



Tissue Engineering

MSE503 Seminar

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Outline

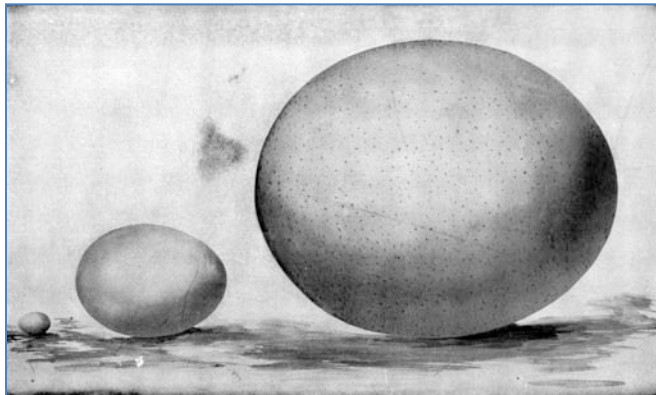
- ❖ Definition of tissue engineering
- ❖ Cells
- ❖ Stem cells
- ❖ Tissues
- ❖ Bioartificial Liver
- ❖ Bioartificial Pancreas

Definition

- ❑ The term “regenerative medicine” is often used synonymously with tissue engineering, although those involved in regenerative medicine place more emphasis on the use of stem cells to produce tissues.
- ❑ The use of a combination of cells, engineering and materials methods, and suitable biochemical and physico-chemical factors to improve or replace biological functions.
- ❑ 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 or a whole organ – **Langer and Vacanti**

Cell

- ❑ The structural and functional unit of all known living organisms.
- ❑ The smallest unit of an organism that is classified as living.
- ❑ *The building block of life.*
- ❑ Bacteria: unicellular (single cell)
- ❑ Humans: multicellular (100 trillion cells; cell size ~10 microns).
- ❑ The largest known cell is an unfertilized ostrich egg cell.

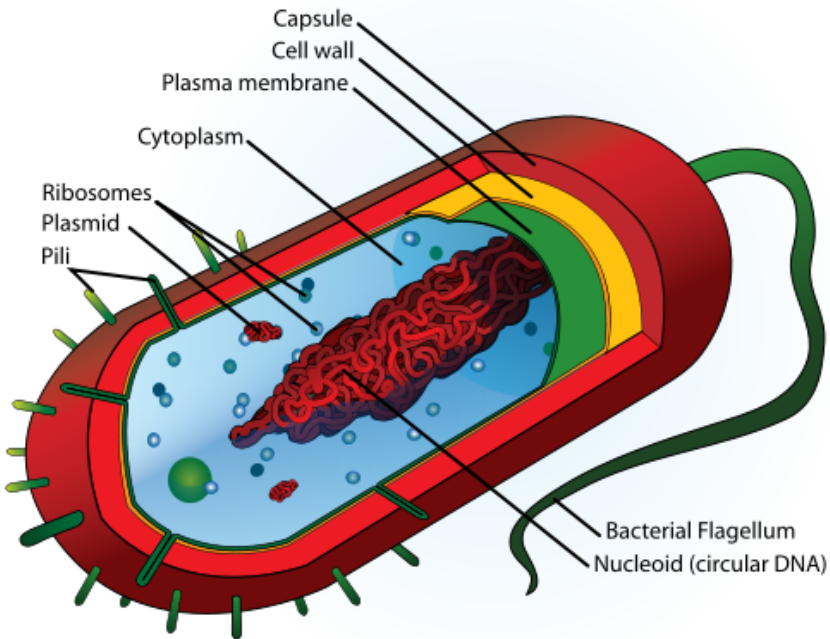


Courtesy: [http://www.newworldencyclopedia.org/entry/Egg_\(biology\)](http://www.newworldencyclopedia.org/entry/Egg_(biology))
http://commons.wikimedia.org/wiki/File:Ostrich_egg.jpg

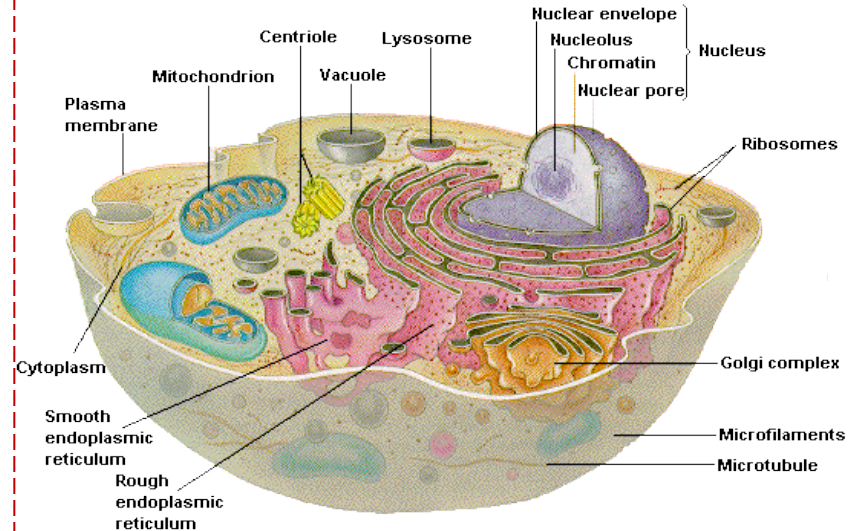


Types of Cells

Prokaryotic cell



Eukaryotic



Courtesy: [http://en.wikipedia.org/wiki/Cell_\(biology\)](http://en.wikipedia.org/wiki/Cell_(biology))

Stem Cells

- Stem cells are the master cells of the human body.
- They can divide to produce copies of themselves and many other types of cells.
- Stem cells taken from embryos that are just a few days old, can turn into any of the 300 different types of cell that make up the adult body.

Stem Cells

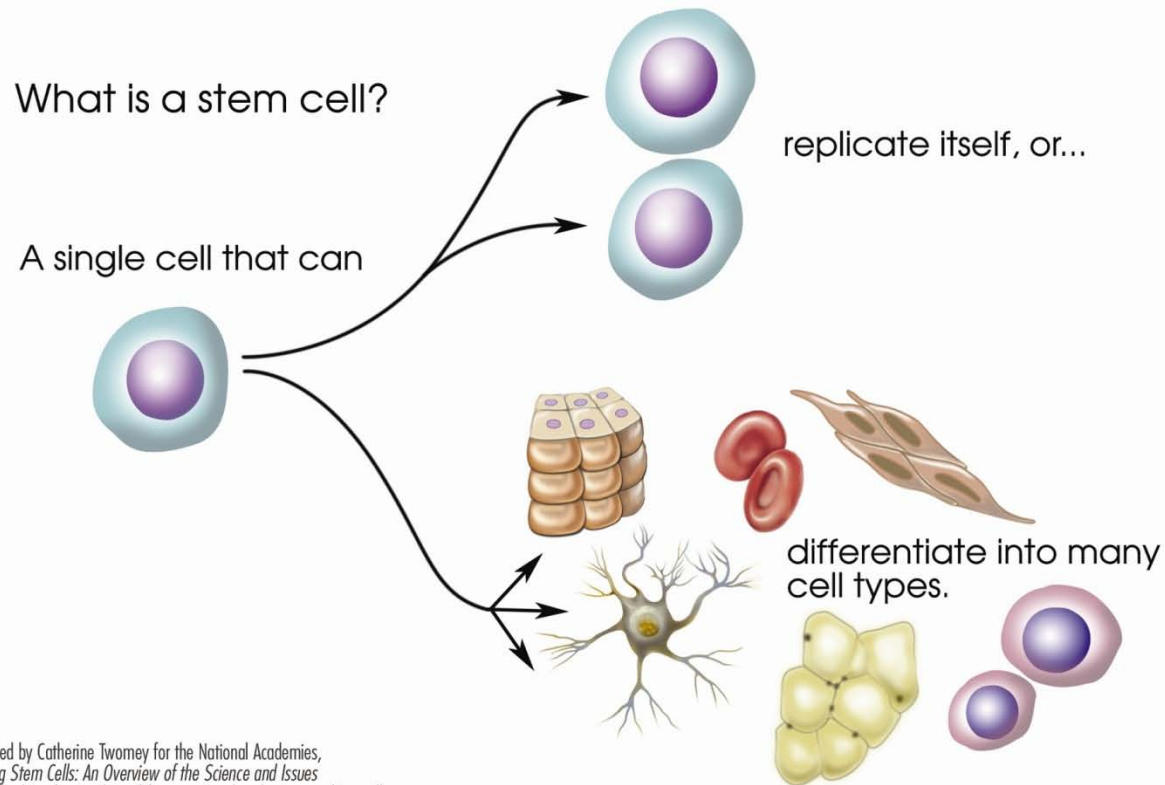


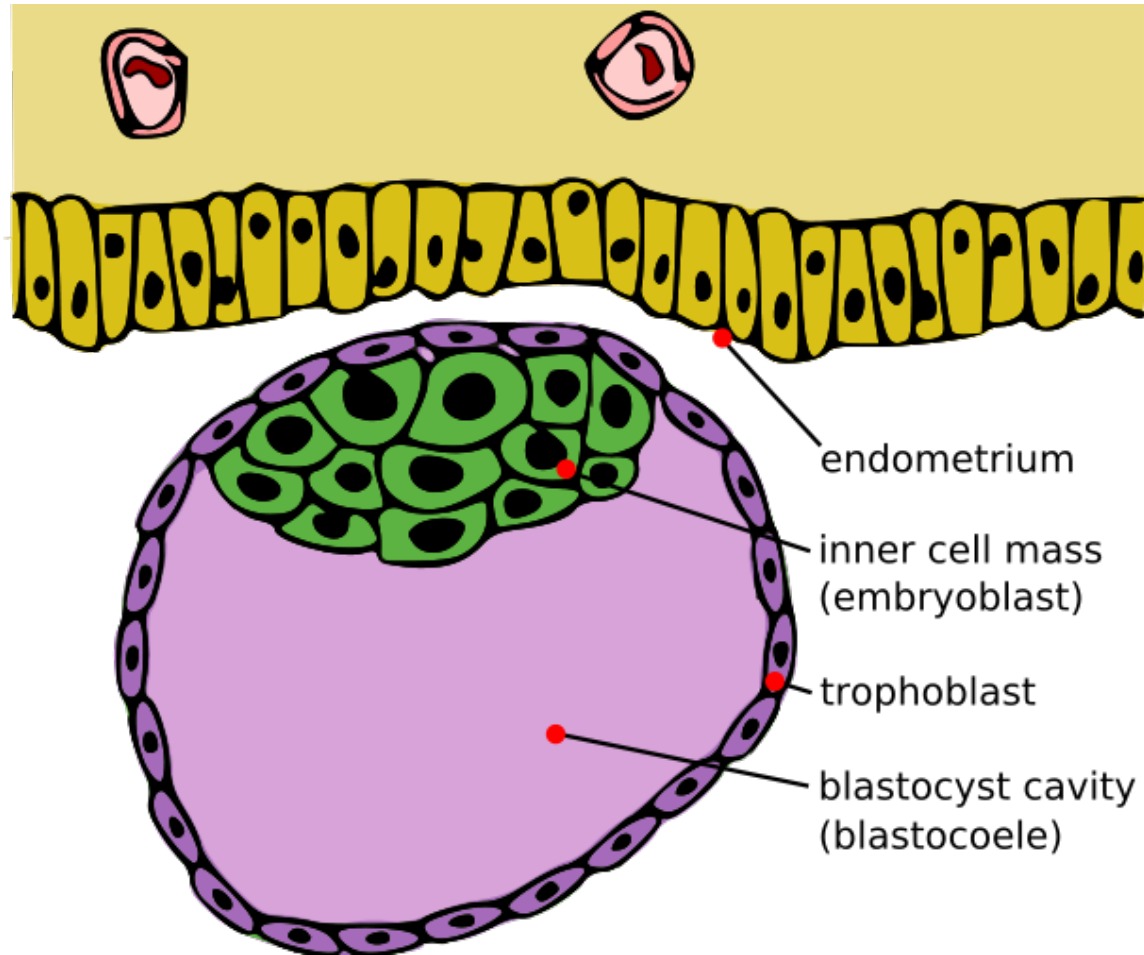
Image prepared by Catherine Twomey for the National Academies, *Understanding Stem Cells: An Overview of the Science and Issues* from the National Academies, <http://www.nationalacademies.org/stemcells>. Academic noncommercial use is permitted.

Courtesy: <http://www.dels.nas.edu/bls/stemcells/what-is-a-stem-cell.shtml>

Types of Stem Cells

Type	Description	Examples
Totipotent	Each cell can develop into a new individual.	Cells from early (1-3 days) embryos.
Pluripotent	Cells can form any (over 200) cell types.	Some cells of blastocyst (5 to 14 days).
Multipotent	Cells differentiated, but can form a number of other tissues.	Fetal tissue, cord blood, and adult stem cells.

Blastocyst



Courtesy: http://en.wikipedia.org/wiki/File:Blastocyst_English.svg

Sources of Stem Cells

1. Embryonic stem cells - are harvested from the inner cell mass of the blastocyst seven to ten days after fertilization.
2. Fetal stem cells - are taken from the germline tissues that will make up the gonads of aborted fetuses.
3. Umbilical cord stem cells - Umbilical cord blood contains stem cells similar to those found in bone marrow.
4. Placenta derived stem cells - up to ten times as many stem cells can be harvested from a placenta as from cord blood.
5. Adult stem cells - Many adult tissues contain stem cells that can be isolated.

Tissues

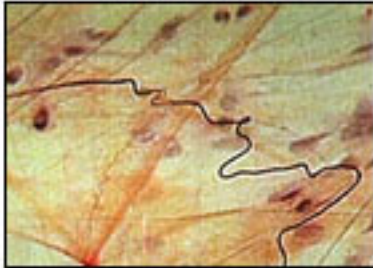
- Tissue is a cellular organizational level intermediate between cells and a complete organism. Hence, a tissue is an ensemble of cells, not necessarily identical, but from the same origin, that together carry out a specific function. Organs are then formed by the functional grouping together of multiple tissues.
- The study of tissue is known as histology or, in connection with disease, histopathology.
- The classical tools for studying tissues are the paraffin block in which tissue is embedded and then sectioned, the histological stain, and the optical microscope

Types of Tissues

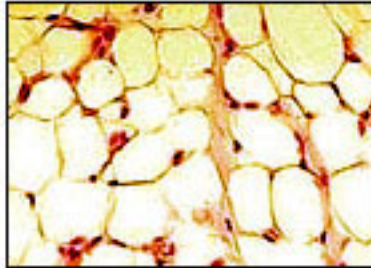
- Animal tissues
 - Connective
 - Muscle
 - Nervous
 - Epithelial

- Plant tissues
 - Epidermis
 - Vascular
 - Ground

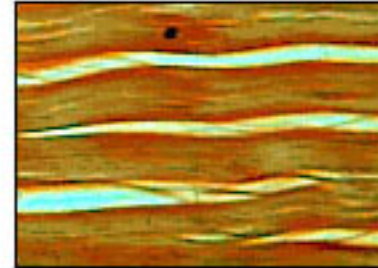
Animal Tissues



Areolar connective tissue



Adipose tissue

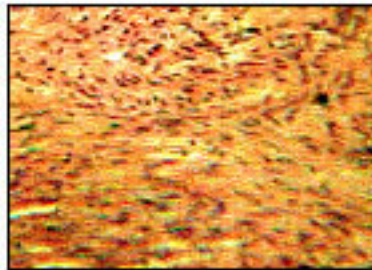


Fibrous connective tissue

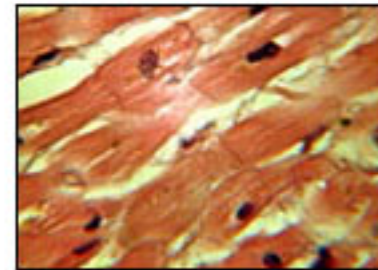
Connective tissues



Skeletal muscle



Smooth muscle

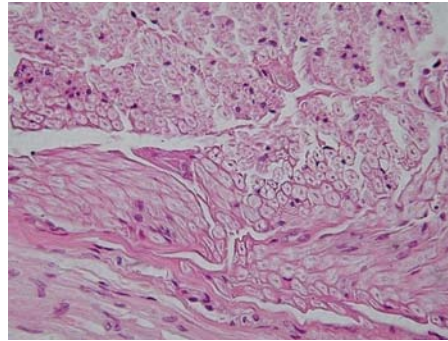


Cardiac muscle

Muscle tissues

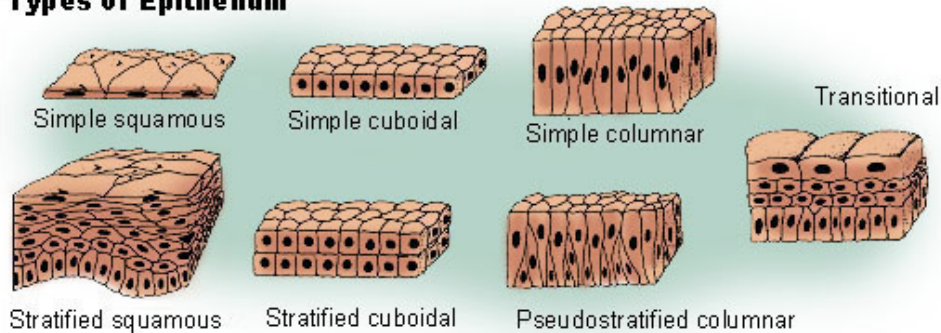
Courtesy: http://en.wikipedia.org/wiki/Connective_tissue
<http://en.wikipedia.org/wiki/Muscle>

Animal Tissues



Nervous tissue

Types of Epithelium



Epithelial tissues

Courtesy: http://en.wikipedia.org/wiki/Nervous_tissue
http://en.wikipedia.org/wiki/Epithelial_tissue

Examples

1. Bioartificial liver device
2. Artificial pancreas
3. Artificial bladders
4. Cartilage
5. Artificial skin
6. Artificial bone marrow
7. Heart (Doris Taylor)

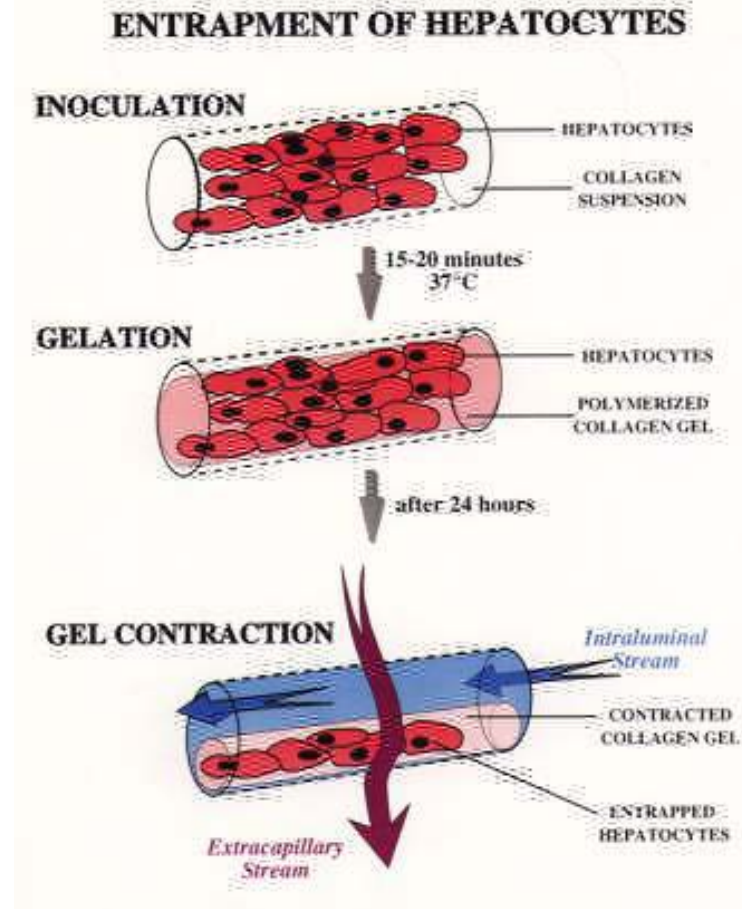
Bioartificial Liver Device (BAL)

- An artificial extracorporeal supportive device.
- It serves as a temporary supportive device.
- It is essentially a bioreactor with embedded hepatocytes.
- It processes oxygenated blood plasma, which is separated from the other blood constituents.
- There are many different types of BALs (including *hollow fiber systems* and *flat membrane sheet systems*).

Hollow Fiber Systems

- It employs a hollow fiber cartridge.
- Hepatocytes are suspended in a gel solution, such as collagen, which is injected into a series of hollow fibers.
- In the case of collagen, the suspension is then gelled within the fibers, usually by a temperature change. The hepatocytes then contract the gel by their attachment to the collagen matrix, reducing the volume of the suspension and creating a flow space within the fibers.
- Nutrient media is circulated through the fibers to sustain the cells. During use, a patient's blood is fed into the space surrounding the fibers. The fibers, which are composed of a semi-permeable membrane, facilitate transfer of toxins, nutrients and other chemicals between the blood and the suspended cells.

Hollow Fiber Systems



Courtesy: <http://hugroup.cems.umn.edu/Research/bal/BAL-howitworks.htm>

Bioartificial Pancreas

- It controls the blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.
- It is fabricated from living and nonliving components.
- The living component is islets of Langerhans, which sense glucose levels and secrete insulin.
- The nonliving component protects the islets from the diabetic's body yet permits the islets inside to thrive.
- The lack of insulin production is the motivation to develop a substitute.

Bioartificial Pancreas

Two goals:

- ❑ To improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia.
- ❑ To ease the burden of therapy for the insulin-dependent.

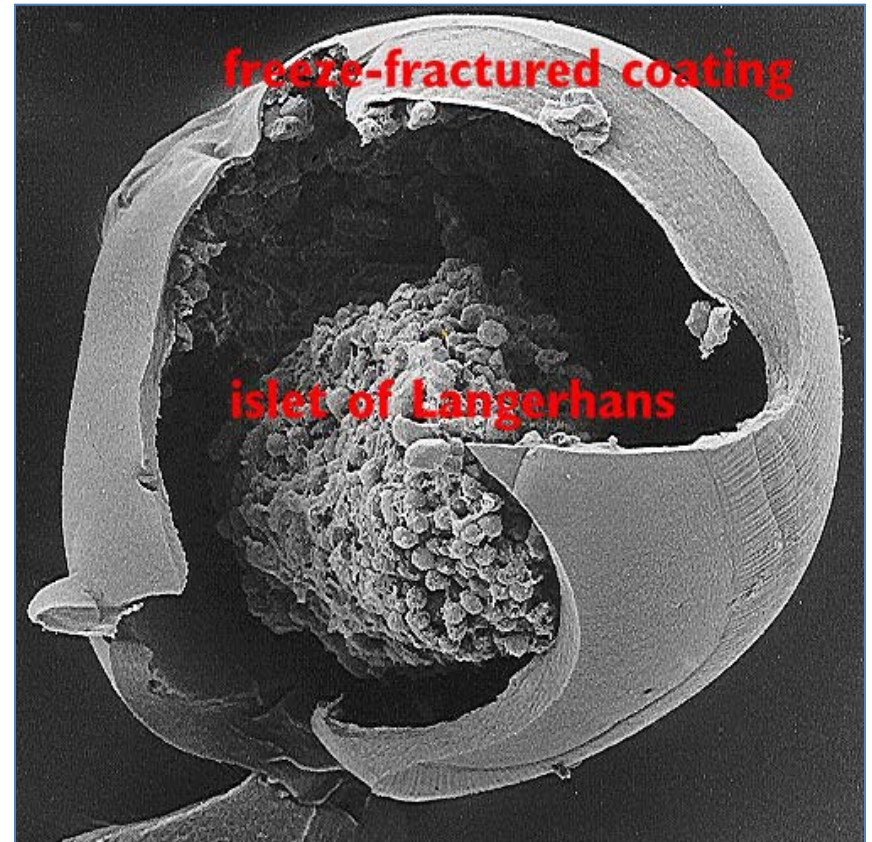
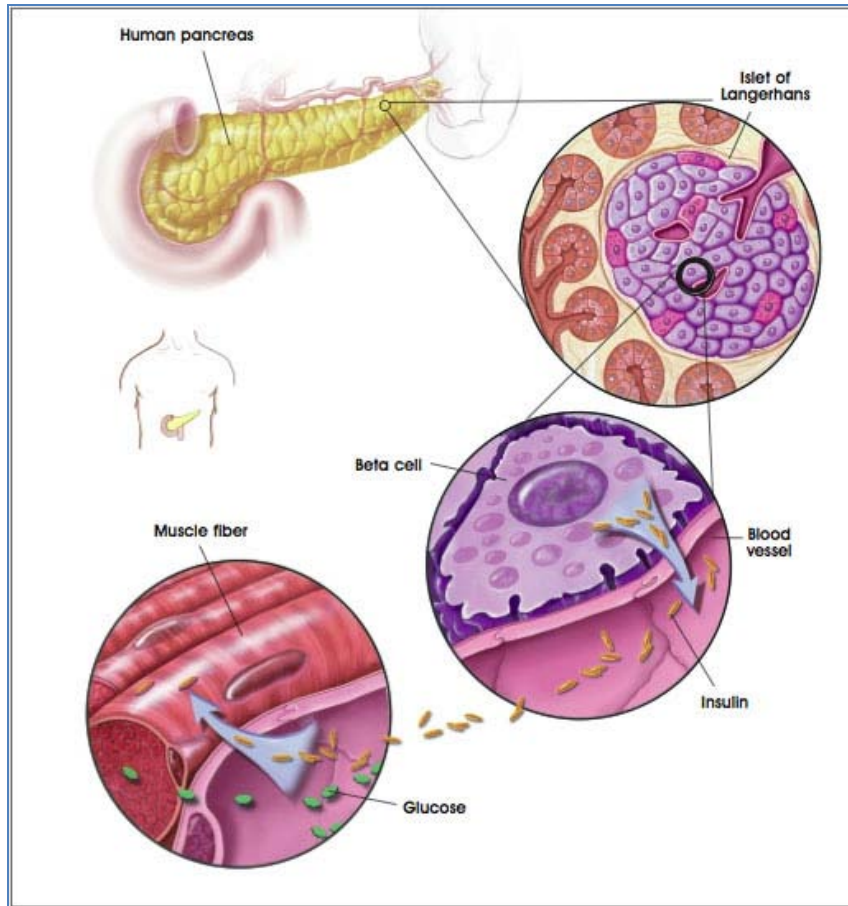
Three major approaches:

- ✓ The medical equipment approach
- ✓ The bioengineering approach
- ✓ The gene therapy approach

Bioartificial Pancreas: The bioengineering approach

- A biological approach to the artificial pancreas is to implant bioengineered tissue containing islet cells.
- They secrete the amount of insulin, amylin, and glucagon needed in response to sensed glucose.
- Islets of Langerhans is the area in which the endocrine (i.e., hormone-producing) cells of the pancreas are grouped.
- After German pathological anatomist **Paul Langerhans** in 1869.

Islet of Langerhans

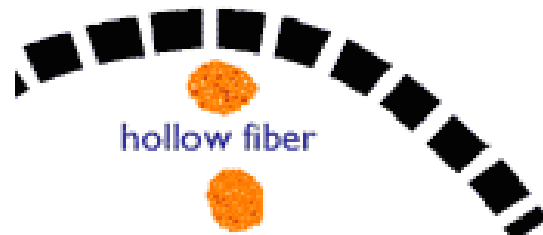


Courtesy: http://www.isletmedical.com/pages/science_islem.htm

Bioartificial Pancreas: The bioengineering approach

- ❑ A bioartificial endocrine pancreas replaces nonfunctioning islets of Langerhans.
- ❑ It responds to changing blood composition with release of hormones including insulin.
- ❑ A bio-artificial pancreas is implanted into the peritoneal cavity of the diabetic and contains two to three million cells.
- ❑ Bio-artificial pancreas designs come in four physical types:
 - Hollow fibers
 - Capsules
 - Coatings
 - Sheets

Bioartificial Pancreas: The bioengineering approach



Courtesy: http://www.isletmedical.com/pages/science_bioartificial.htm

Problems with the Bioartificial Pancreas

- ❑ The islets inside most bio-artificial pancreases die of starvation.
- ❑ The dimensions of most bio-artificial pancreases do not permit oxygen to penetrate to the core of the device.

Design Objectives of a Bioartificial Pancreas

- ❑ Keeps the islets alive and functioning
 - material contacting islets must be biocompatible
 - process for fabrication must not damage islets
 - dimensions must permit rapid diffusion of nutrients
 - dimensions must permit rapid diffusion of insulin

- ❑ Prevent destructive host response
 - outer surfaces must be totally biocompatible (provoking no fibrotic response)
 - all islets must be completely covered (to prevent immune sensitization)
 - permeability must be controllable

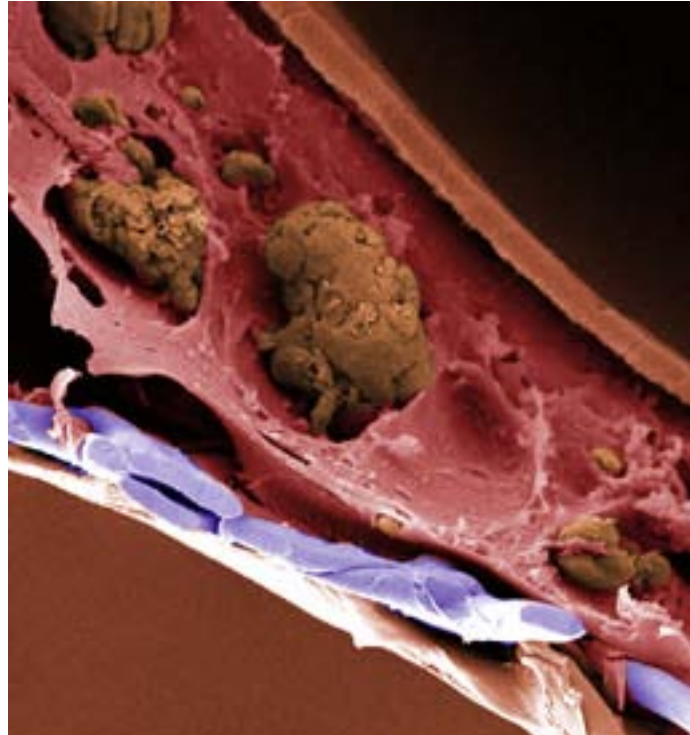
Design Objectives of a Bioartificial Pancreas

- Assure practical surgical implantation
 - islet density must be high (sheet size is not too large)
 - must be retrievable
 - must be bio-stable
 - must be chemically durable
 - must be physically durable
 - must be surgically acceptable

The Islet Sheet

- ❑ In the Islet Sheet, islets are kept alive by diffusion of oxygen, glucose and other nutrients into the sheet; insulin, hormones and waste products diffuse out of the sheet.
- ❑ The sheet is so thin that diffusion alone allows sufficient nutrients to reach the center of the sheet.
- ❑ A coat on the exterior of the sheet prevents contact between the cells inside and immune effector cells of the host as well as inhibiting diffusion of antibody and complement.
- ❑ No immune suppression drugs are needed.
- ❑ The sheet may be removed or replaced at any time.

The Islet Sheet



An electron micrograph of an Islet Sheet

Courtesy: http://www.isletmedical.com/pages/science_bioartificial.htm

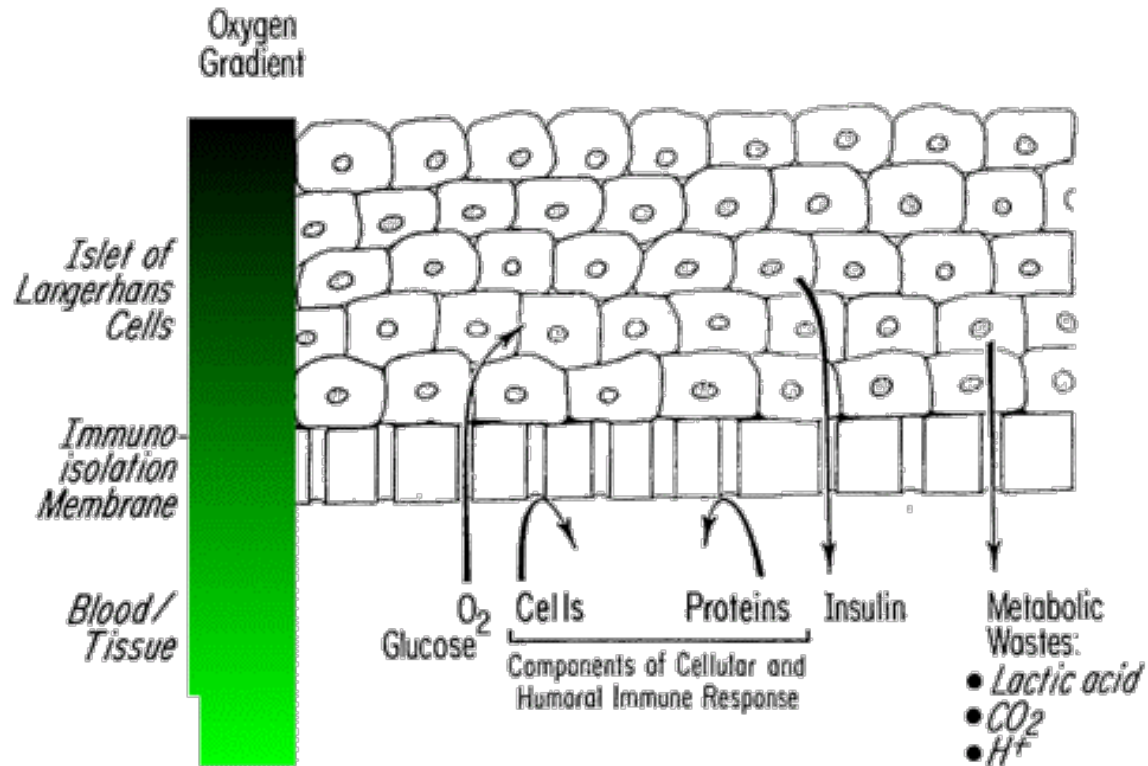
Materials

- ❑ The material used to make the immunoisolation barrier must be compatible with the cells inside as well as the host outside. The material comprising the device and all solvents and reagents used to make it must be nontoxic. For example, organic solvents can dessicate living tissue.
- ❑ The method must not be damaging to the islets. For example, some methods of forming droplets around islets produce high shear forces that damage islet cells. Free radical polymerization can damage the cell membrane.

Nutrition

- ❑ Nutritional requirements of islets are not fully understood.
- ❑ Many small molecules are consumed fairly rapidly and must be freely available.
- ❑ The larger molecules are not consumed at the same high rate. Thus, it is sufficient if these large molecules diffuse slowly through the device.
- ❑ At least in the short term, the limiting nutrient is oxygen.

Nutrition



Courtesy: Colton, C. K. (1995) Cell Transplant 4, 415-436.

Insulin Diffusion

- ❑ The islets must respond quickly to changes in glucose.
- ❑ If the islets are far from the surface of the immunoisolation membrane, it will take a long time from normalization of blood glucose to normalization in the fluid immediately surrounding the islets.

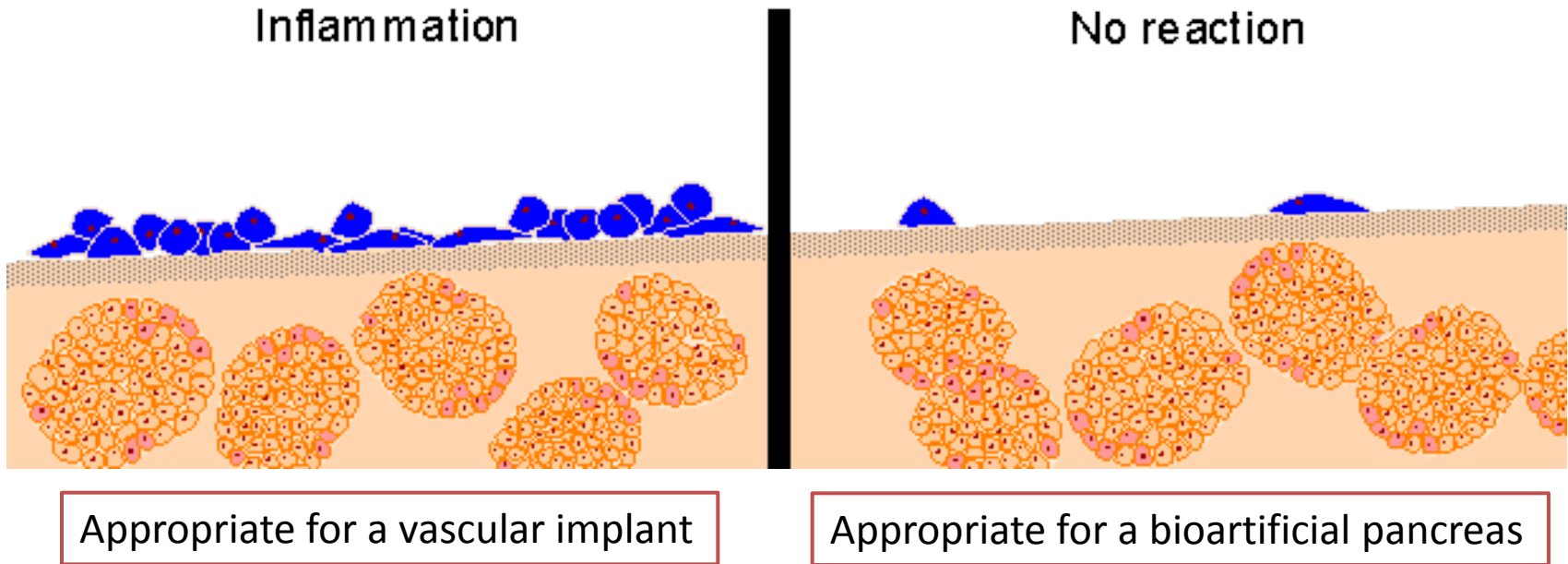


Courtesy: http://www.isletmedical.com/pages/science_bioartificial_3.htm

Biocompatibility

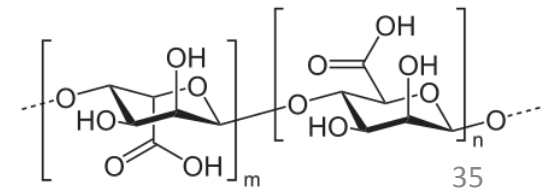
- The material exposed to body tissues must be completely free of fibrogenic character.
- The most common term to describe a substance that is ignored by the body was "biocompatible."
- Device and transplantation people use the term "biocompatible" to mean different things. For a vascular device, "biocompatible" means that the material induces engraftment; the vascular graft is covered with a layer of collagen fibers permitting overgrowth of endothelial cells. However, such overgrowth will starve a cellular implant!
- For a cellular transplant, "biocompatible" means lacking collagen fibers or any material that will promote cellular adhesion.

Biocompatibility



✓ Islet sheets are made from highly purified alginic acids (alginate)

Courtesy: http://www.isletmedical.com/pages/science_bioartificial_4.htm
<http://en.wikipedia.org/wiki/File:Algins%C3%A4ure.svg>

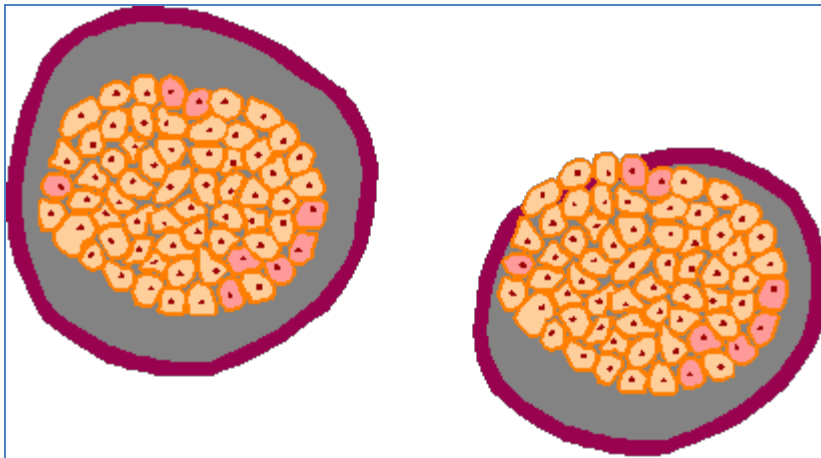


Protecting Islets

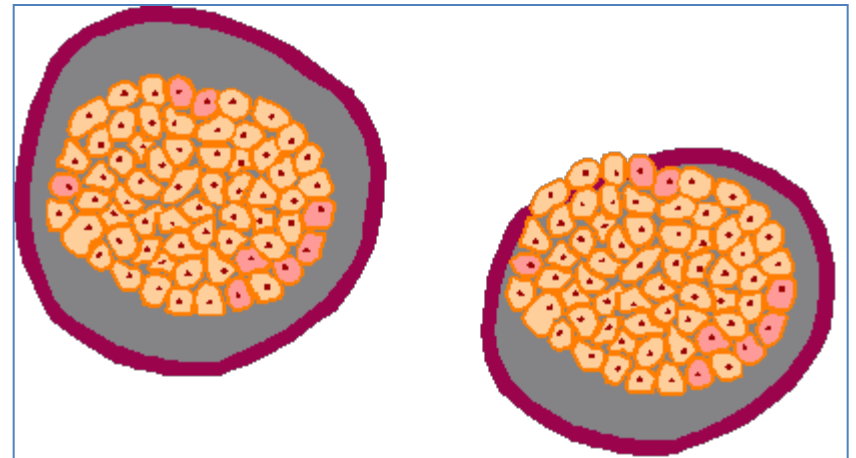
- Some membrane configurations do not cover the entire islet surface.
- If even a small bit of the islet is uncovered, macrophages can infiltrate and destroy the entire islet .
- The cellular attack and destruction sensitize the immune system, leading to a humoral (antibody) response, which can then destroy even those cells that are completely covered.
- Thus, complete coverage of all of the islets is required to protect the islet cells from both cellular and humoral immune responses.

Protecting Islets

A few exposed cells



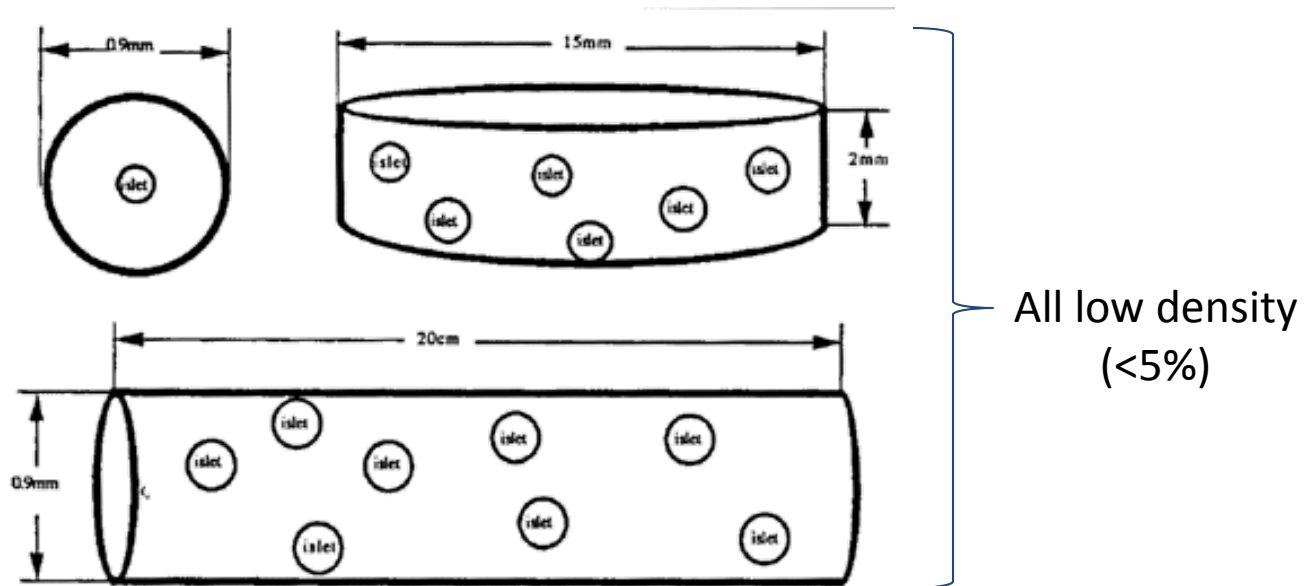
Through the capsules



Courtesy: http://www.isletmedical.com/pages/science_bioartificial_5.htm

High Islet Density

- To minimize trauma, the volume of the final implant should be minimized, as a rule only 2-5 times the volume of the islet.
- Some devices are mostly 'dead space' and therefore are too large for convenient implantation.



Courtesy: http://www.isletmedical.com/pages/science_bioartificial_7.htm

Stable, Durable, Retrievable

- Islets of Langerhans have been implanted into hundreds of diabetics. By far the most common choice is infusion into the portal vein.



Liver

Red and **dark blue**: the hepatic artery and vein.

Green: the bile duct

Light blue: the portal vein

A syringe is used to infuse isolated islets. They travel with the portal blood and lodge in the liver.

Courtesy: http://www.isletmedical.com/pages/science_bioartificial_8.htm

Stable, Durable, Retrievable

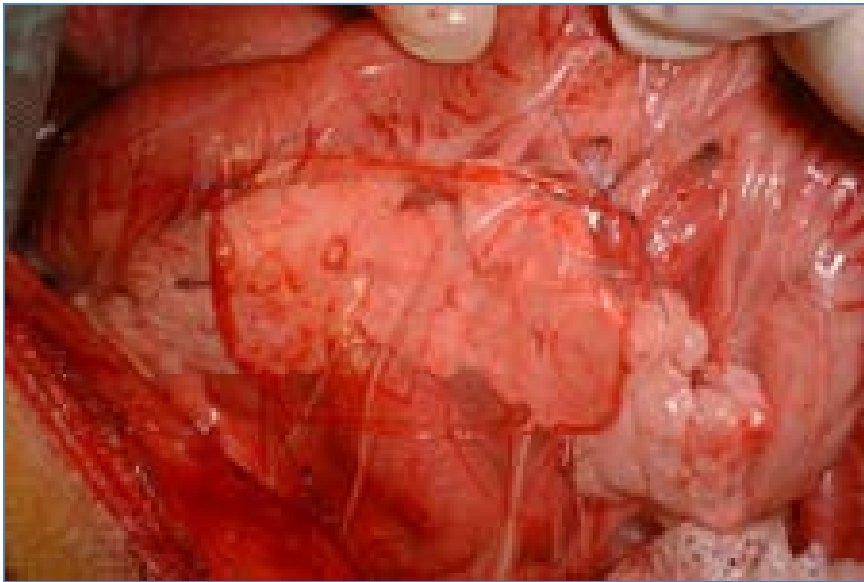
- Biostable: The immunoisolation membrane must remain chemically unchanged in the presence of cells and intercellular fluid.
- Durable: The device must be resistant to cracking and breaking from mechanical stress.
- Retrievable: The device should be retrievable if the graft fails.

The Islet Sheet is biostable, durable and retrievable.

 Cerco Medical LLC

The Islet Sheet

Just after being sutured to a dog



Nine weeks later



Courtesy: http://www.isletmedical.com/pages/science_bioartificial_8.htm

Artificial Heart



Taylor_Correct_Super-small.flv



Questions??

Thanks !!