Stem Cell Engineering-What, Why, How??

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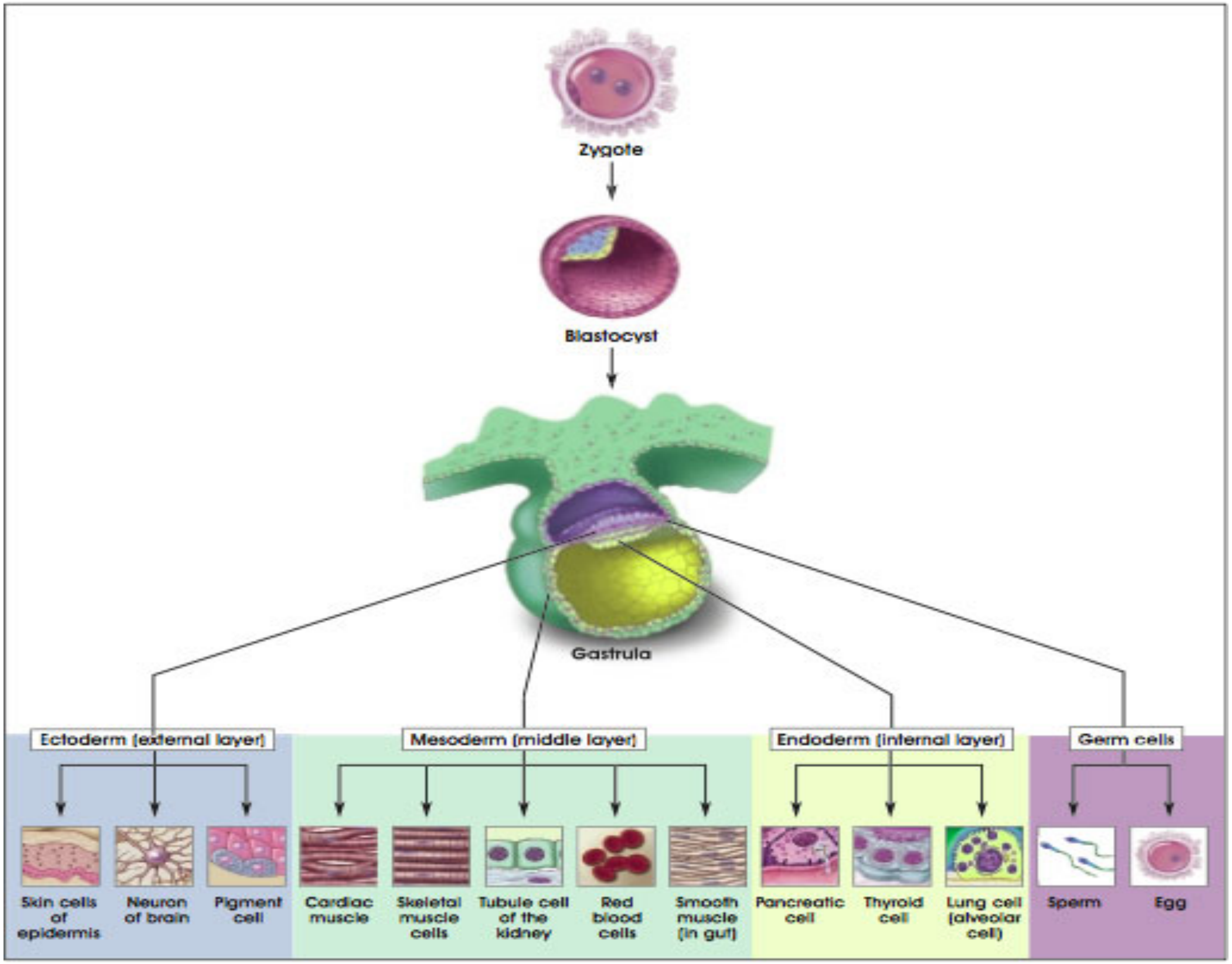
Cells of the Human Body

- The human body is composed of many different types of cells
  - e.g. muscle cells, skin cells, liver cells, cardiovascular cells, etc.
- Not all cells have the same potential
  - Some cells remain “immature”—these are **stem cells**
  - When stem cells “mature,” they turn into the different cells of the body

What are Stem Cells?

Stem Cells are extraordinary because they can:



http://stemcells.nih.gov/info/basics/

Classification of Stem Cells

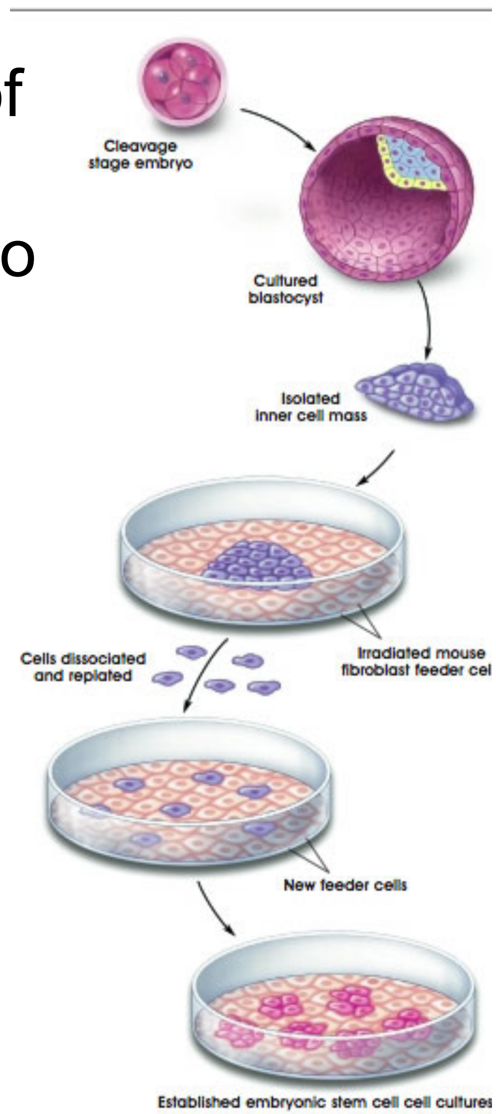
- Embryonic stem cells
- Adult stem cells
- Induced Pluripotent stem cells

Embryonic Stem Cells

- come from embryos called a *Blastocyst* (~5 days old, a hollow microscopic ball of cells)
- are **pluripotent** – they can differentiate to become almost EVERY cell in the body
- Highest level of pluripotency
  - All somatic cell types
- Unlimited self-renewal
  - Enhanced telomerase activity
- Markers
  - Oct-4, Nanog, SSEA-3/4

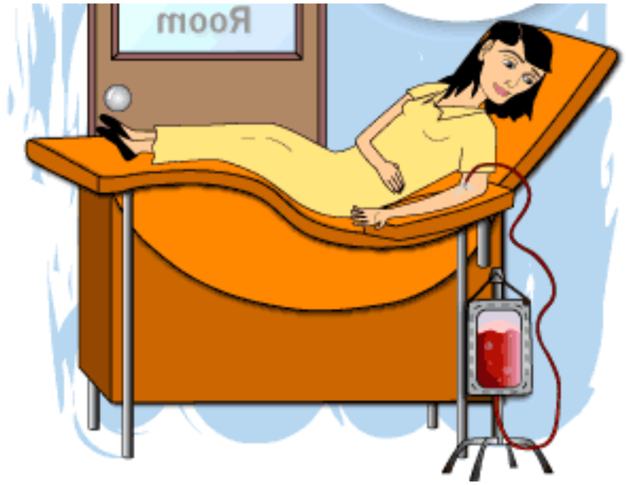
Limitations

- Teratoma Formation
- Animal pathogens
- Immune Response
- Ethics



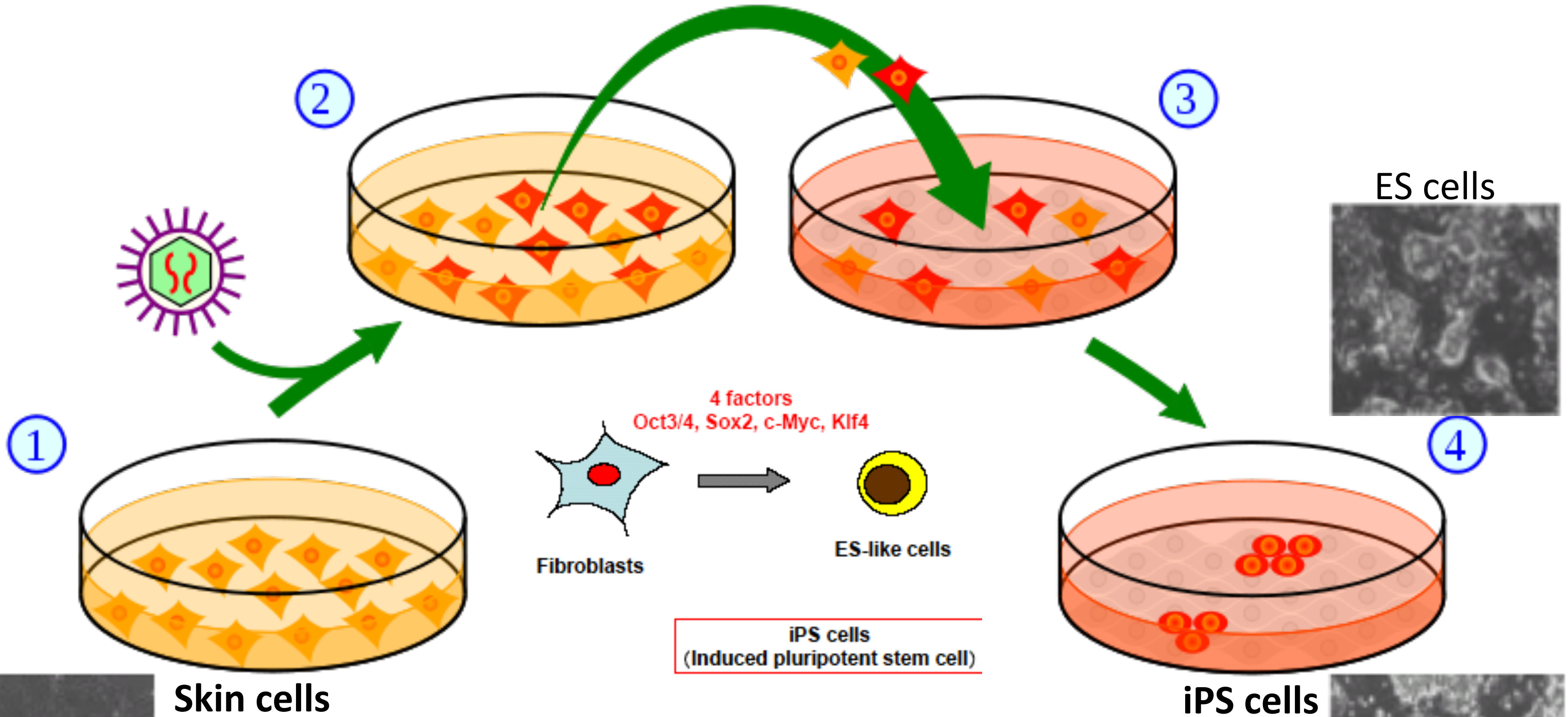
Adult Stem Cells

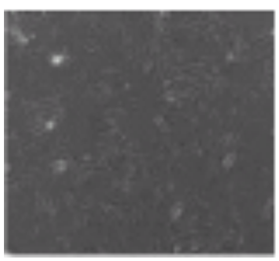
- found in adult tissue
- can self-renew many times
- are ***multipotent*** –can differentiate to become only the types of cells in the tissue they come from.
  - **hematopoietic stem cells** – give rise to blood cells
  - **mesenchymal stem cells** – give rise to cells of connective tissues and bones
  - **umbilical cord stem cells** – a rich source of hematopoietic stem cells
- Strengths
  - Ethics, not controversial
  - Immune-priviledged
  - Many sources
- Limitations
  - Differentiation capacity?
  - Self-renewal?
  - Rarity among somatic cells

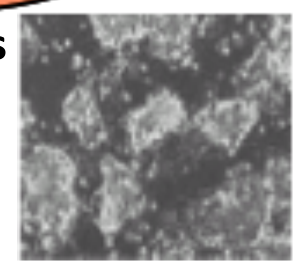


Induced Pluripotent Stem (iPS) Cells

Genetically engineering new stem cells







Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]

Cell 131, 1–12, November 30, 2007

Pros and Cons of iPS Cells

- Pros:
  - Cells would be genetically identical to patient or donor of skin cells (no immune rejection!)
  - Do not need to use an embryo
- Cons:
  - Cells would still have genetic defects
  - One of the pluripotency genes is a cancer gene
  - Viruses might insert genes in places we don't want them (causing mutations)

Stem Cell Research

- Stem cell field is still in its infancy
- Human embryonic stem cell research is a decade old, adult stem cell research has 30-year head start
- Holds hope for curing or improving treatments for 70+ diseases

How can <u>you</u> help to shape the direction of this field?

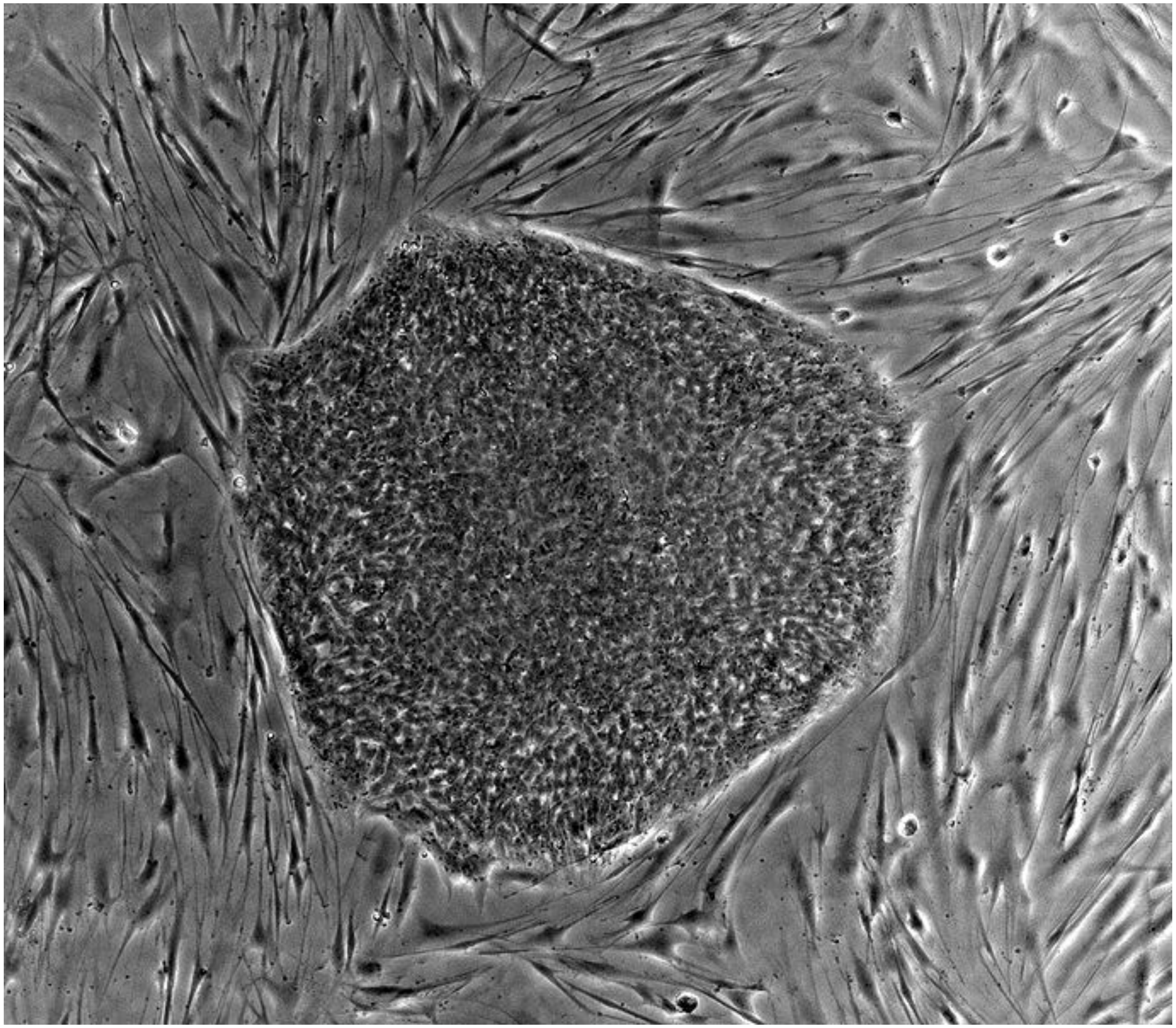
Importance of Stem Cell Research

- Stem cells allow us to study how organisms grow and develop over time.
- Stem cells can replace diseased or damaged cells that can not heal or renew themselves.
- We can test different substances (drugs and chemicals) on stem cells.
- We can get a better understanding of our "genetic machinery."

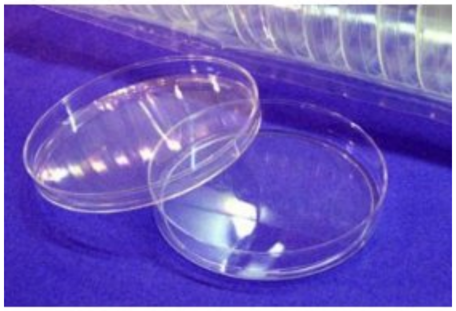
Stem Cell Therapy has the Potential to:

- Regenerate tissues/organs
- Cure diseases like diabetes, multiple sclerosis, etc.

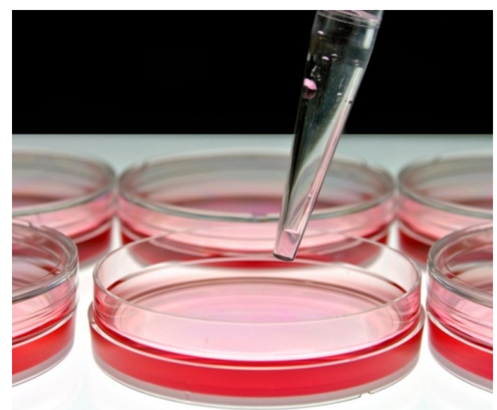
Stem Cells in a Dish



Culture Methods



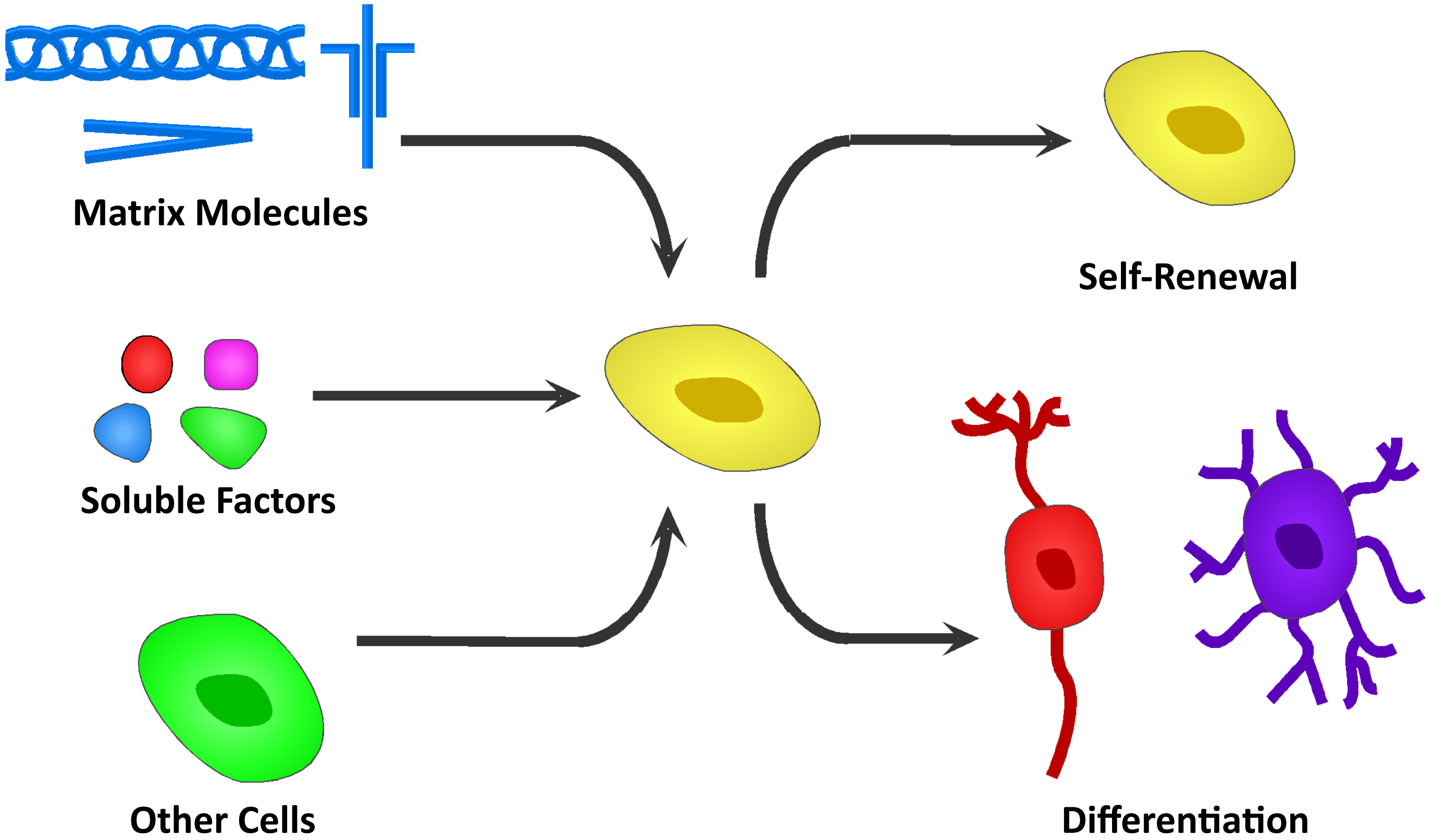
7.0 - Neutral



pH 6.8 – slightly acidic

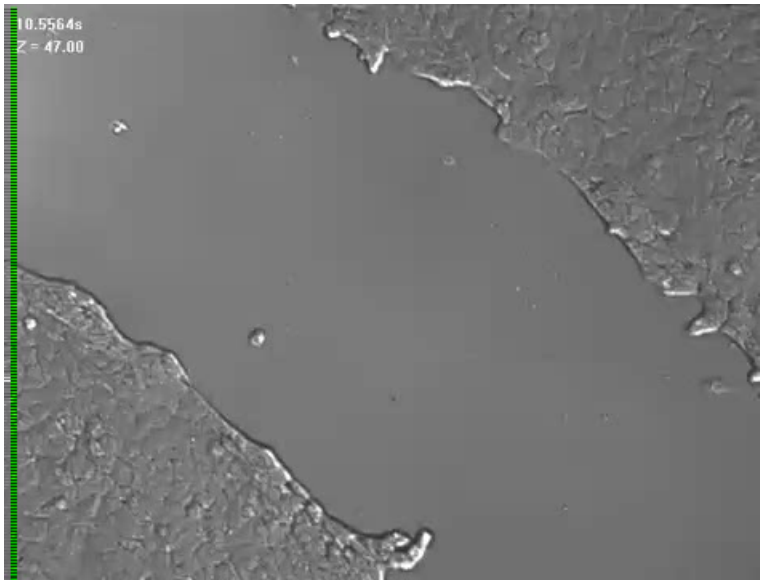
8.4 – slightly basic

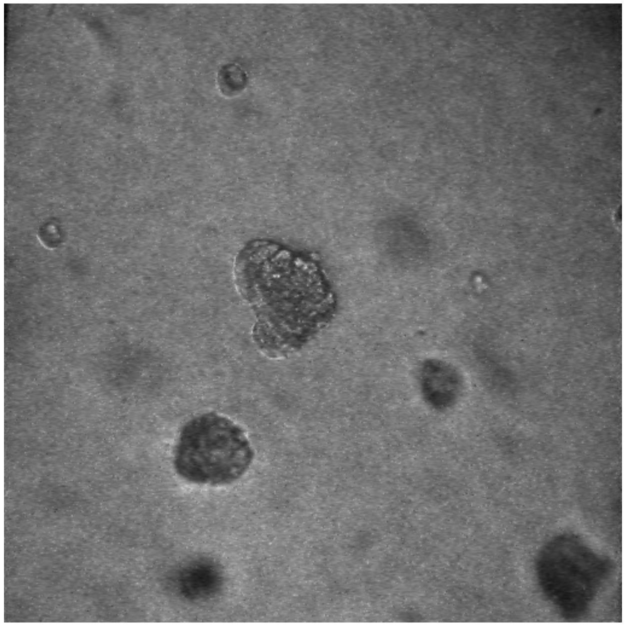
Signals to Stem Cells



Solution in Engineering??

- Cells can be grown in 2D or 3D

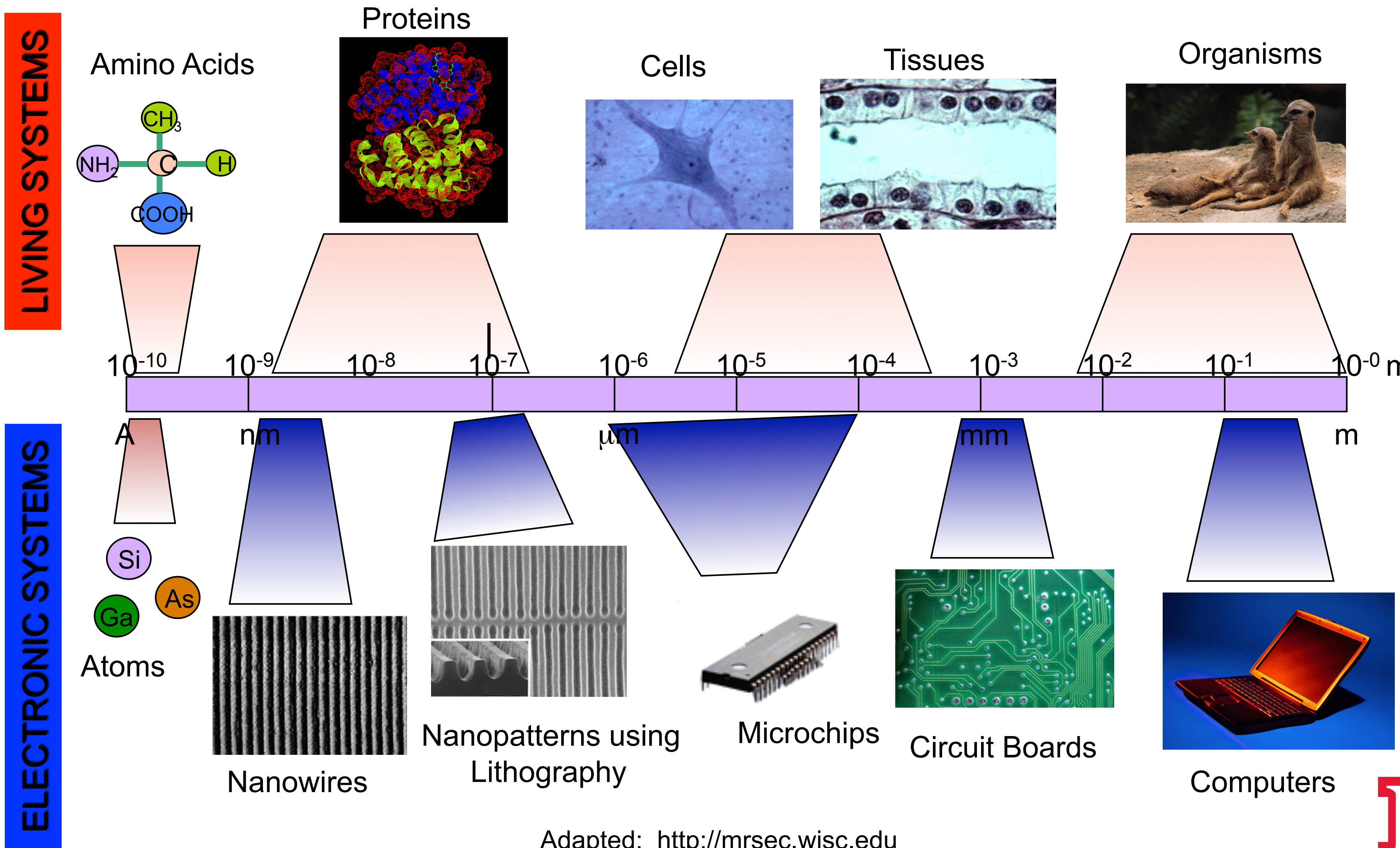




- Engineers find new surfaces to grow cells on/ in that promote proliferation or differentiation

Nanotechnology

Nanotechnology : understanding and control of matter at dimensions of roughly 1 to 100 nm, where unique phenomena enable novel applications



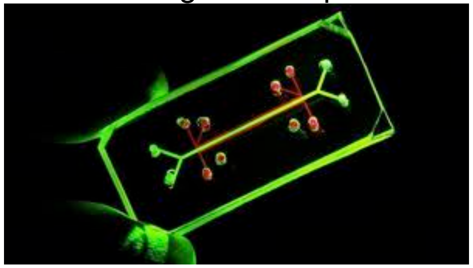
Adapted: http://mrsec.wisc.edu

Transformative Research Vision

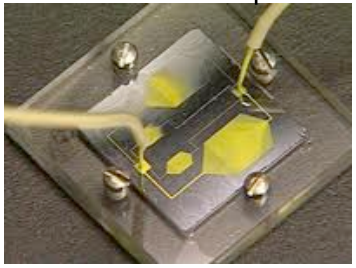
Adapt emerging techniques from nanotechnology including microelectronics industry to develop transformative and versatile strategies for treating and detecting diseases

Clean room for making computer chips

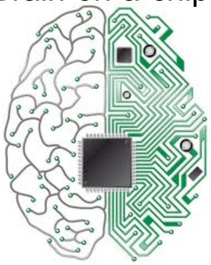
Lung-on-a-chip



Liver-on-a-chip

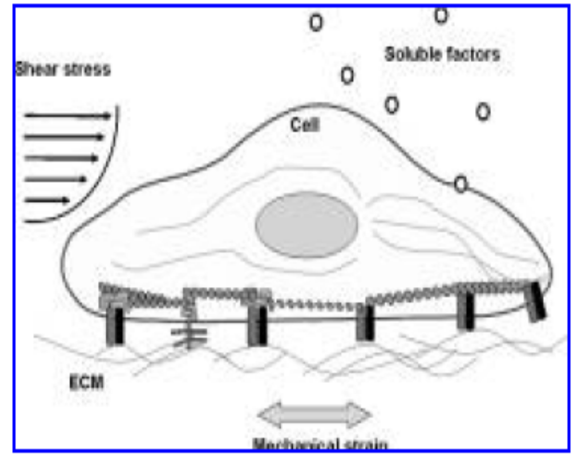


Brain-on-a-chip



Tissue Engineering

- Repair/replace damaged tissues
  - Enhance natural regeneration



Cell Source

Embryonic stem cells
Adult stem cells
Progenitor cells

Signals

Growth factors
Drugs
Mechanical forces

ECM

Metals
Ceramics
Synthetic polymers
Natural polymers

Important Variables

- Delivery
  - Cell Suspensions
  - Tissue-like constructs (scaffolds)
- Chemical properties
  - Growth factors
  - Degradation particles
  - ECM surface
- Physical properties
  - Structure
  - Topography
  - Rigidity
  - Mechanical Loading

<u>Modify Cell Behavior</u>

Survival

Organization

Migration

Proliferation

Differentiation

Optimize Cellular Response

Soluble Chemical Factors

- Transduce signals
  - Cell type-dependent
  - Differentiation stage-dependent
    - Timing is critical
  - Dose-dependence

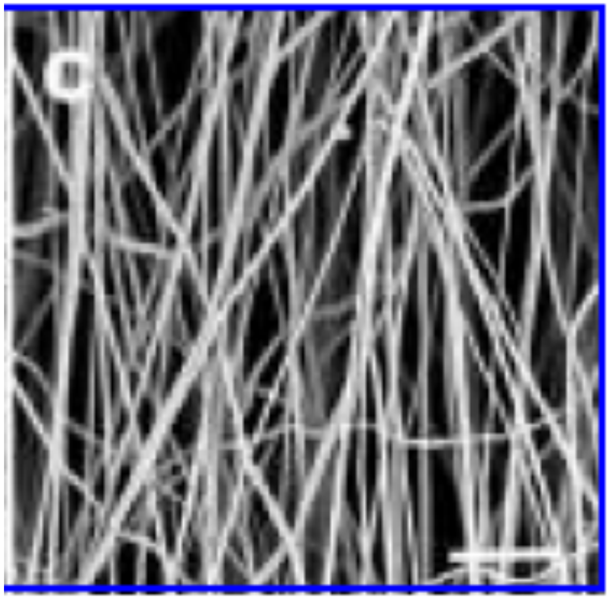
↓

- Growth
- Survival
- Motility
- Differentiation

Factor	Cell or Tissue of Origin	Selected Target Cells or Tissue
EGF	macrophages, monocytes	epithelium, endothelial cells
FGF	monocytes, macrophages, endothelial cells	endothelium, fibroblasts, keratinocytes
GMCSF	macrophages, fibroblasts, endothelial cells	hematopoietic, inflammatory cells, neutrophils, fibroblasts
HGH	pituitary gland	hepatocytes, bone, fibroblasts
IL-1	lymphocytes, macrophages, keratinocytes	monocytes, neutrophils, fibroblasts, keratinocytes
PDGF	platelets, macrophages, neutrophils, smooth muscle cells	fibroblasts, smooth muscle cells
TGF-ß	platelets, bone, most cell types	fibroblasts, endothelial cells, keratinocytes, lymphocytes, monocytes

Scaffold Purpose

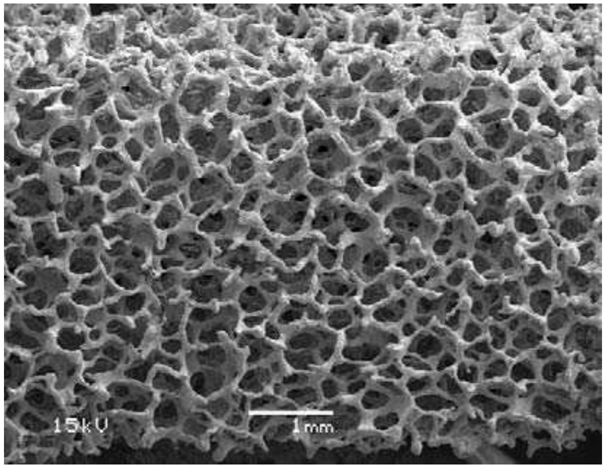
- Temporary structural support → Structural
  - Maintain shape
- Cellular microenvironment → Surface coating
  - High surface area/volume
  - ECM secretion
  - Integrin expression
  - Facilitate cell migration



“Natural” Materials

- Polymers
  - Collagen
  - Laminin
  - Fibrin
  - Matrigel
  - Decellularized matrix
- Ceramics
  - Hydroxyapatite
  - Calcium phosphate
  - Bioglass

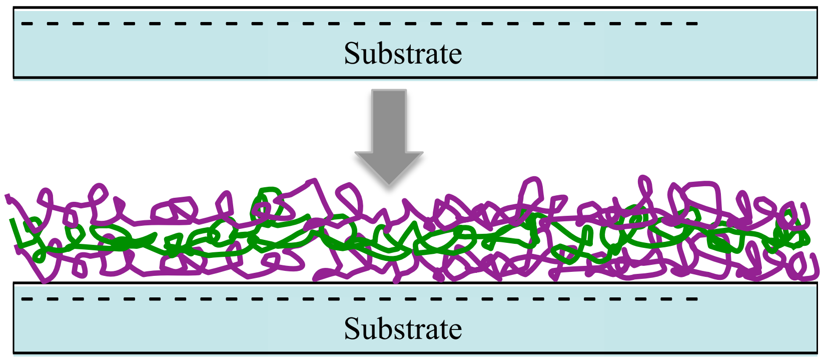
Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart.
Ott, et al.
Nat Med. 2008 Feb;14(2):213



Important Scaffold Variables

- Surface chemistry
- Matrix topography
  - Cell organization, alignment
  - Fiber alignment -> tissue development
- Rigidity
  - 5-23 kPa
- Porosity
  - Large interconnected
  - small disconnected

Biomaterials for Stem Cell Culture



Control over:

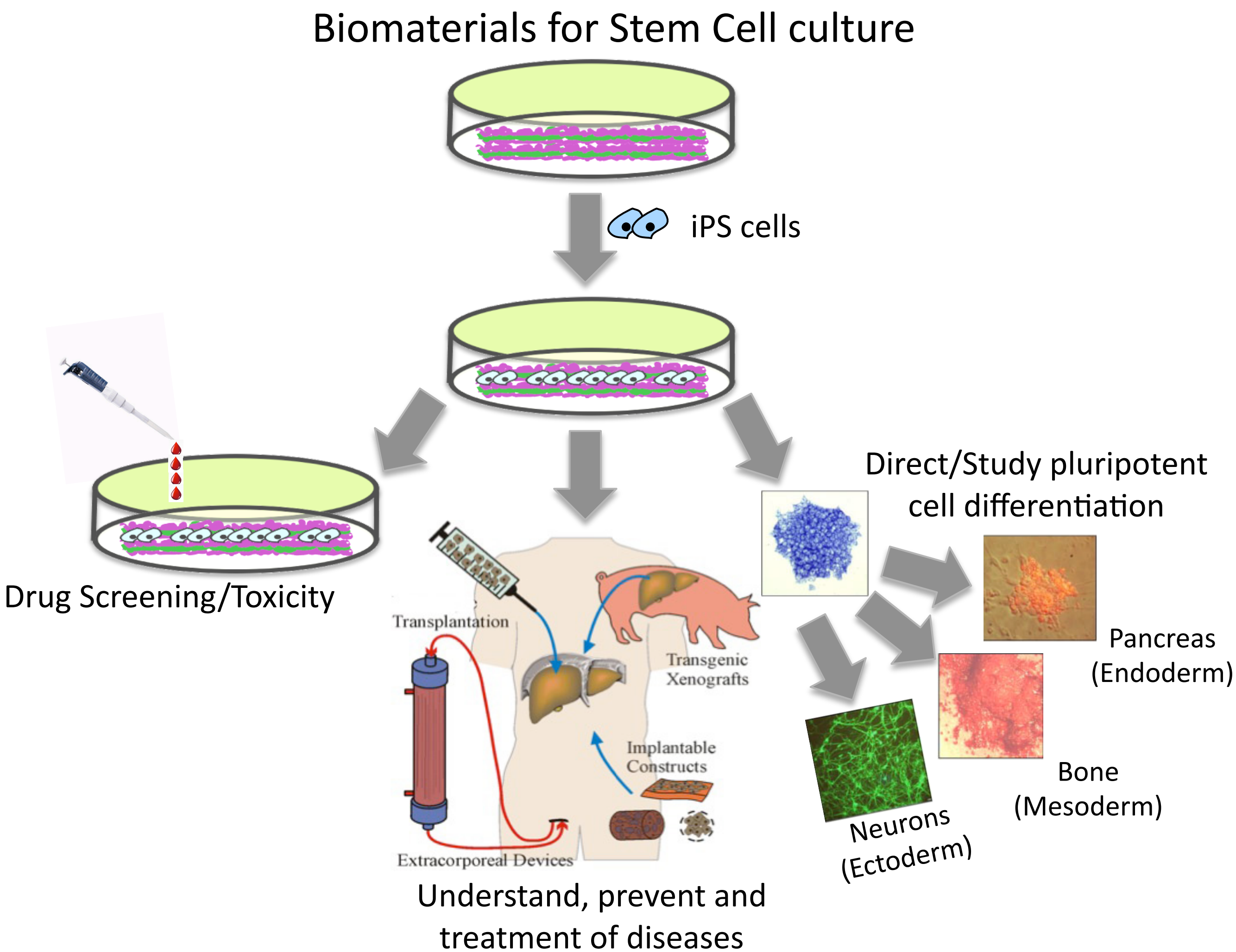
- Chemical properties
- Internal structure
- Physical properties
- Mechanical properties
- 2-D and 3-D structures

Cell adhesion & differentiation

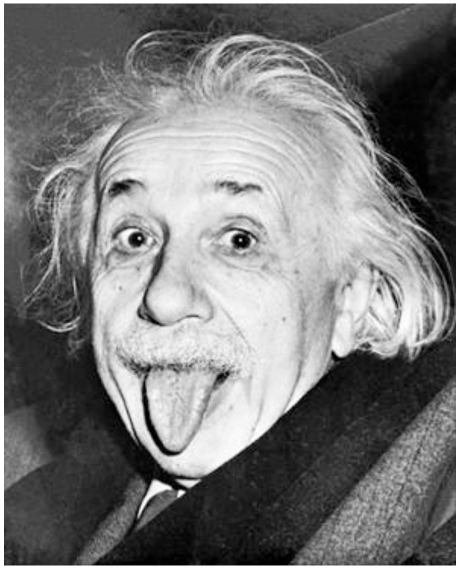
Bioactivity (peptides, proteins, lipids..)

Spatial-temporal control

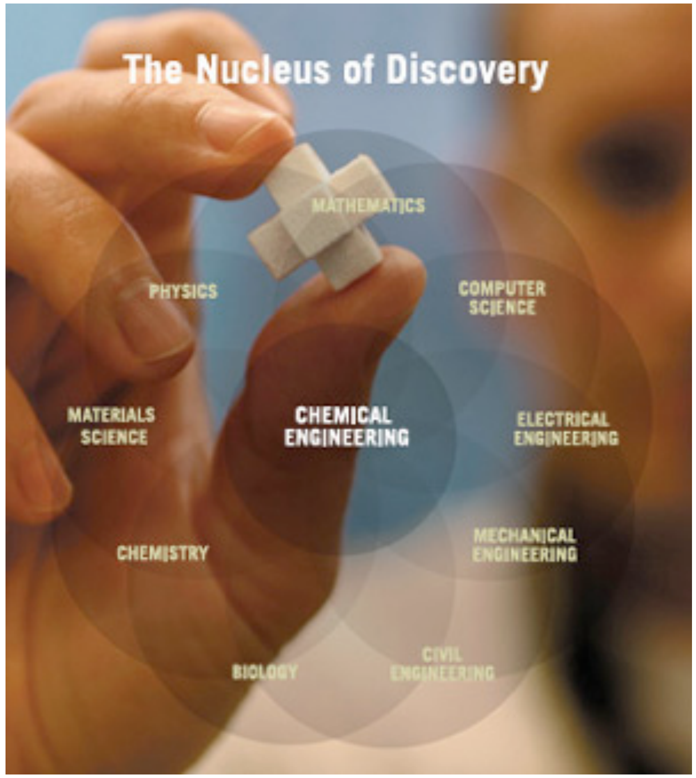
Biomaterials for Stem Cell Culture



Questions



"In the middle of difficulty lies great opportunity"



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