BME2105 Introduction to Biomedical Engineering

WELCOME !

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Engineering

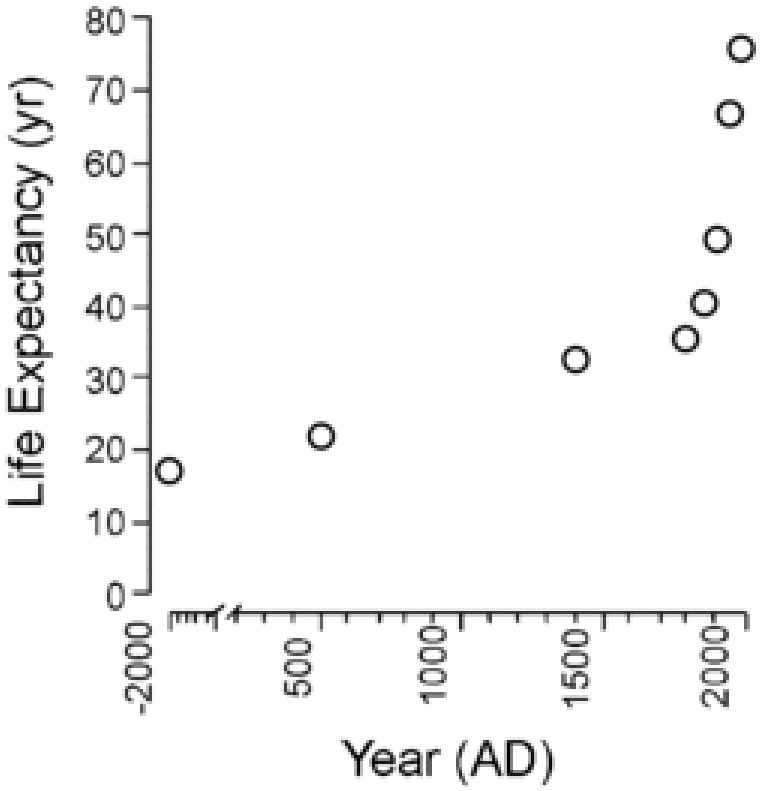
From Merriam-Webster Dictionary:

- *engineering noun:*
  a) the application of **science** and **mathematics** by which the properties of matter and the sources of energy in nature are made useful to people;
  b) the design and manufacture of complex products.

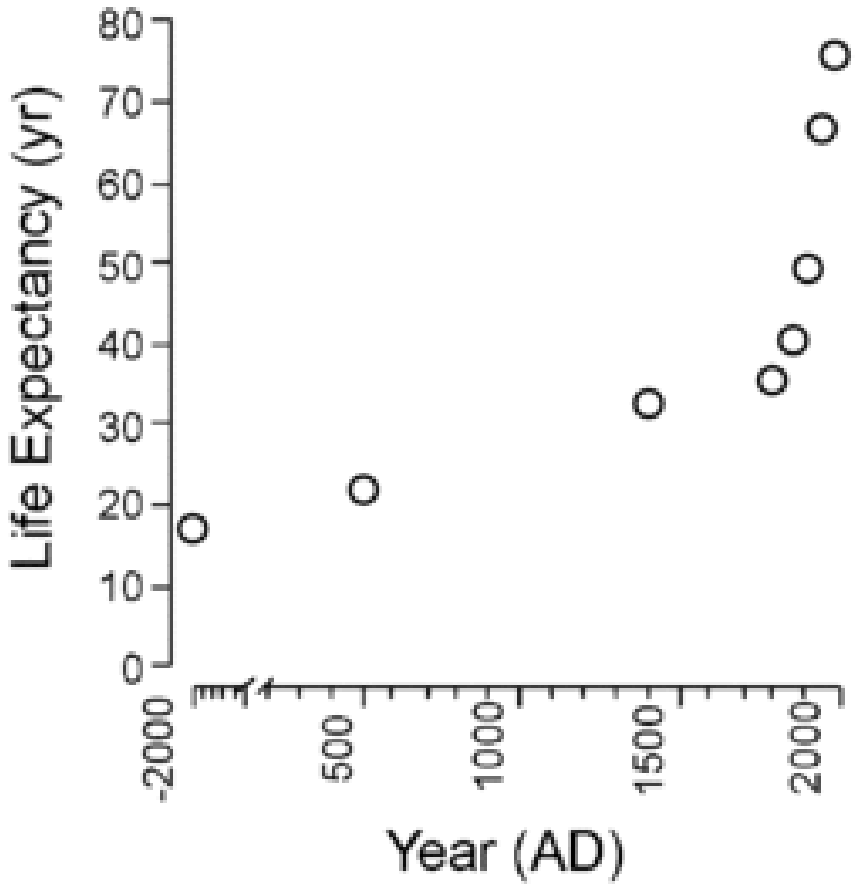
Engineering disciplines

- Mechanical Engineering
- Electrical Engineering
- Civil Engineering
- Chemical Engineering
- Material Engineering
- Bioengineering/Biomedcial Engineering

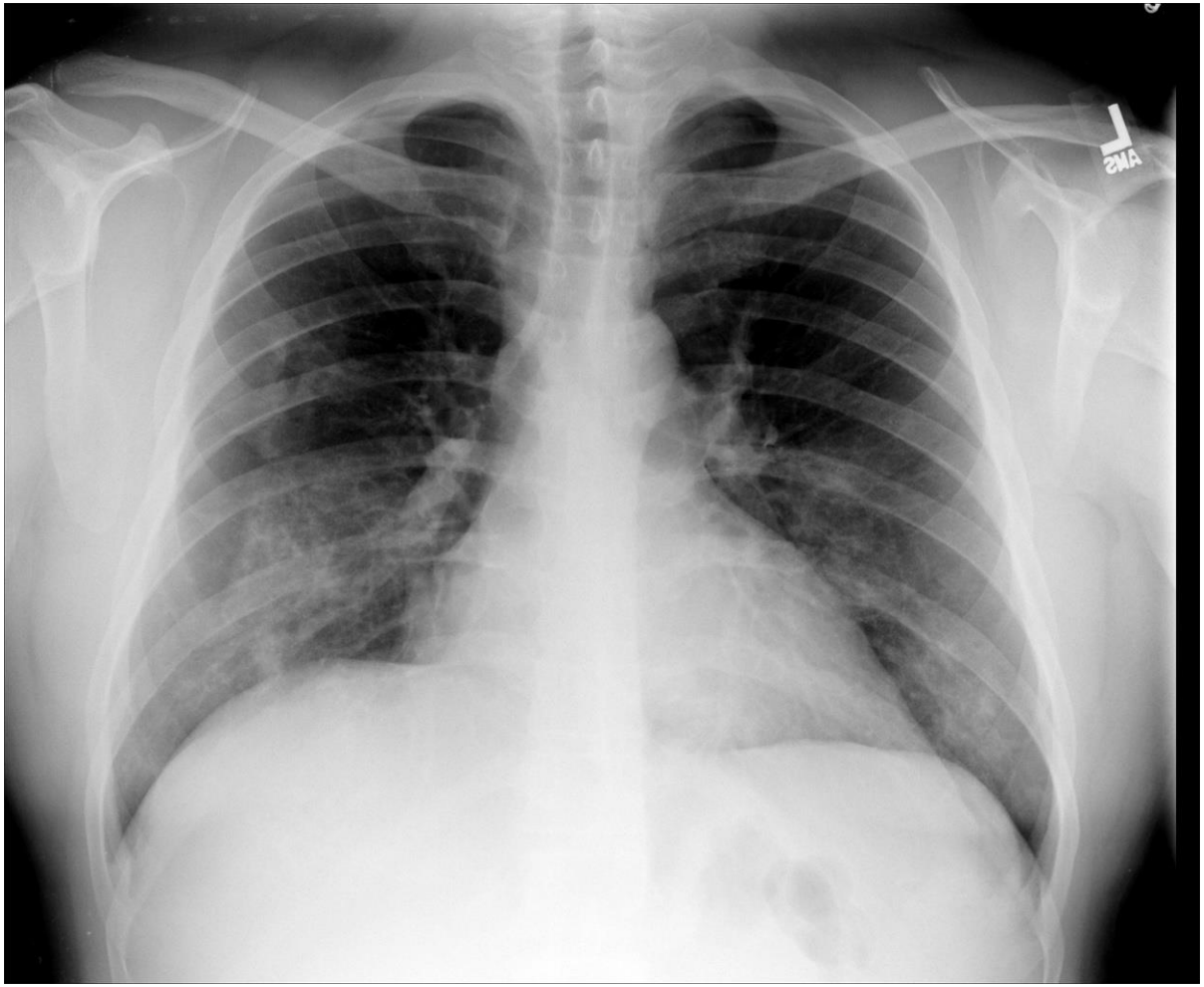
Life Expectancy



Why People are living longer?

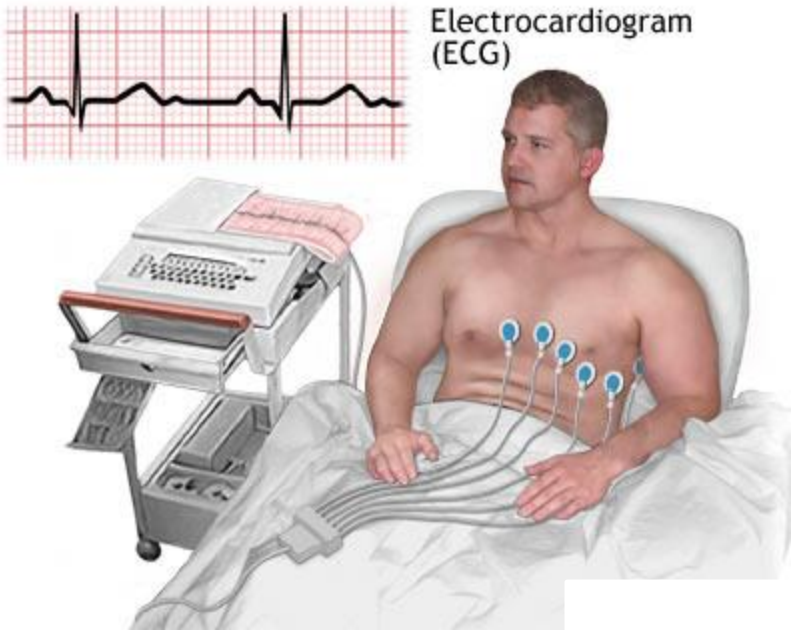


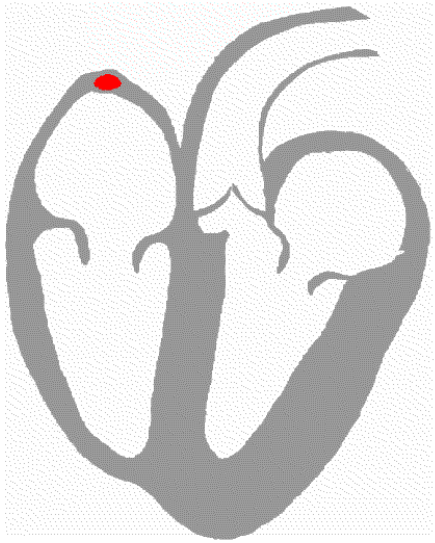
X-ray



Heart and Lung Machine

ECG (Electrocardiograph)





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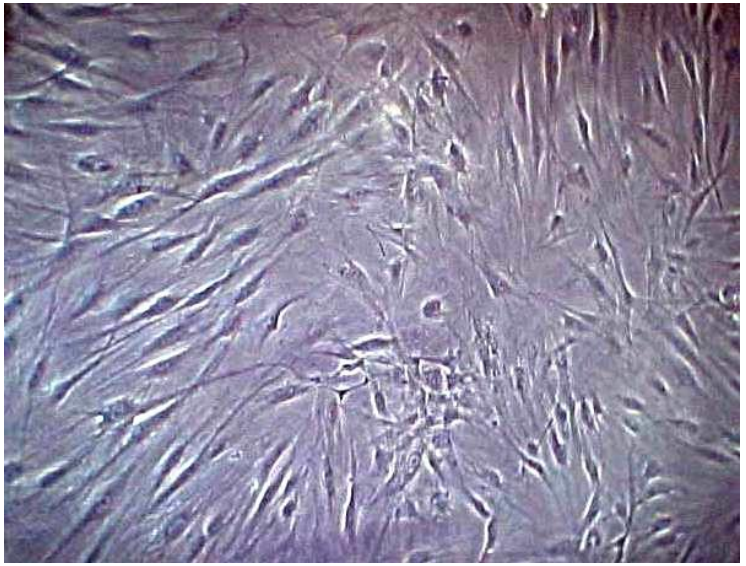
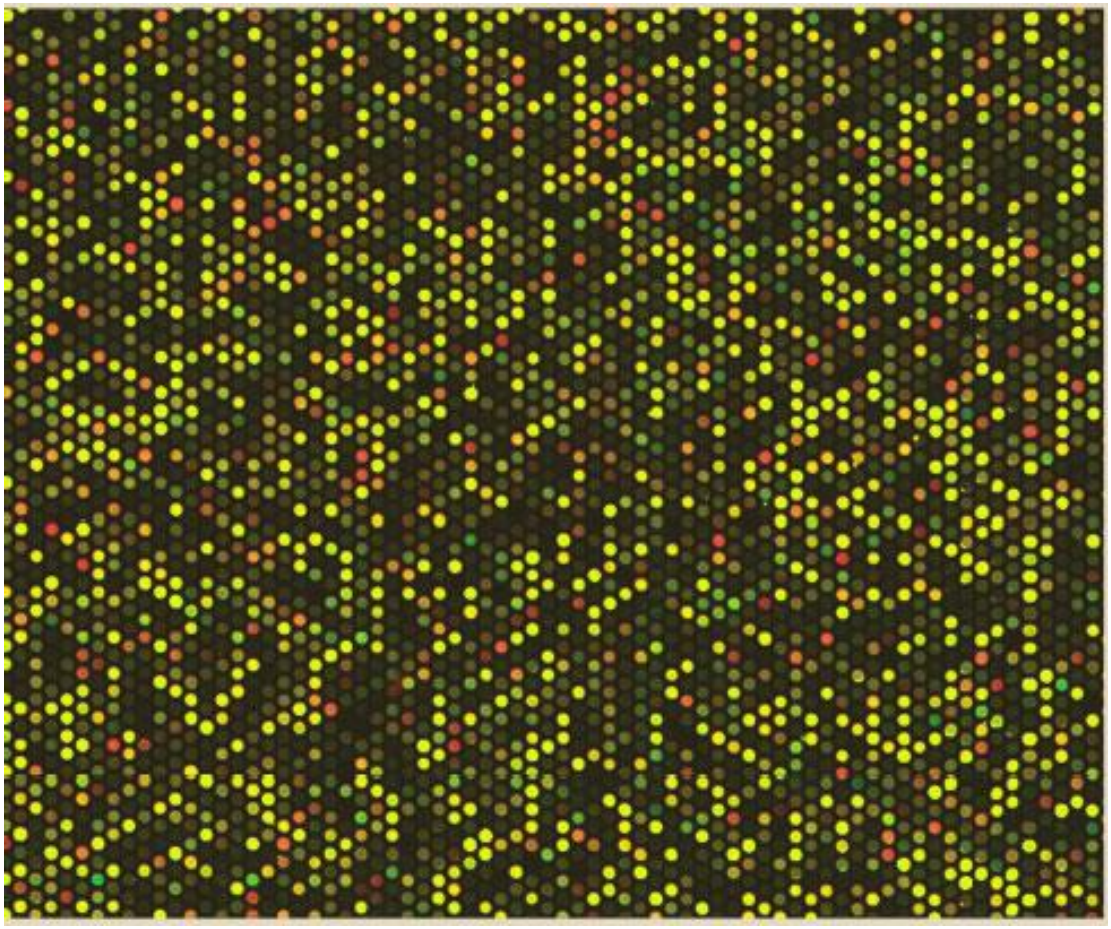
Cell Culture Technology



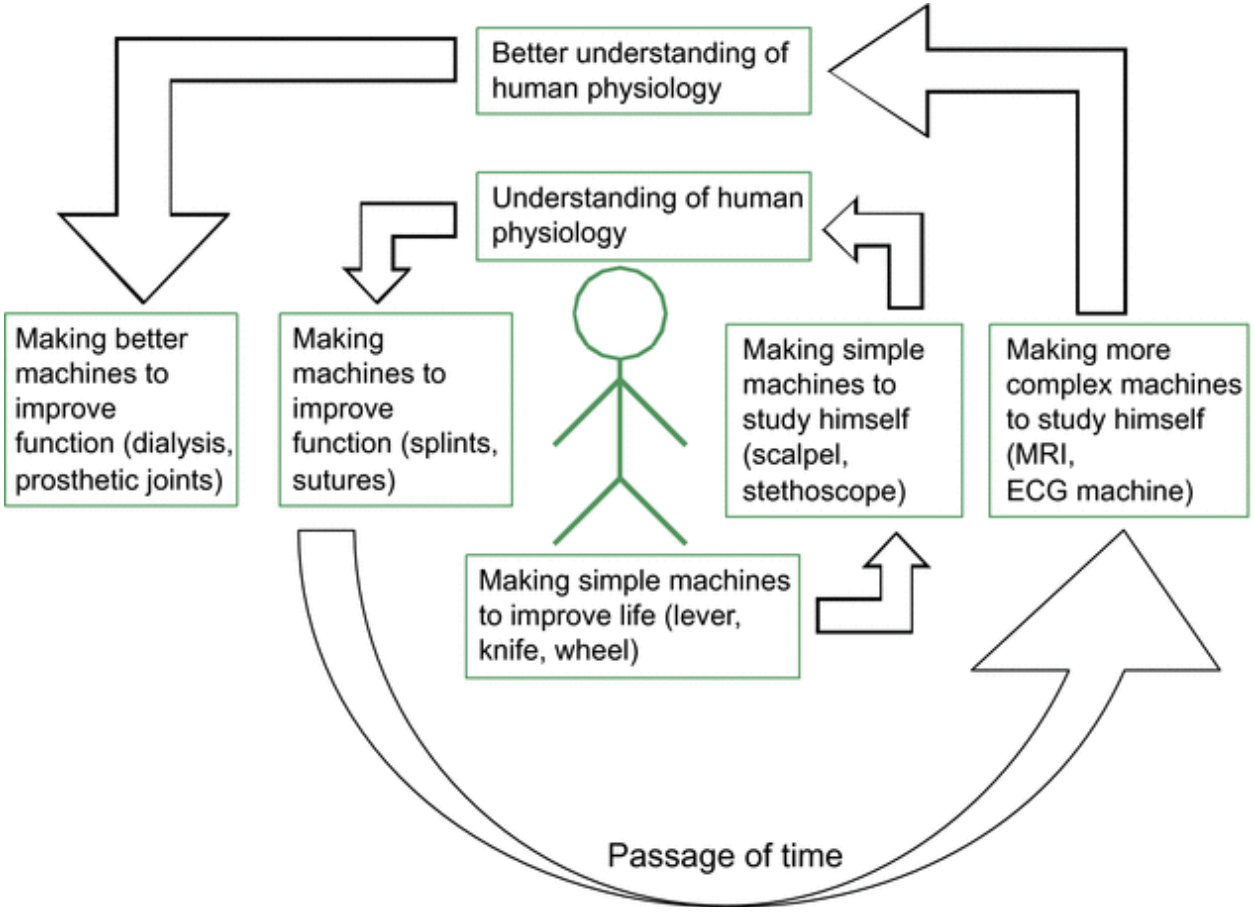
Cell Culture Technology: Artificial Skin

Artificial Heart

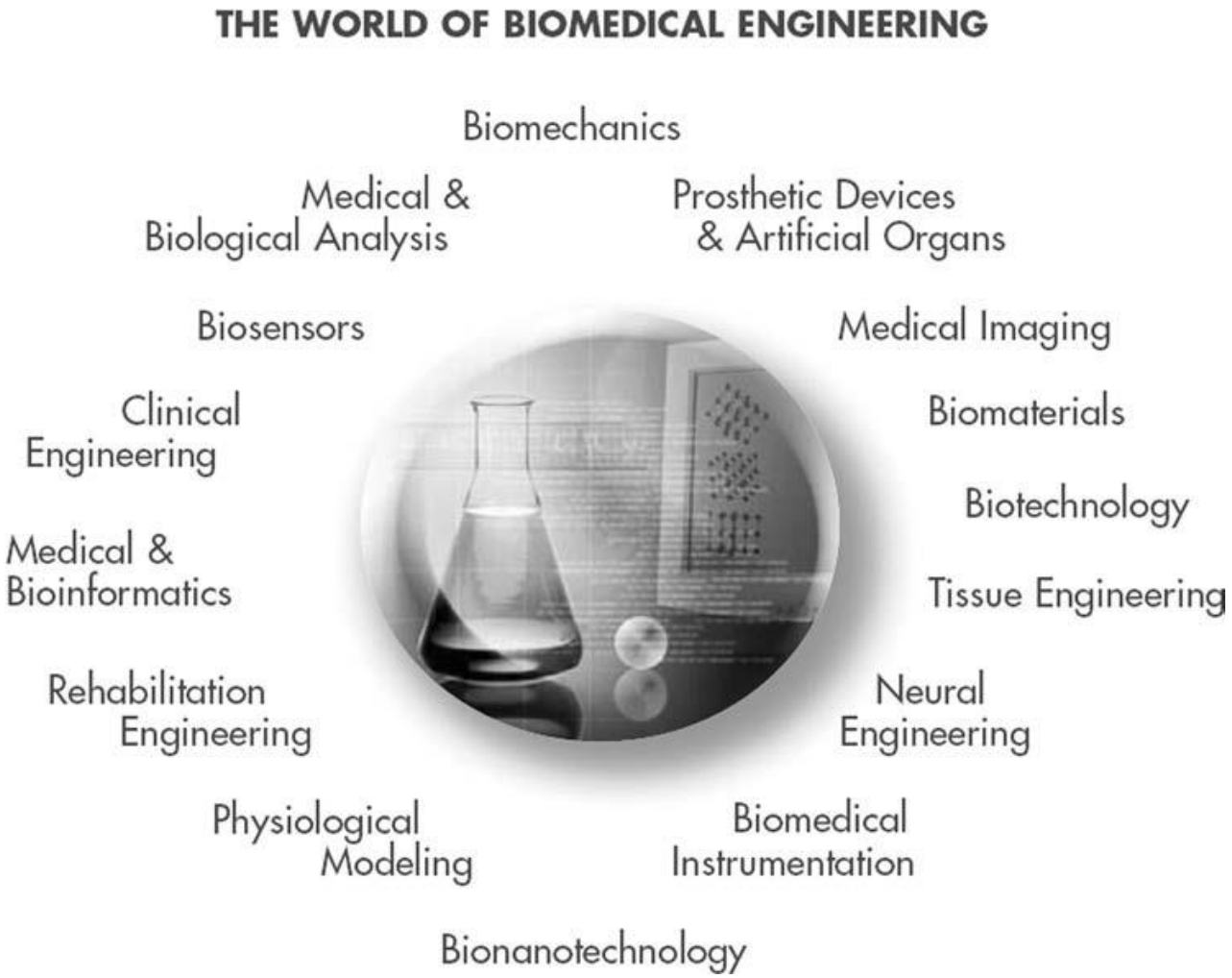
Gene Chip Technology



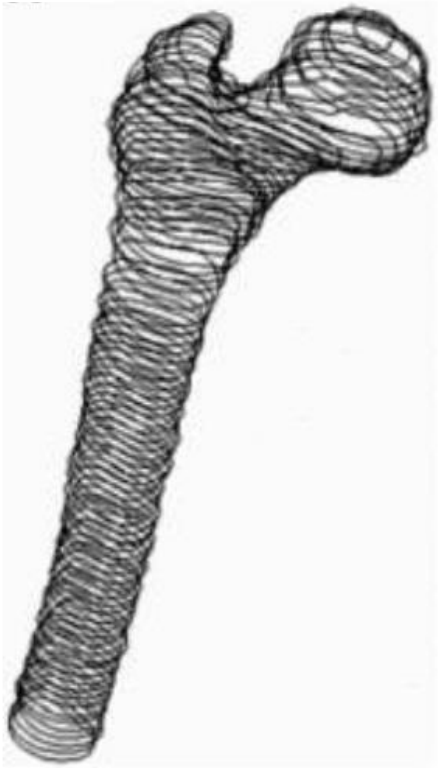
Evolution of the Engineering for Health& Medicine

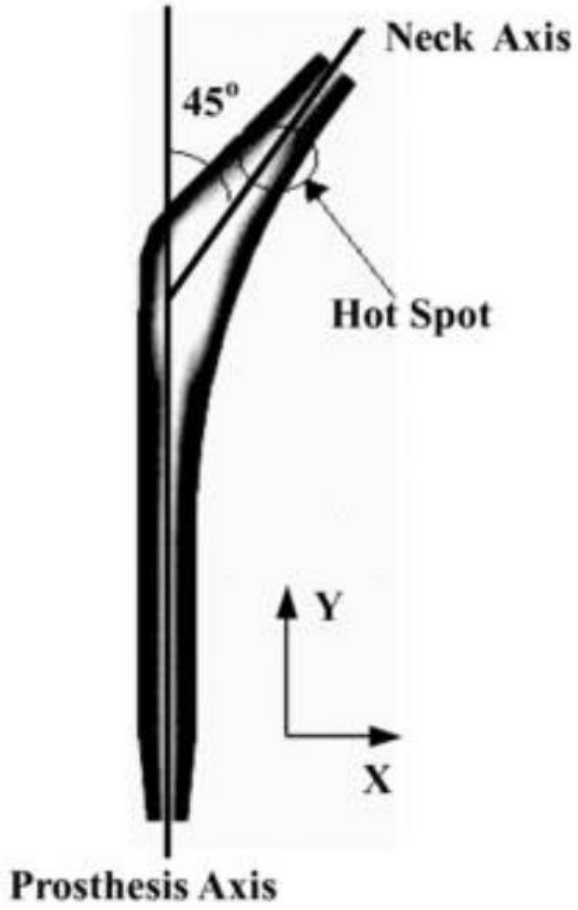


Multidiciplinary Areas

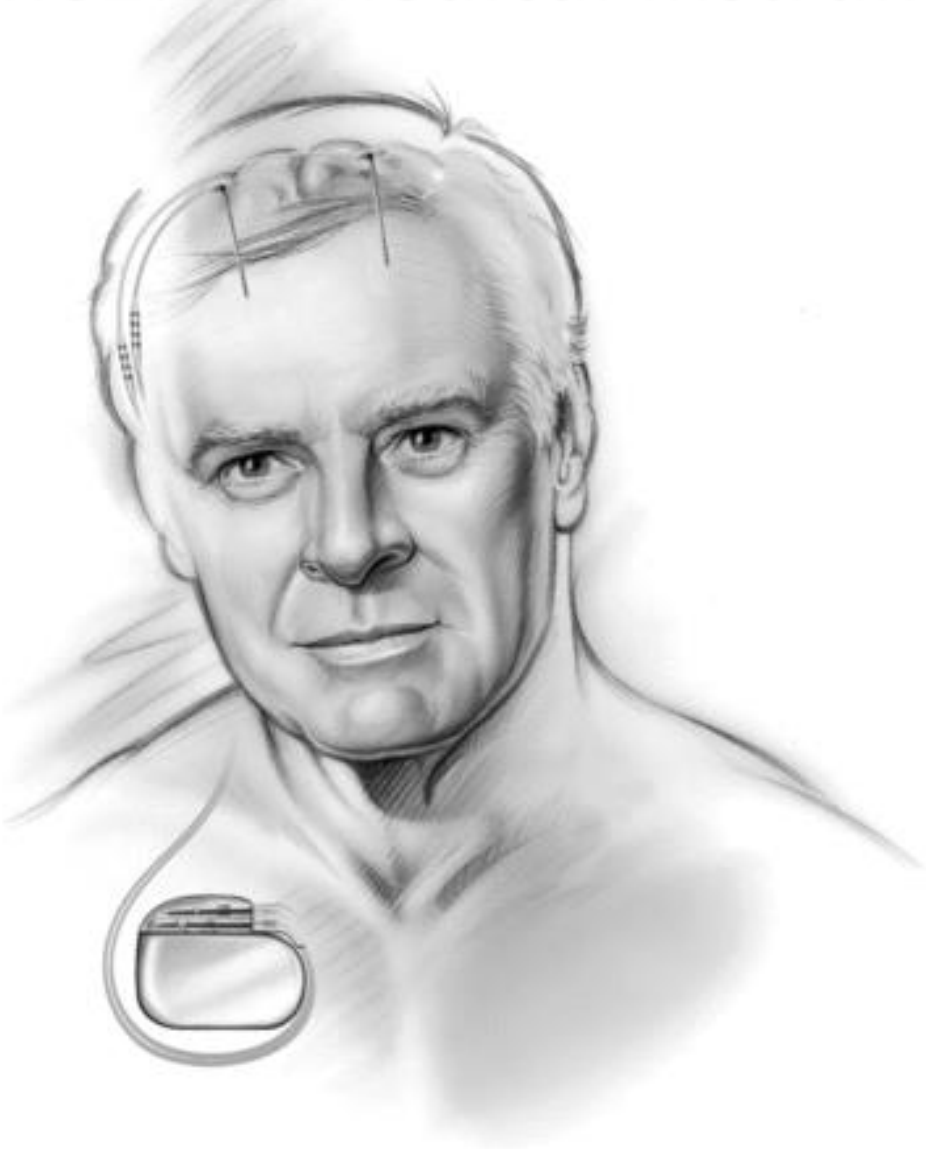


Subdicipline1: Physiological Modeling

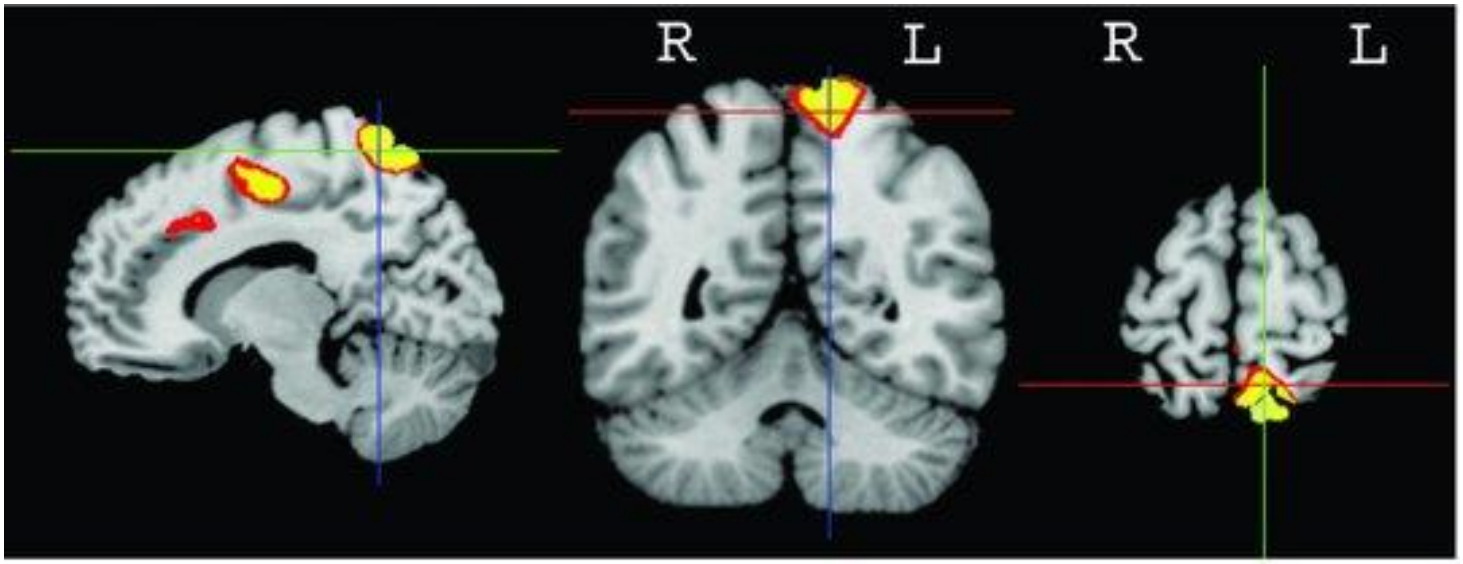


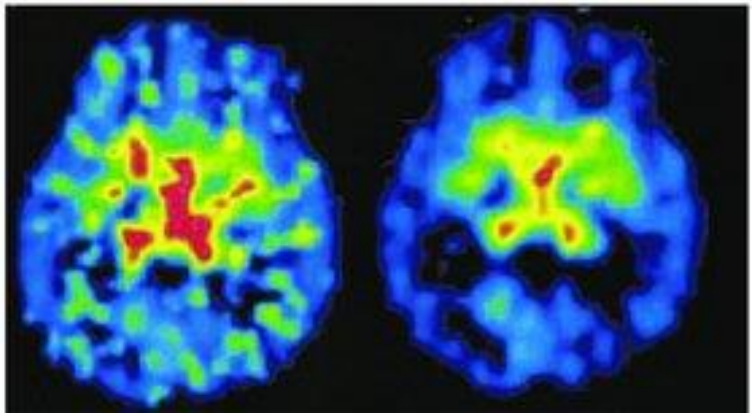


Subdicipline2:Biomedical Instrumentation



Subdicipline3: Biomedical Imaging





Subdicipline 4: Biomechanics

Subdicipline 5: Cellular and Molecular Engineering

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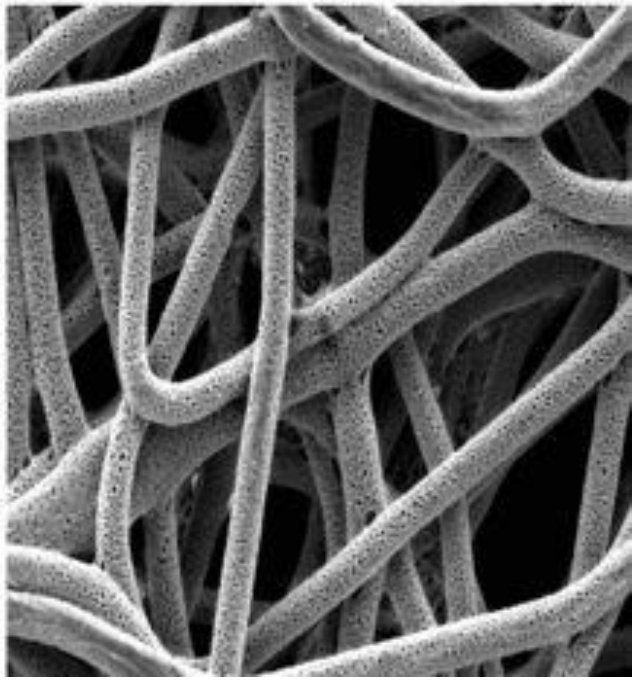


Lecture Contents

- Molecular Fundamentals
- Genetic Engineering
- Cell and Tissue Engineering
- Cardiovascular System and Engineering
- Neural Engineering
- Immune System and Engineering
- Biomedical Imaging
- Technology and Cancer
- Biomechanics and Orthopedics

Course Grading

- Homework (10%)
- Midterm Exam (30%)
- Final Exam (30%)
- Project (30%)

Reference:

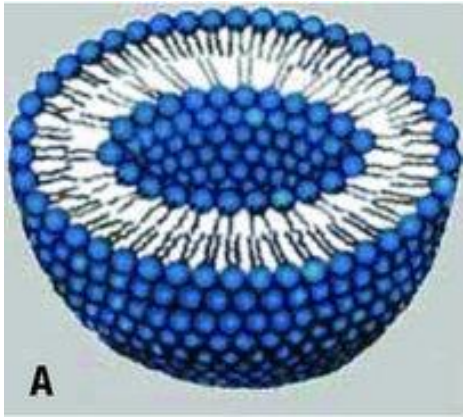
W. Mark Saltzman, Biomedical Engineering: Bridging Medicine and Technology, Cambridge University Press, 2009. (http://books.google.com.hk/books?id=4b4Mxsiw9gIC&hl=zh-TW&source=gbs_book_other_versions)

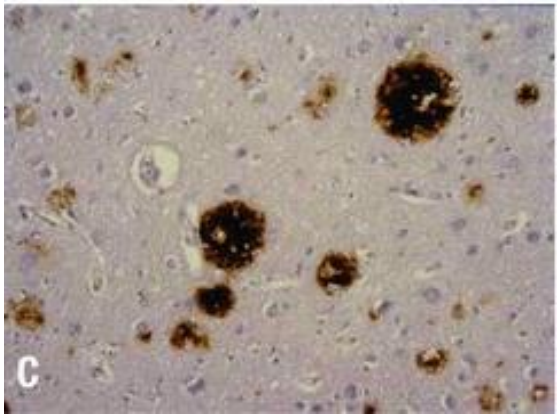
Molecular and Cellular Fundamentals

Biological Molecules

Knowing how molecules interact with each other and with their environments helps engineers to manipulate these molecules to create new tools for treating disease.

- Nucleic acids
- Proteins
- Carbohydrates
- Lipids





Bonding between atoms and molecules

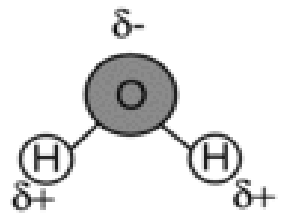
- Ionic bonds

  formed when electrons are transferred from one atom to another (NaCl, Salt).

- Covalent bonds

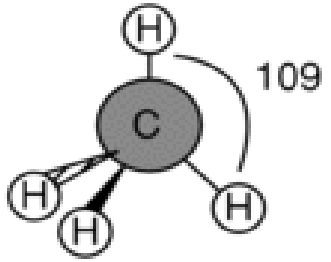
  Sharing electrons: polar or nonpolar

Water H_2O



Polar
Unequal sharing of electrons results in polar distribution of charges

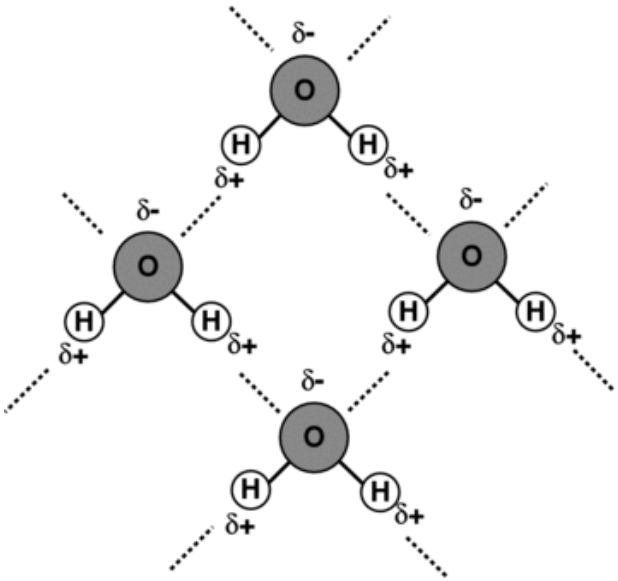
Methane CH_4



Nonpolar
Charges are distributed symmetrically

Bonding between atoms and molecules

- Hydrogen bonds

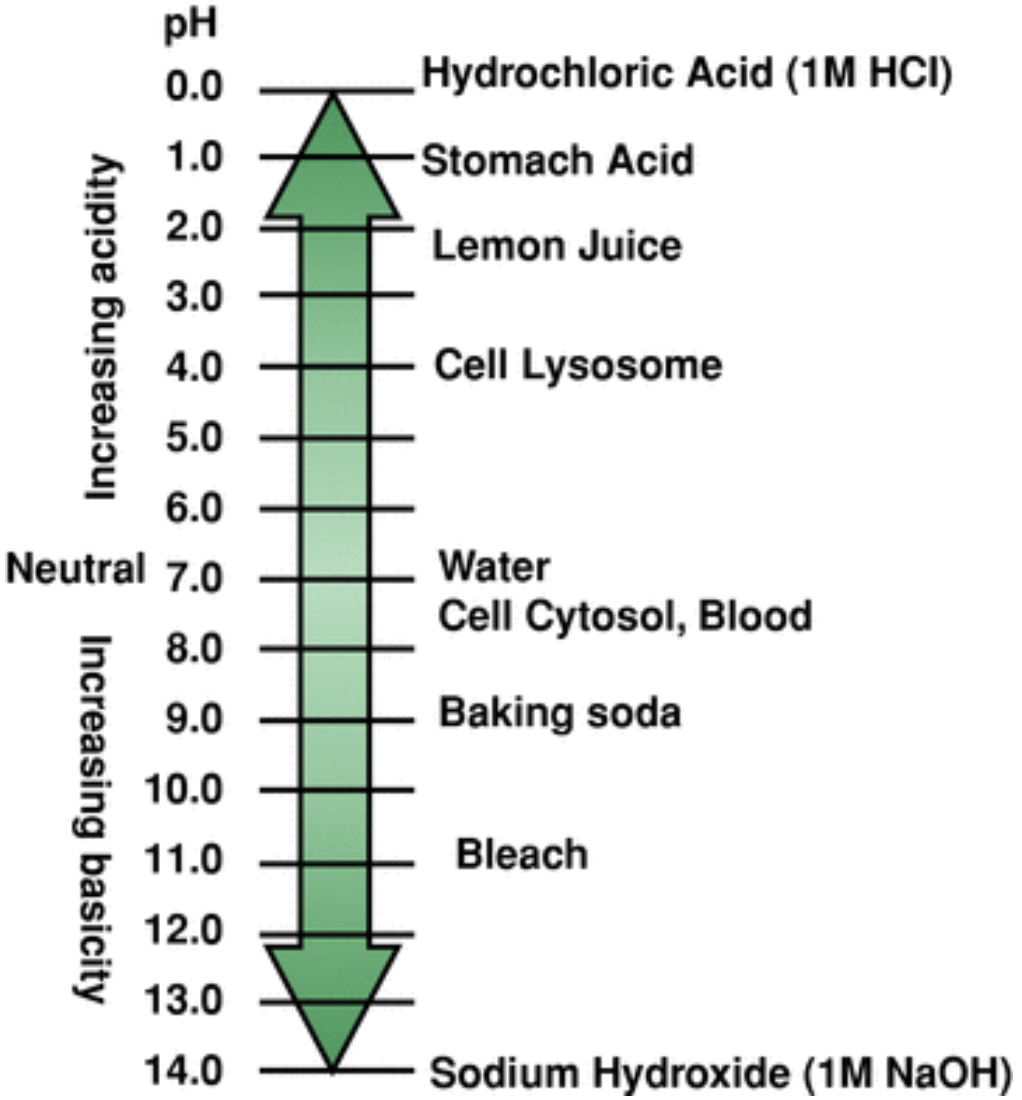


Bonding between atoms and molecules

- Van der Waals interactions

Water: The medium of life

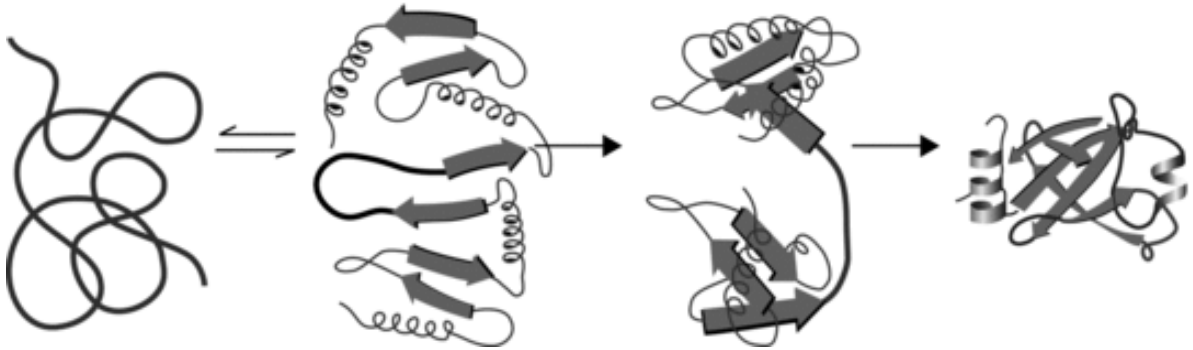
- The right pH



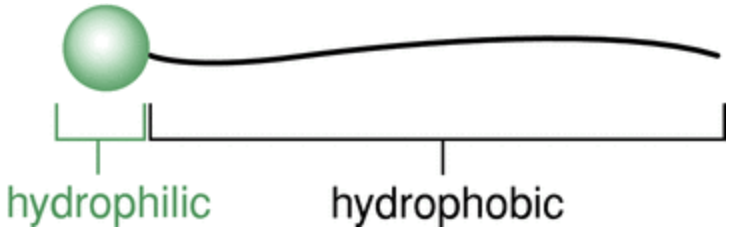
Water: The medium of life

- Hydrophilic: “water loving”
- Hydrophobic: “water fearing”

Nonpolar molecules aggregate together, example: protein folding

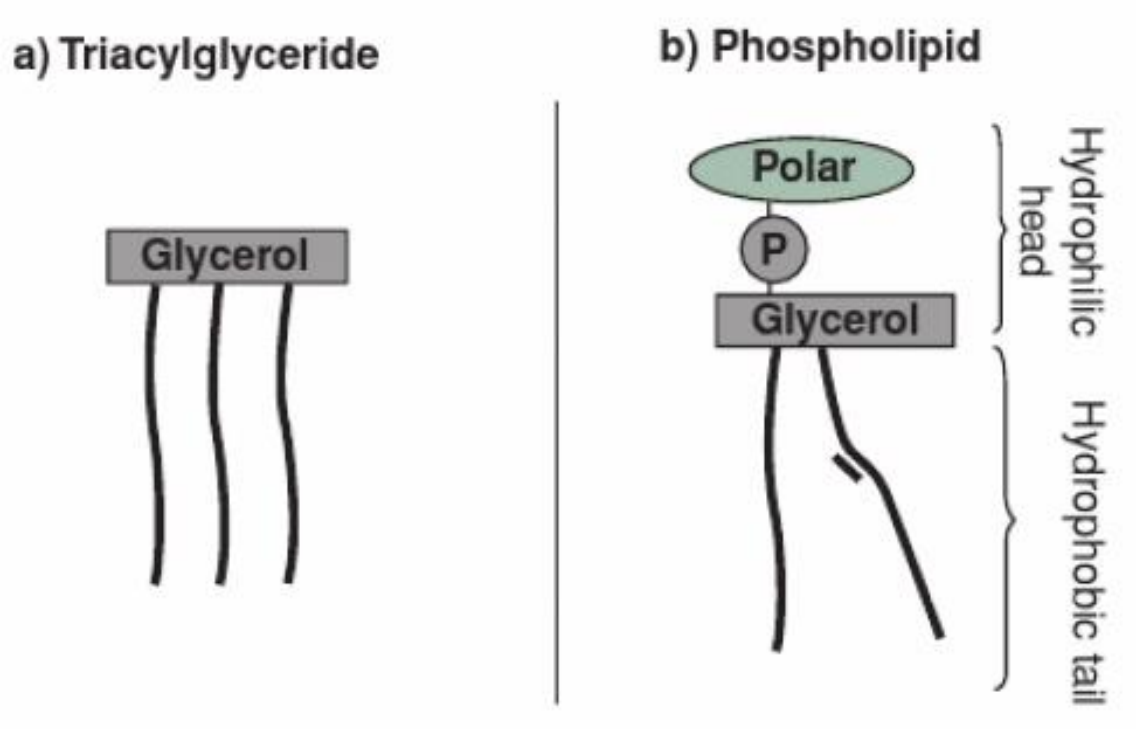


Amphiphilic molecule



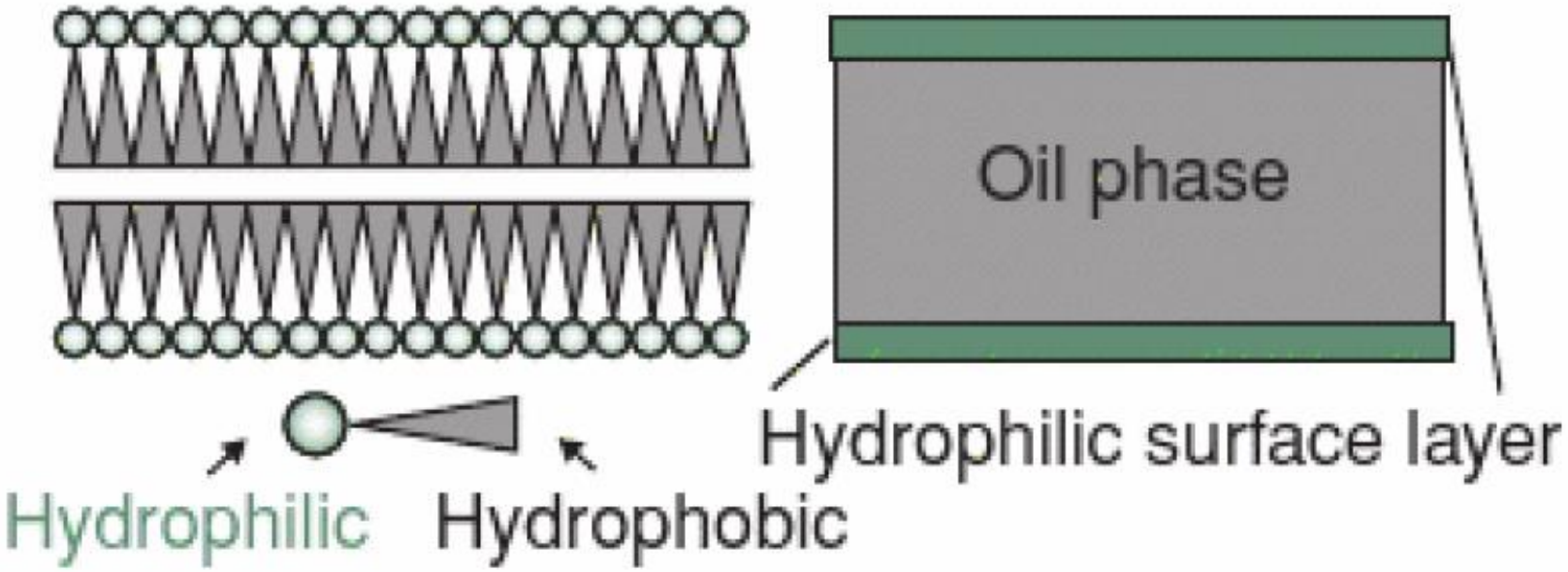
Lipids

- Two types of lipids:
  - Triglyceries (energy storage)
  - Phospholipids



Phospholipids

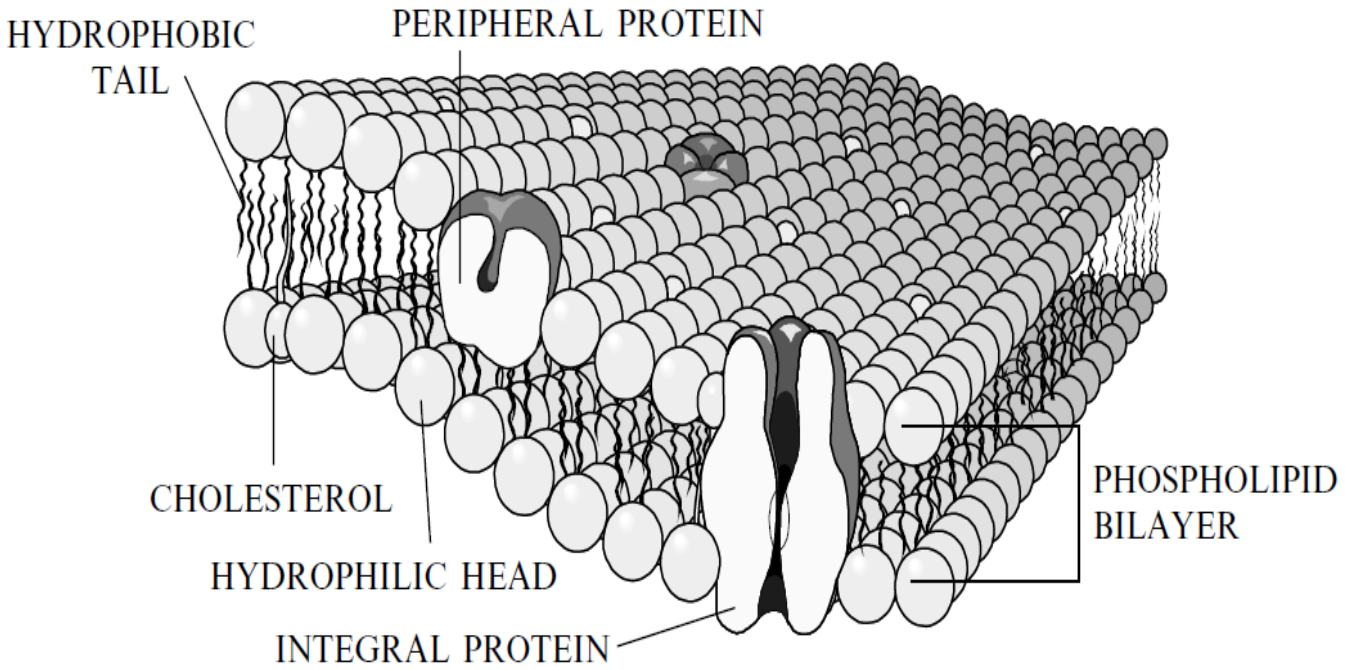
- Self-assembly in water:



- Solve problem for cells: separate interior water from outside water

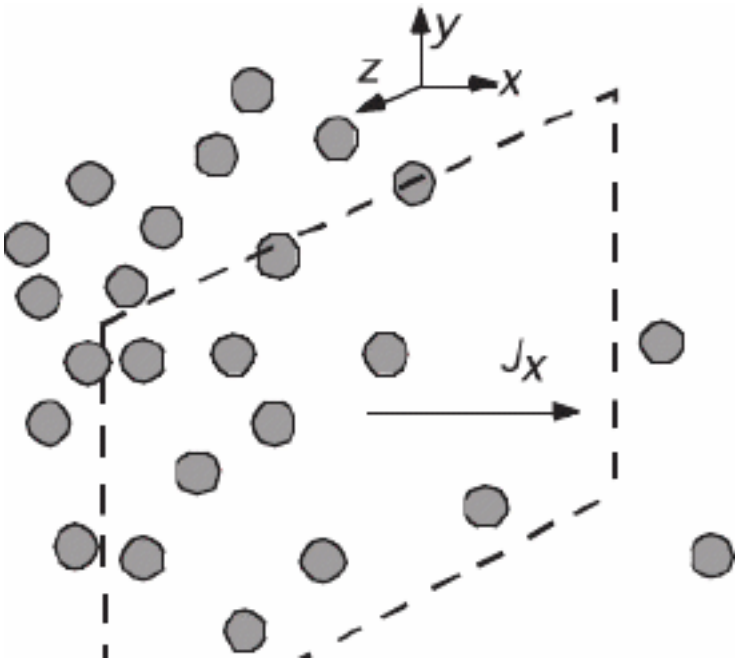
Cell Membrane

- Phospholipids are major component of the cell membrane.



Transport across the cell membrane

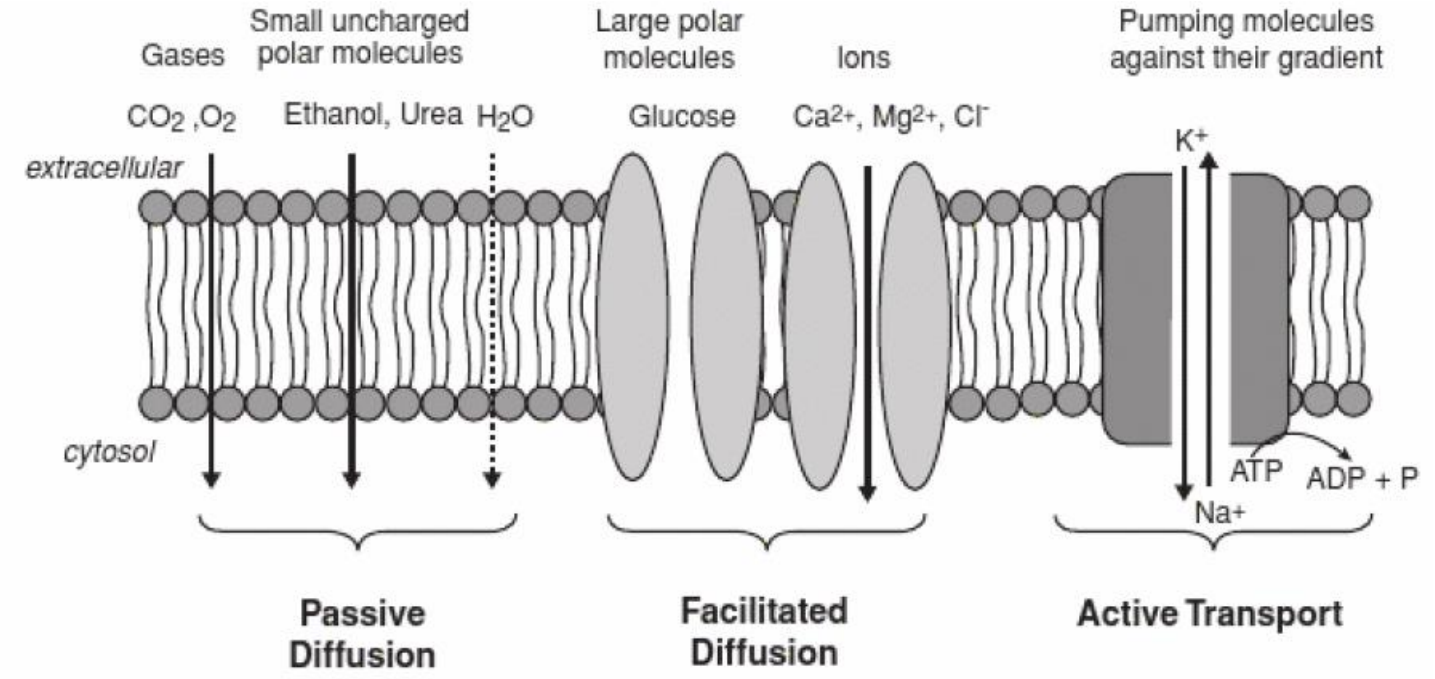
- Diffusion:



- Passive, depend on the concentration difference, O_2, CO_2, etc…
- Diffusion of water (Osmosis)

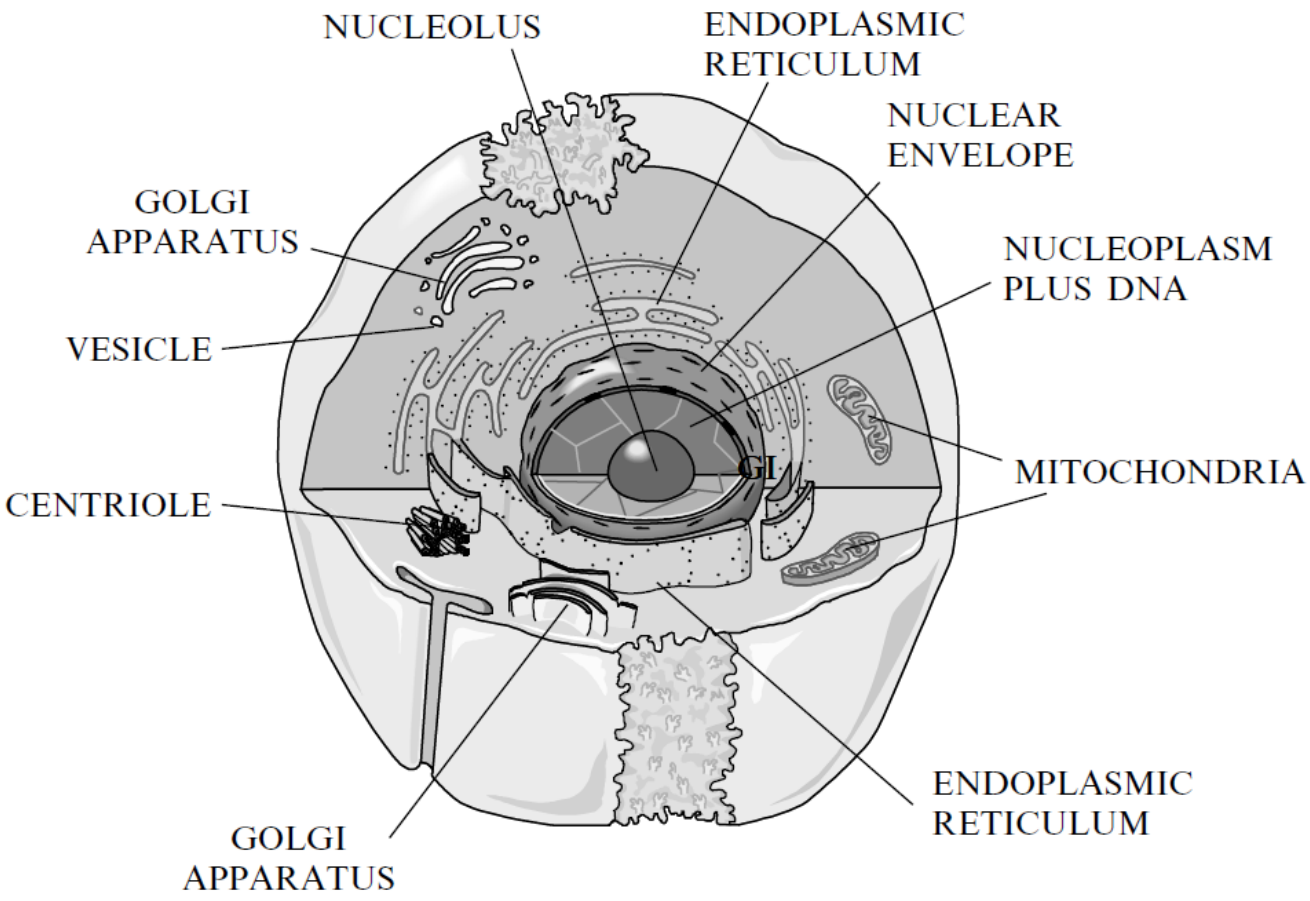
Transport across the cell membrane

- Facilitated Diffusion
- Active transport (energy consuming)

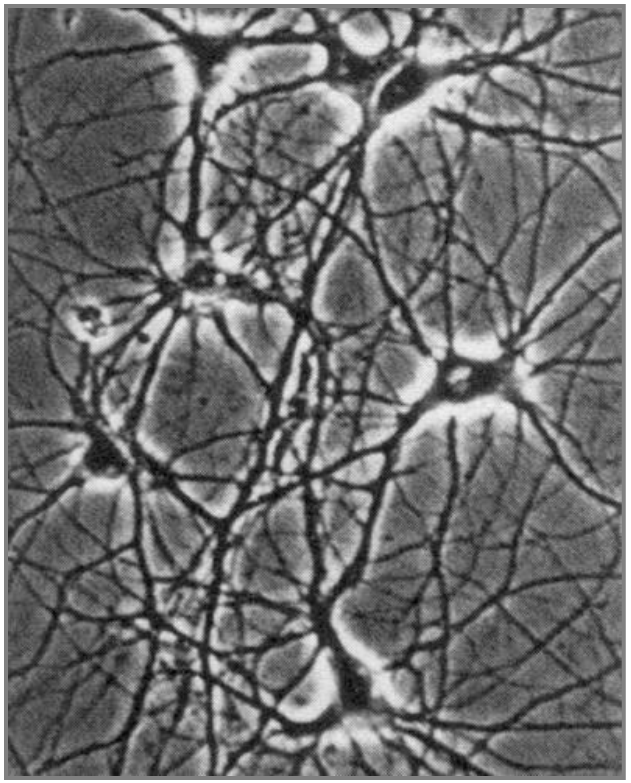


Inside a Cell

- Nucleus, cytosol, organelles, structure proteins



Cell culture



- Convenient model of cell function
- Protein/biomolecule production – yeast and plant cultures
- Growth of cells for tissue engineering applications

Cell culture - challenges

Equipment / techniques of cell culture seek to replicate and control specific aspects of the tissue environment:

- Temperature
- pH
- Nutrients delivery
- Waste removal
- Anchorage

- Experimental observation and manipulation

Modern materials

Cell culture

Year	Event
1885	**Roux** demonstrates that chick cells can be kept alive in saline
1907	**Harrison** cultures frog spinal cord cells on clotted lymph, basis of neuronal doctrine
1913	**Carrel** established extended cultures through regular feeding under aseptic conditions
1948	**Earle**: single cells isolated and cultured, giving rise to the L cell line
1950s	initial use of serum in media
1952	**Gey** established HeLa cell line from a human cervical carcinoma
1955	**Eagle** systematic investigation into nutrient formulations.
1958	**Temin** and **Rubin** viral transformation of chick cells accomplished in the laboratory
1964	**Kato** and **Takeuchi** grow complete carrot from single plant cell
1965	**Harris** and **Watkins**: viral-induced fusion of mouse and human cells
1975	**Köhler** and **Milstein**: first monoclonal antibody-secreting hybridoma cell lines
1976	**Sato** demonstrates in serum-free culture that different cells need different media
1970's	**Boyer** and **Cohen** develop recombinant DNA-technology
1977	**Wigler** and **Axel** introduce mammalian genes into cultured cells
1986	**Martin** and **Evans** isolate and culture mouse embryonic stem cells
1998	**Thomas** and **Gearhart** isolate human embryonic stem cells

Cell culture media – Dulbecco's Modified Eagle's Medium

Amino acids (mg/L)

- L-Arginine•HCl (84.0)
- L-Cystine (48.0)
- L-Glutamine (584.0)
- Glycine (30.00)
- L-Histidine•HCl•H_2O (42.0)
- L-Isoleucine (104.8)
- L-Leucine (104.8)
- L-Lysine•HCl (146.2)
- L-Methionine (30.0)
- L-Phenylalanine (66.0)
- L-Serine (42.0)
- L-Threonine (95.2)
- L-Tryptophan (16.0)
- L-Tyrosine (72.0)
- L-Valine (93.60)

Other components (mg/L)

- Glucose (4500)
- Phenol Red (15.0)
- Sodium Pyruvate (110.00)

Salts (mg/L)

- $CaCl_2$ (200.0)
- $Fe(NO_3)_3$•$9H_2O$ (0.1)
- KCl (400.0)
- $MgSO_4$•$7H_2O$ (200.0)
- NaCl (6400.0)
- $NaHCO_3$ (3700.0)
- NaH_2PO_4•H_2O (125.0)

Vitamins (mg/L)

- D-Ca Pantothenate (4.0)
- Choline Chloride (4.0)
- Folic Acid (4.0)
- *i*-inositol (7.0)
- Nicotinamide (4.0)
- Pyridoxine•HCl (4.0)
- Riboflavin (0.4)
- Thiamine•HCl (4.0)

Cell culture media – focus on pH

$$pH = -\log\left[H^+\right]$$

general buffering concept

$$A^- + H^+ \leftrightarrow HA$$

bicarbonate buffering system

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

bicarbonate (soluble)	carbonic acid (soluble)	carbon dioxide (gas)

- Carbon dioxide dissolved in media and in the atmosphere regulate pH
- Primary mechanism of pH regulation in animal tissues
- Phenol red in the media changes color with respect to pH.
  - Orange-red at correct pH.
  - Purple at high pH
  - Yellow at low pH (*e.g.* in the presence of a lot of lactic acid)

Cell culture incubators – pH and temperature

Cell culture incubator

- Maintain temperature
  - 37° C for most mammalian cells
- Maintain humidity
- Maintain 5% CO_2/air mixture
  - Bicarbonate buffer
  - pH 7.4

Outside the incubator

- Relatively easy to control temperature
- Control of pH ~ 7.4
  - bicarbonate for closed system
  - HEPES buffer - good
  - Tris buffer – okay

MCO-20AIC with world recognized SANYO Electronics microprocessor control. Shown with five adjustable shelves, included.

This all acts in concert with cell growth geometry

Cell culture media – antibiotics

Reduce growth of bacteria, yeasts, fungi, *etc.*

- Penicillin-G, Streptomycin (bacteria)
- Gentamycin (bacteria)
- Fungizone (Amphotericin B) (fungi, yeasts)
- Ampicillin, Neomycin, Kanamycin (bacteria)
  - important in recombinant DNA technology

Cell culture media – serum

With the components describe to here, cells can live, but don't thrive

Serum, isolated from clotted animal blood, was a critical discovery leading to modern cell culture

Serum is a mix of proteins, carbohydrates, vitamins,minerals, much more.

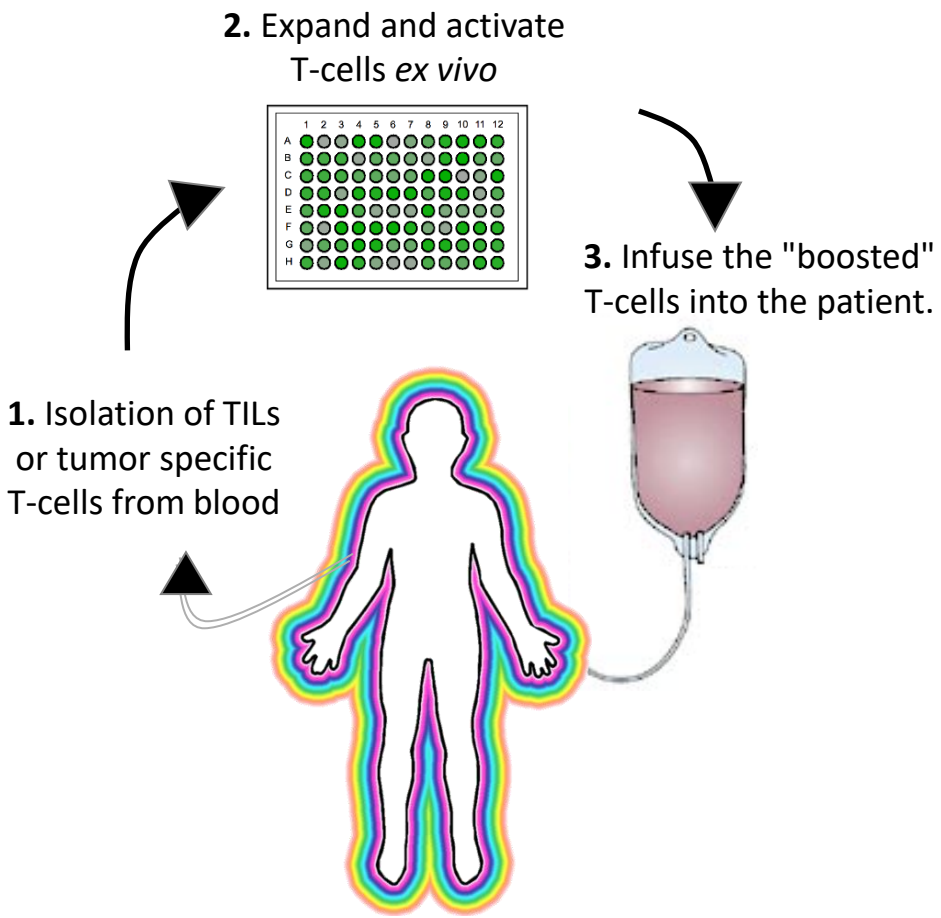
Full understanding of what each component does is not clear, but some important players are:

- Growth factors (<100 ng/ml, each):
  - Epidermal Growth Factor (EGF), Platelet-derived Growth Factor (PDGF), IGF-1, IGF-2, FGF, IL-1, IL-6
- Hormones (<100 ng/ml each):
  - Insulin - promote uptake of glucose and amino acids
- Other components (which are particularly important for this class):
- Albumin (20-50 mg/ml) – lipid transport. The "globular protein". Non-cell adhesive
- Fibronectin (1-10 μg/ml) – cell adhesive protein

Why is cell culture useful?

Example

Adoptive T cell therapy



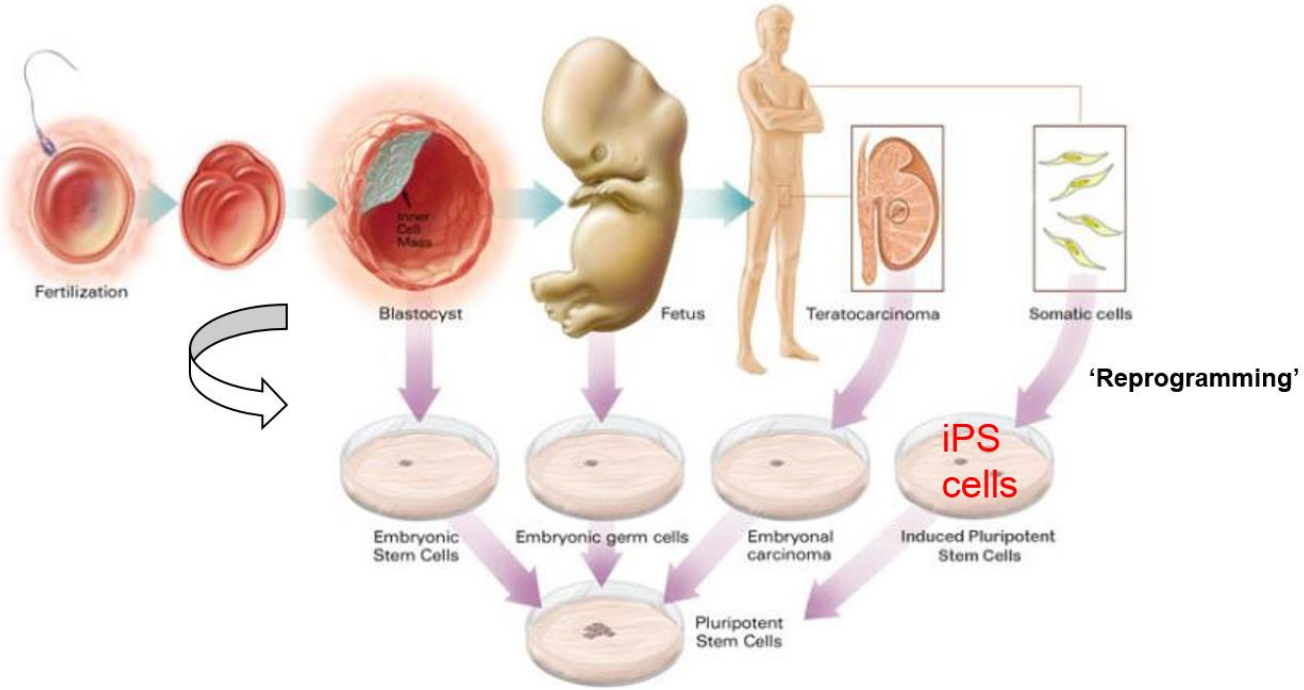
- **Target therapy with Tumor specific T cells**
  - Cancer: Melanoma
  - Autologous tumor infiltrating lymphocytes (TILs); “Live drug”
- **Advantages**
  - High response rate (>50%),
  - Long-term remission,
  - Less toxic & gentler to the patient
- **Limitation:**
  - Extraction of TILs,
  - Cell manufacturing
- **Possible alternate**
  - T cell Engineering (CAR-T cells)

Rosenberg SA & Dudley ME 2009 Current Opinion of Immunology

Stem cell therapy

Pluripotent stem cells

- Can proliferate indefinitely in the lab: unlimited cell source
- Pluripotent: can give rise to any cells type in the body



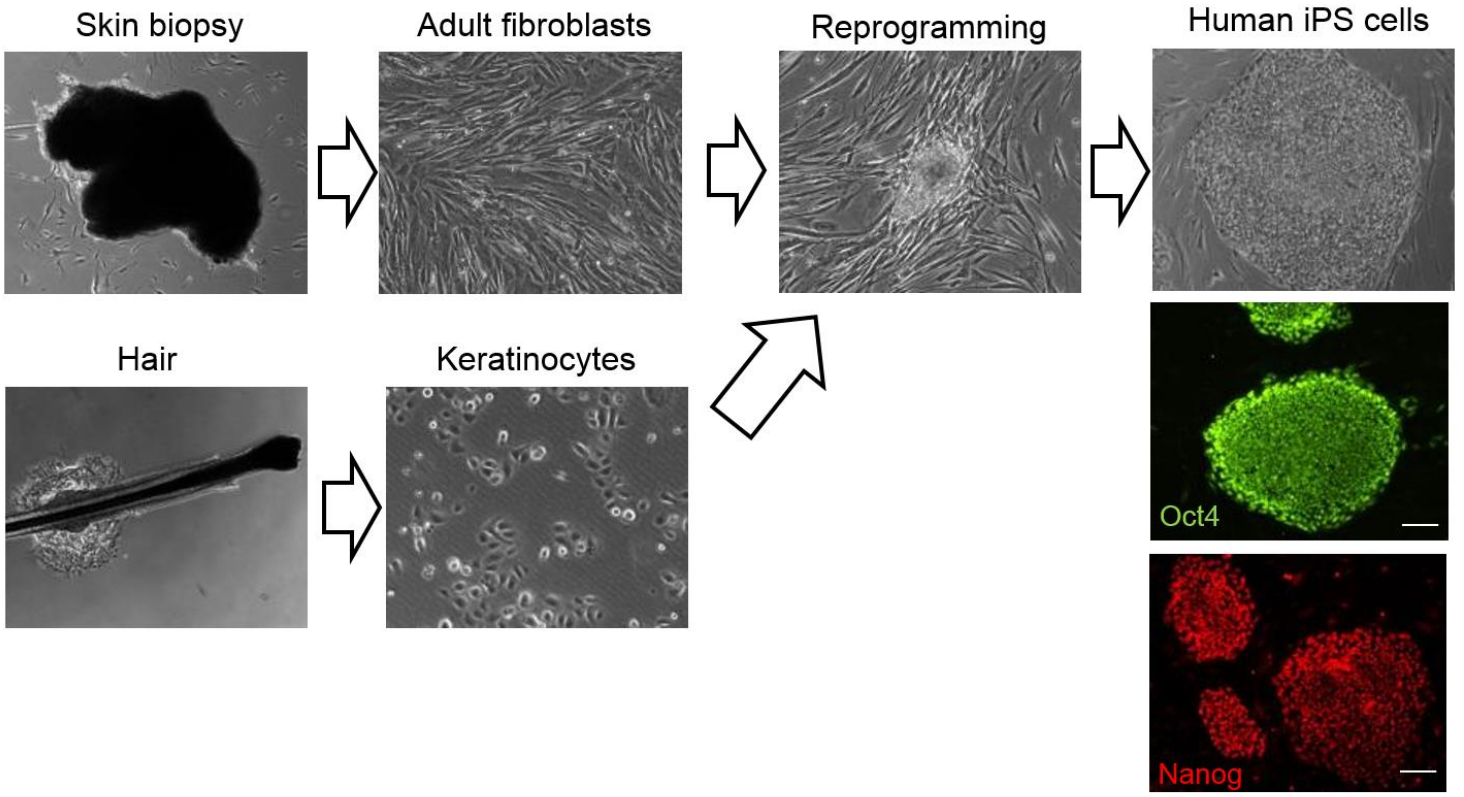
Why is cell culture useful?

Example

Stem cell therapy

Reprogramming to make iPS cells

- 'Switch on' several genes => 'add' several proteins in the cells



Stem cell therapy

Potentials of iPS cells: