devices and to properly regulate biomaterials?

➢ Regulation.

- To prevent inadequately tested devices and materials from coming on the market, and to screen out those clearly unqualified to produce biomaterials, the United States government has evolved a complex regulatory system administered by the US Food and Drug Administration (FDA).

- The International Standards Organization (ISO) has introduced international standards for the world community.