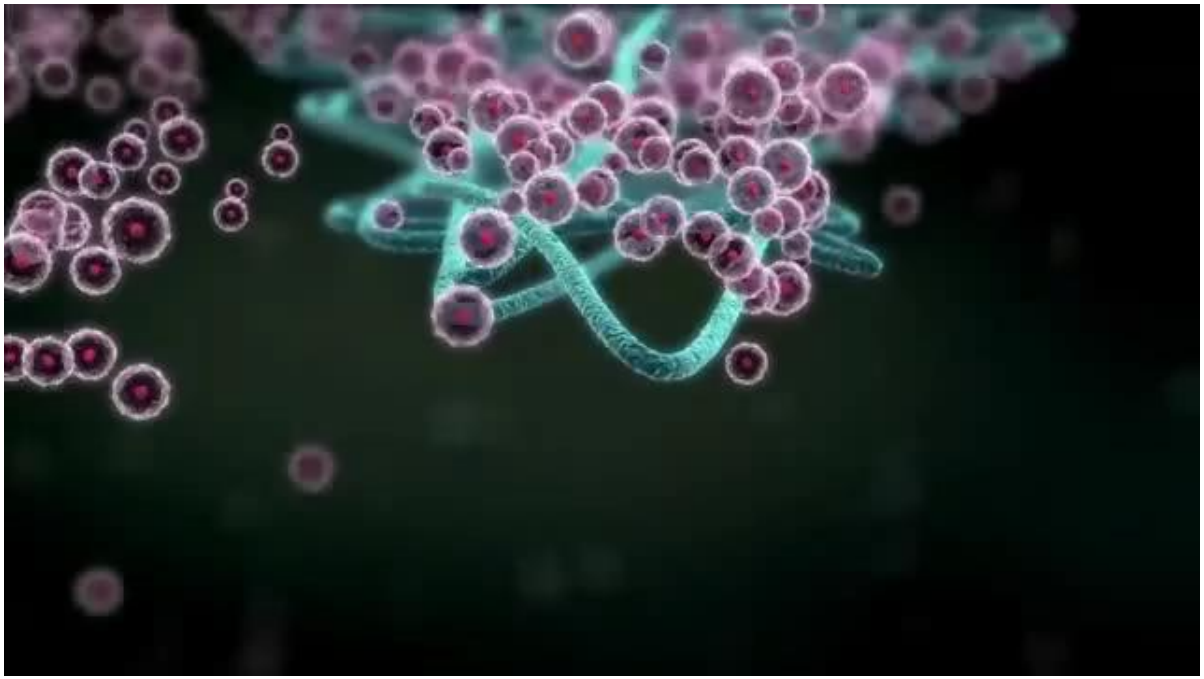
Cardiac System and Tissue Engineering



To be discussed

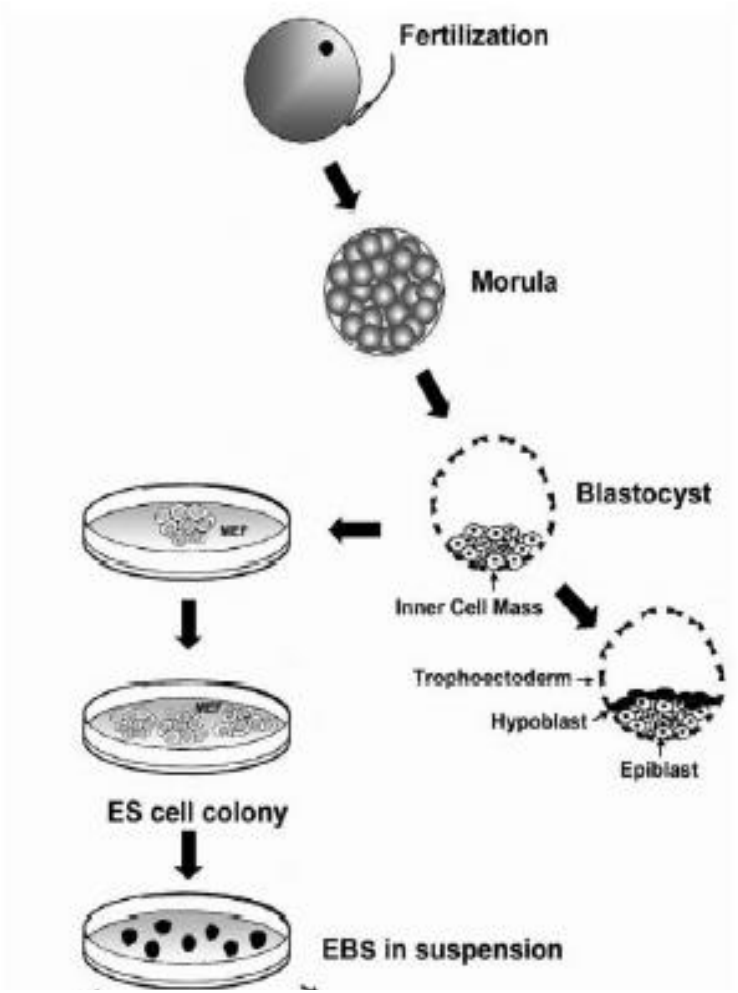
- Biomaterials
- Cells
- Tissue Engineered Heart Valves
- Tissue Engineered Blood Vessels
- Tissue Engineered Myocardium
- Discussion

Biomaterials

- Provide cells/tissue with a scaffold
- Synthetic biomaterials provide a number of parameters:
  - mechanical,
  - chemical,
  - Biological
- Design criteria:
  - proper mechanical and physical properties,
  - adequate degradation rate without the production of toxic degradation products,
  - suitable cell adhesion, integration into surrounding tissue without extensive inflammatory response or support of infection,
  - proper mass transfer

Embryonic Stem Cells (ESCs)

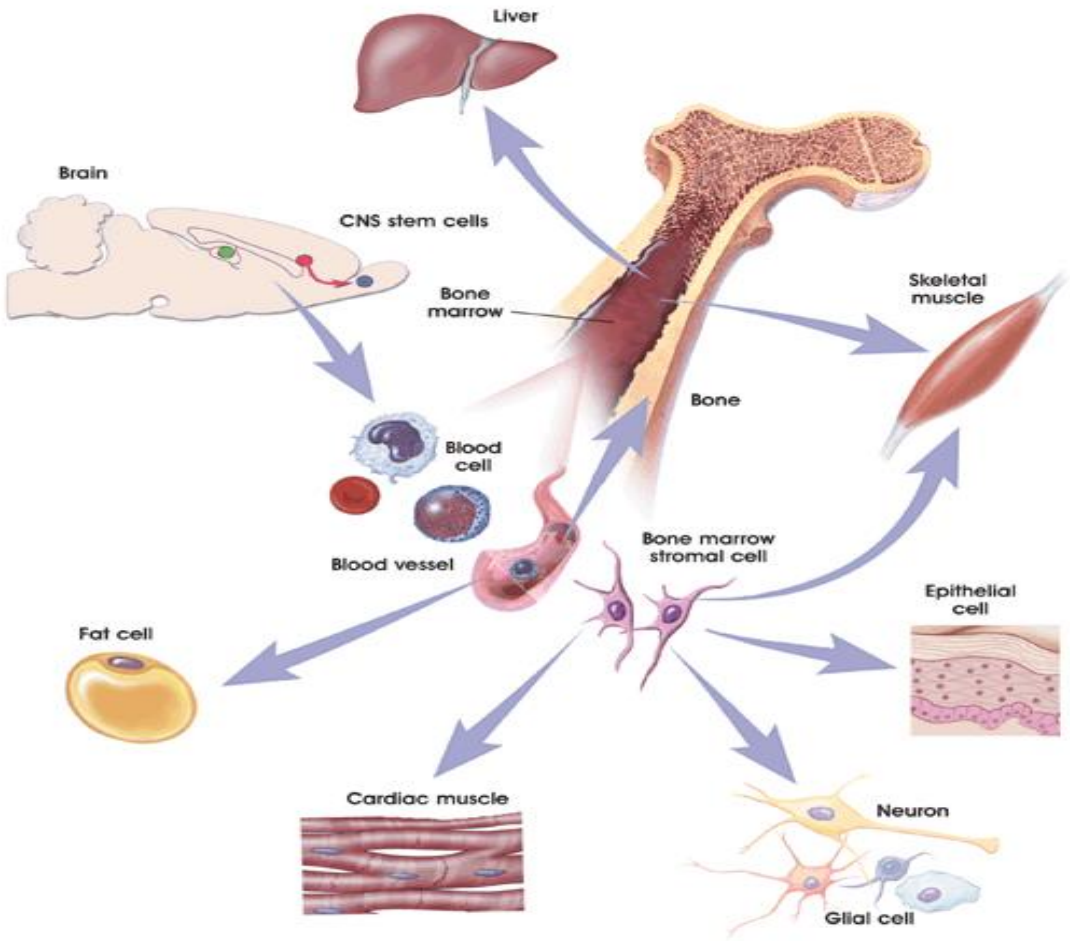
- Collected at the blastocyst stage (day 6) of embryogenesis
- Give rise to cells from all three germ layers of the body (ectoderm, endoderm, and mesoderm)
- Capable of self-renewal and undifferentiated proliferation in culture for extended periods of time



Adapted from Gepstein,L. Circ. Res, 91:866; 2002

Mesenchymal Stem Cells (MSCs)

- Have been found in many tissues and organs of the body
- Are multipotent and possess extensive proliferation potential
- Bone marrow-derived adult stem cells have been differentiated to a number of cell types including bone, cartilage, and fat
- Use of adult stem cells allows for autologous cell transplantation



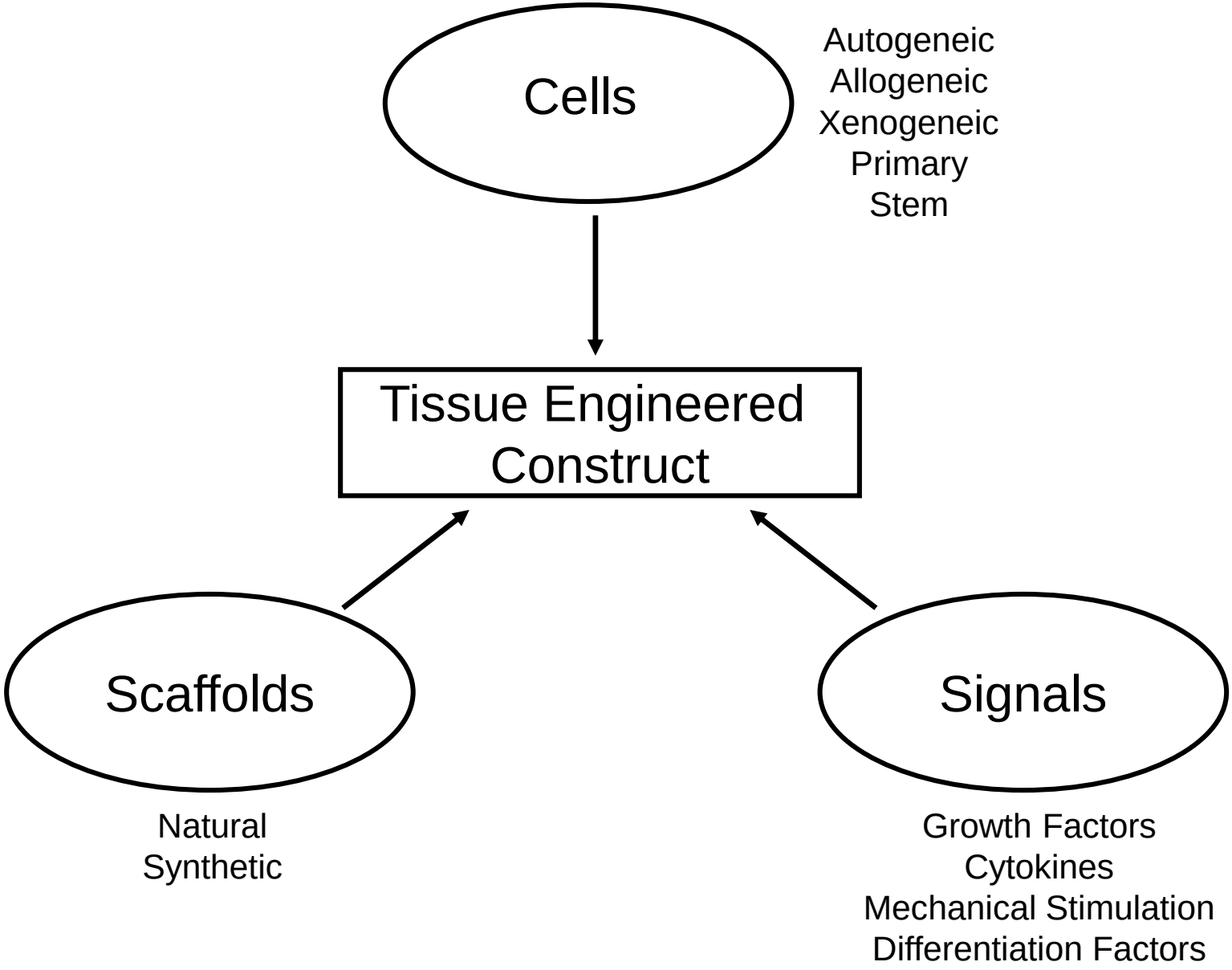
Adapted from www.nih.gov

Cells

- There has recently been much excitement surrounding the use of stem cells for tissue repair and regeneration
- *In vitro* differentiation of stem cells via humoral factors and direct *in vivo* utilization of these cells have been proposed as a method for tissue regeneration
- The use of a biomaterial to guide stem cell commitment provides cells a scaffold on which to grow and permits cell differentiation *in vivo* while minimizing *in vitro* manipulation
- The ideal cell source for various TE applications is still elusive

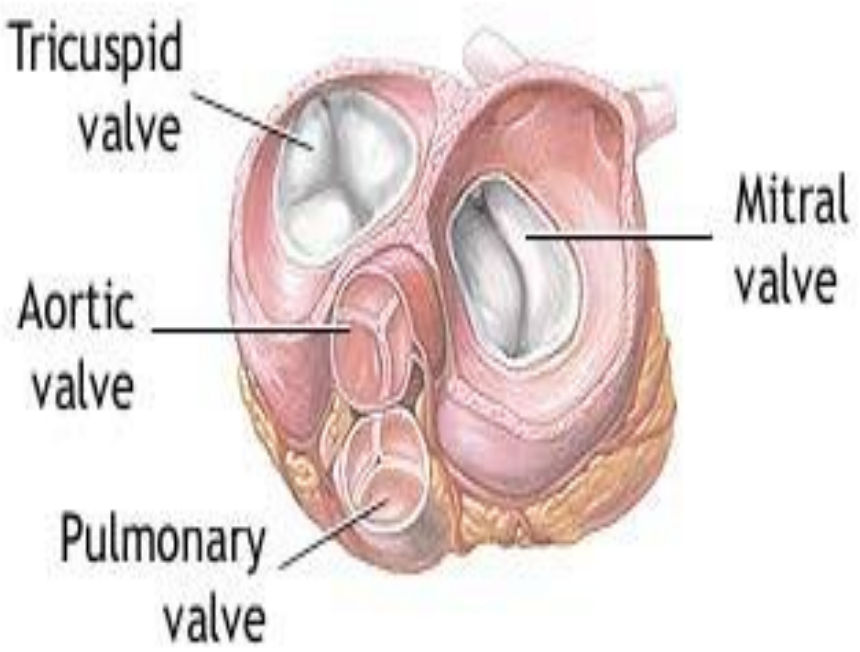
3-Dimensional Environment

- The context in which a cell is grown is critical to its development and subsequent function
- Cells cultured *ex vivo* on TCPS are in a 2-D environment which is far-removed from the 3-D tissue from which the cells originated as well as the 3-D tissue into which the cells will be implanted for tissue engineering applications
- Culture of cells in a 3-D vs. 2-D environment has been shown to alter cell behavior, gene expression, proliferation, and differentiation



From *An Introduction to Biomaterials.* Ch 24. Fig. 1. Ramaswami, P and Wagner, WR. 2005.

Tissue Engineered Heart Valves (TEHV)



Adapted from http://z.about.com/d/p/440/e/f/19011.jpg

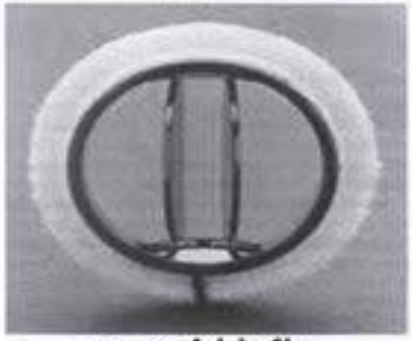
Heart valve disease occurs when one or more of the four heart valves cease to adequately perform their function, thereby failing to maintain unidirectional blood flow through the heart

Surgical procedures or total valve replacement are necessary

TEHV Replacements

a - upper left

b - upper right



c - mid left

d - mid right

e - lower left

Mechanical prostheses

Bioprostheses

Homografts

Each of these valve replacements has limitations for clinical use

Can you think of any limitations?

Infection
Thromboembolism
Tissue deterioration
Cannot remodel, repair, or grow

Requirements for a TEHV

- **Biocompatible**

  Should not elicit immune or inflammatory response

- **Functional**

  Adequate mechanical and hemodynamic function, mature ECM, durability

- **Living**

  Growth and remodeling capabilities of the construct should mimic the native heart valve structure

What's being done?

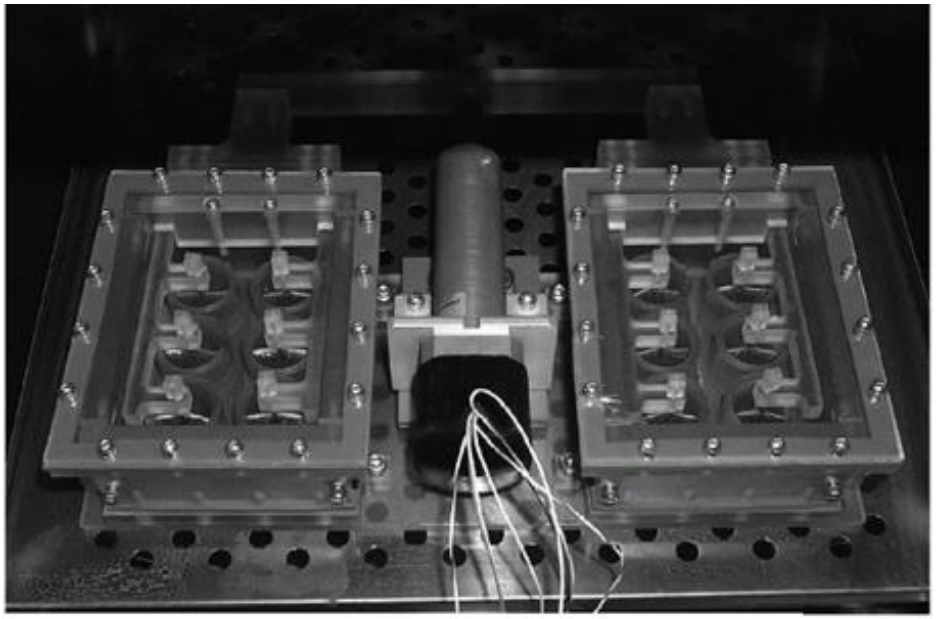
- Cells
- Vascular cells
- Valvular cells
- Stem cells (MSCs)

Scaffolds

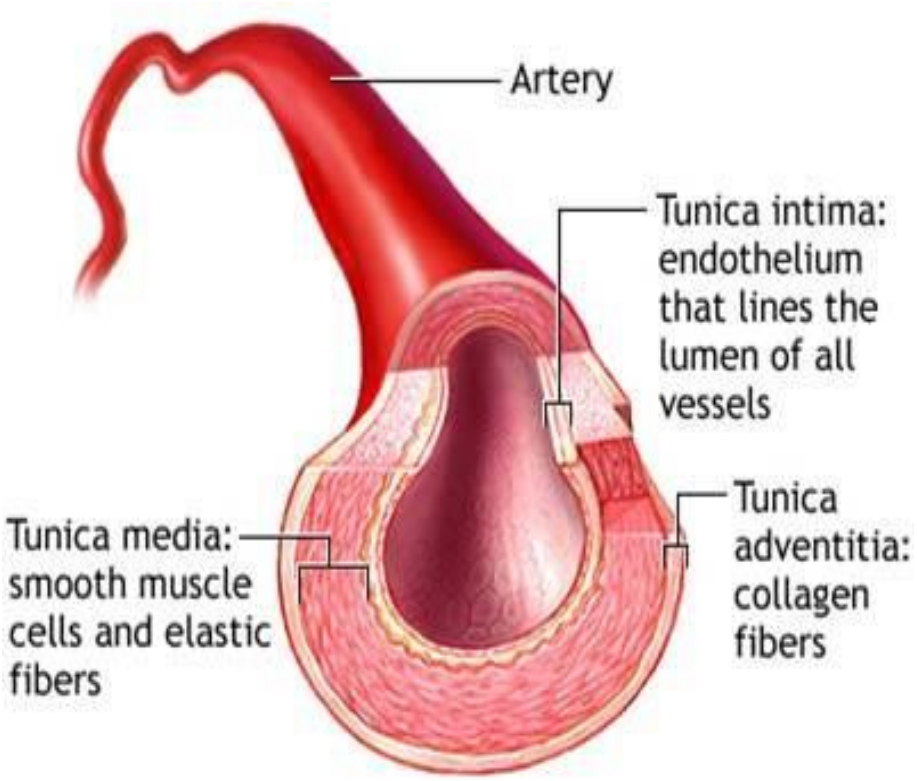
- Synthetic (PLA, PGA)
- Natural (collagen, HA, fibrin)
- Decellularized biological matrices

Mechanical Stimulation

- Pulsatile Flow Systems
- Cyclic flexure bioreactors



Tissue Engineered Blood Vessels (TEBV)



From *An Introduction to Biomaterials.* Ch 24.
Fig.4 Ramaswami, P and Wagner, WR. 2005.

Many patients do not have suitable vessels due to age, disease, or previous use

Synthetic coronary bypass vessels have not performed adequately to be employed to any significant degree

TEBV Replacements

Synthetic Grafts

- Work well in large-diameter replacements
- Fail in small-diameter replacements

Requirements for a TEBV

- **Biocompatible**

  Should not elicit immune/inflammatory response

- **Functional**

  Adequate mechanical and hemodynamic function, mature ECM, durability

- **Living**

  Growth and remodeling capabilities of the construct should mimic the native blood vessel structure

LOOK FAMILIAR???

What's being done?

Cells

- **Endothelial cells**
- **Smooth muscle cells**
- **Fibroblasts & myofibroblasts**
- **Genetically modified cells**
- **Stem cells (MSCs & ESCs)**

Scaffolds

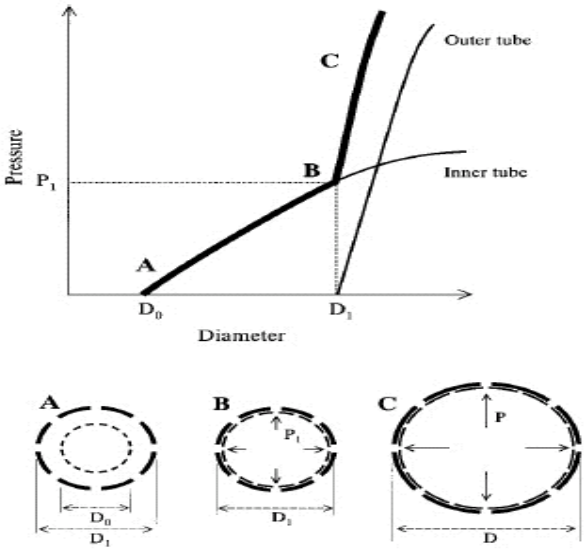
- Synthetic (PET, ePTFE, PGA, PLA, PUs)
- Natural (collagen)
- Decellularized biological matrices

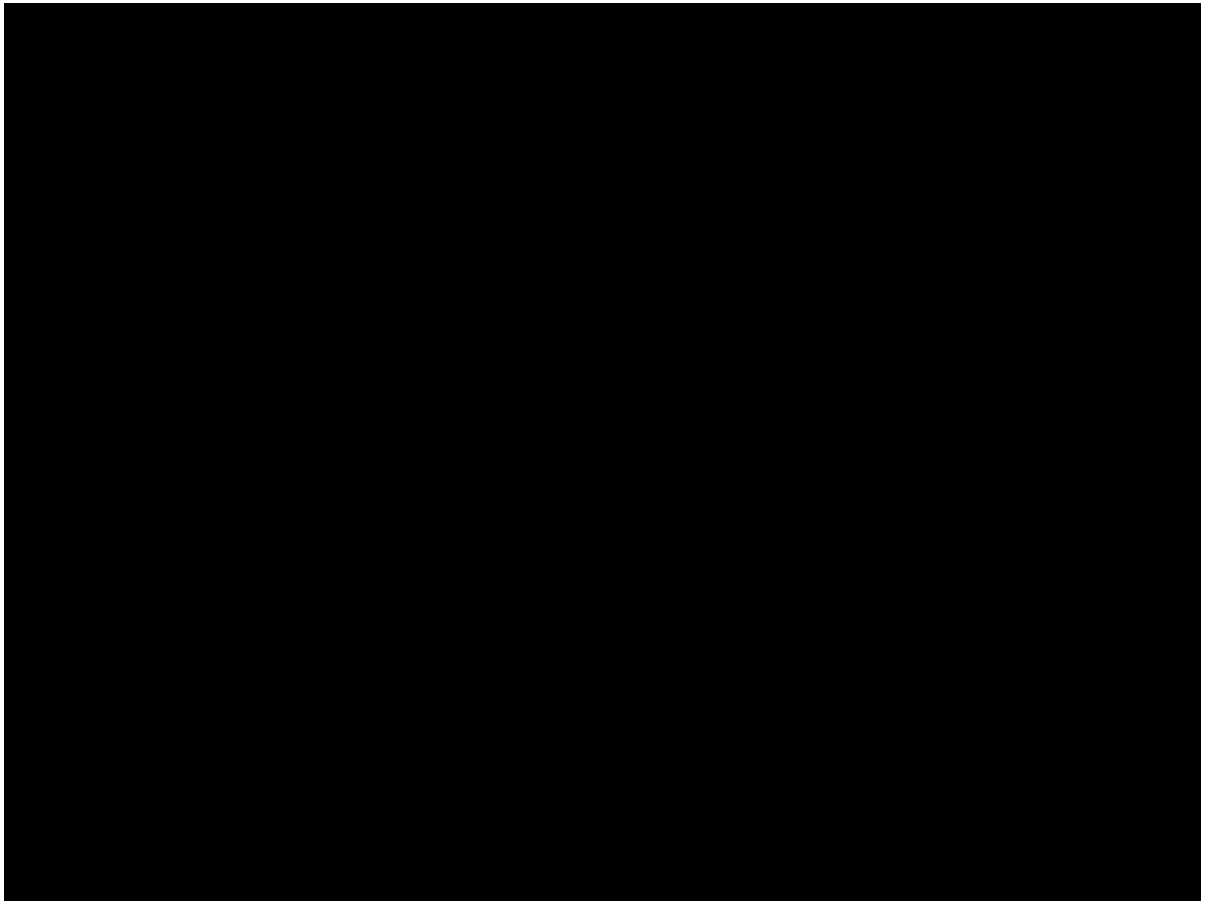
Mechanical Stimulation

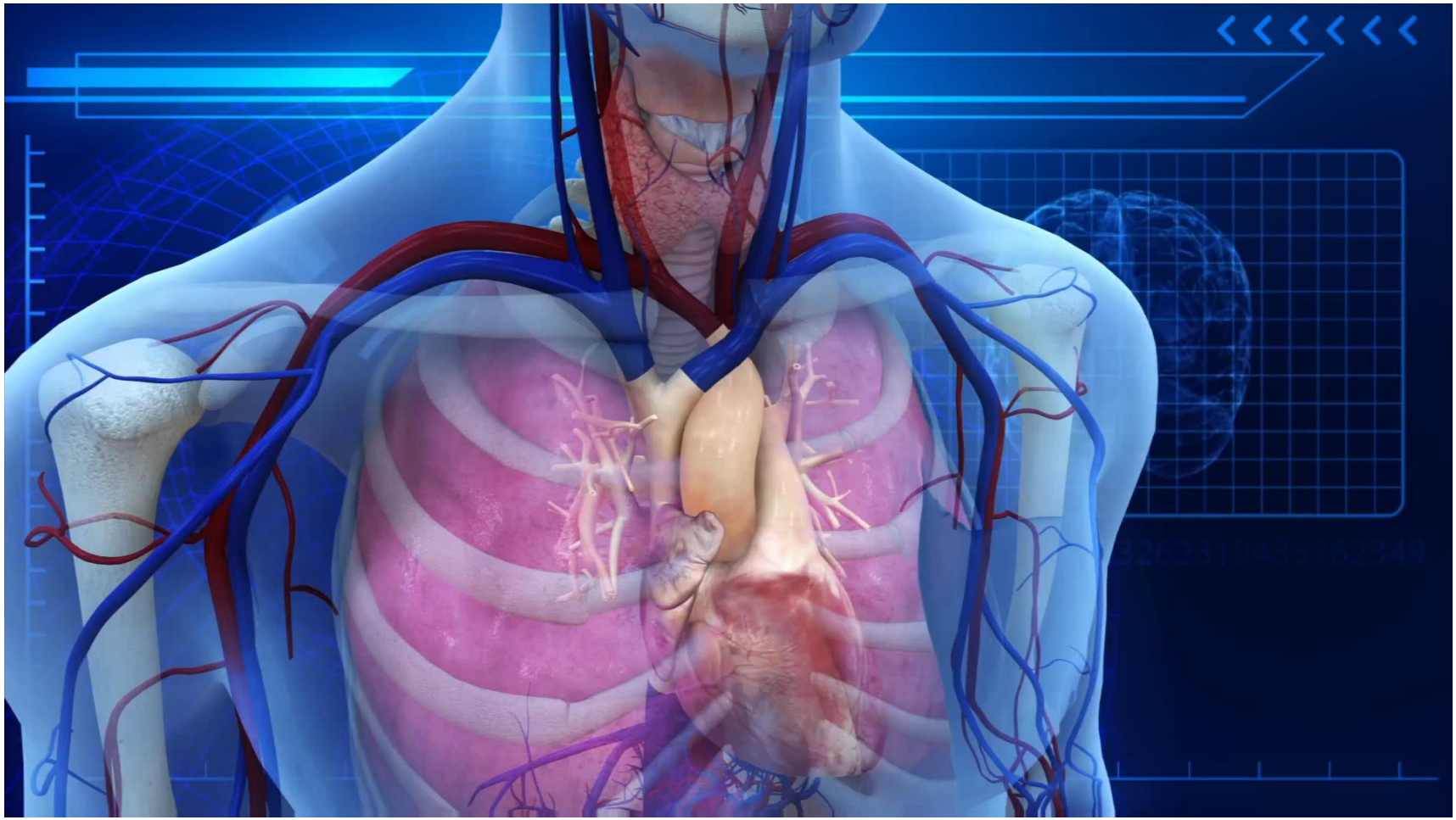
- Pulsatile Flow Systems
- Cyclic & longitudinal strain

Signalling Factors

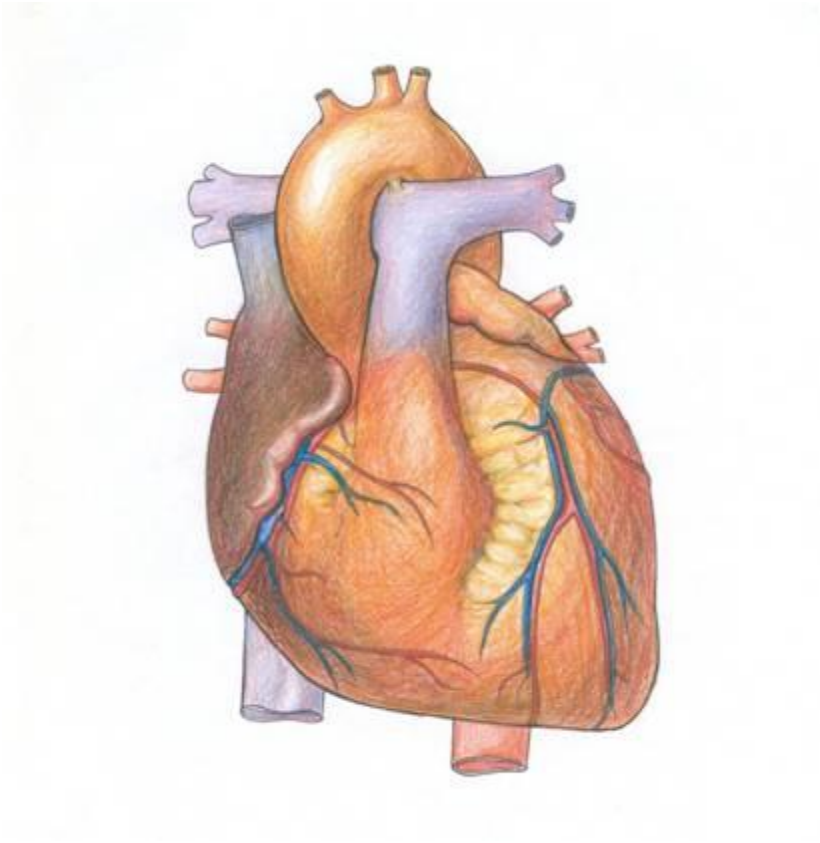
- Growth Factors (bFGF, PDGF, VEGF)
- Cytokines







Tissue Engineered Myocardium



From www.aic.cuhk.edu.hk/web8/Hi%20res/Heart.jpg

Ischemic heart disease is one of the leading causes of morbidity and mortality in Western societies with 7,100,000 cases of myocardial infarction (MI) reported in 2002 in the United States alone

Within 6 years of MI, 22% of men and 46% of women develop CHF

MI and CHF will account for $29 billion of medical care costs this year in the US alone

Cardiac transplantation remains the best solution, but there is an inadequate supply of donor organs coupled with the need for life-long immunosuppression following transplantation

Requirements for a Myocardial Patch

- Biological, Functional, and Living (same as TEHV and TEBV)

- High metabolic demands
- High vascularity
- Mechanical and Electrical anisotropy

VERY DIFFICULT!!!

What's being done?

Cells

- **Cardiocytes**
- **Cardiac progenitor cells**
- **Skeletal muscle cells**
- **Smooth muscle cells**
- **Stem cells (MSCs & ESCs)**

Scaffolds

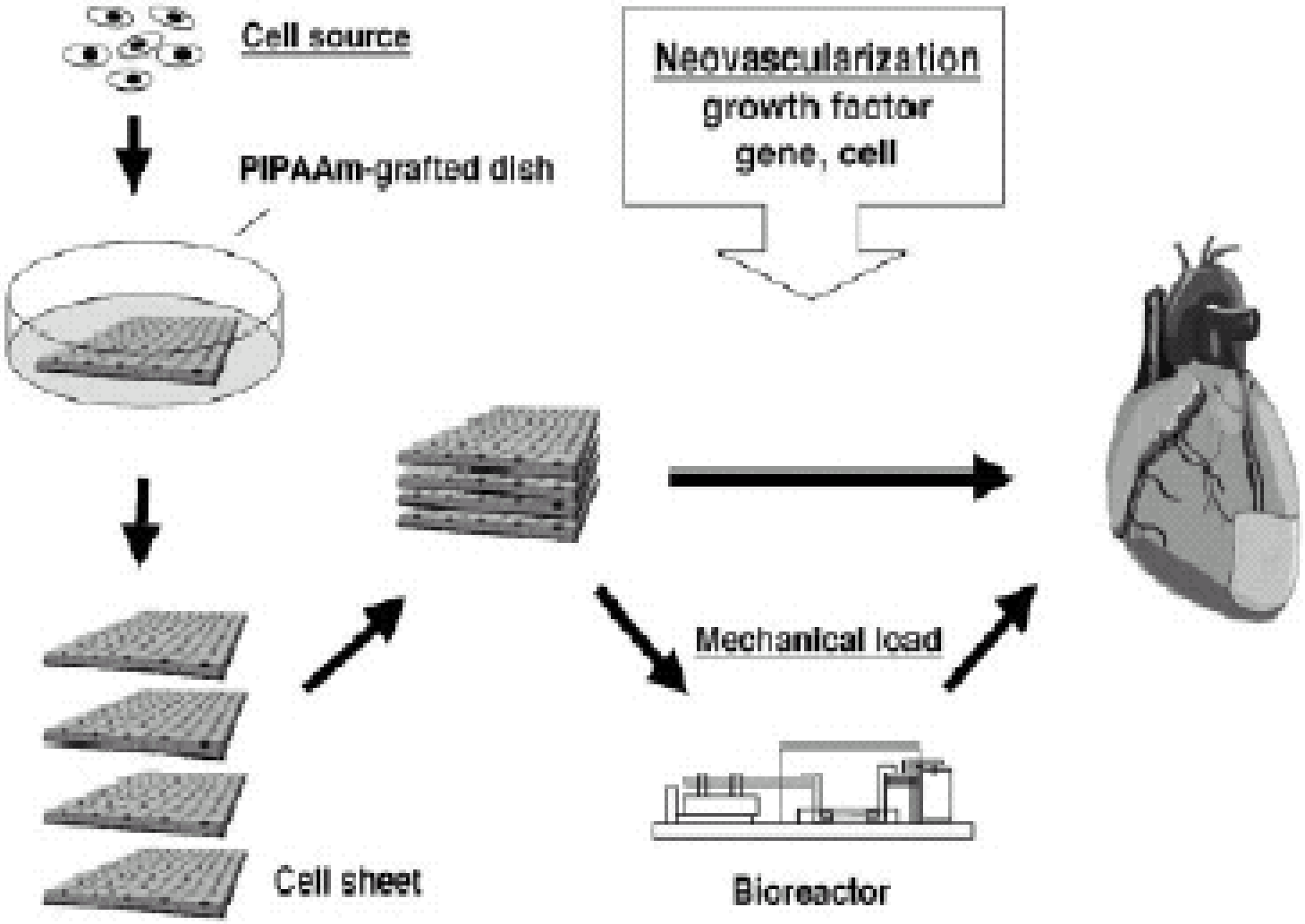
- Synthetic (PET, ePTFE, PEUU)
- Natural
  (collagen, ECM proteins, alginate)
- Cell sheets

Mechanical Stimulation

- Pulsatile Flow Systems
- Rotational seeding
- Cyclic mechanical strain

Signalling Factors

- Growth Factors
  (Insulin, transferrin, PDGF, 5-azacytidine)
- Cytokines
- Conditioned media
- Co-culture`


Cell source
PIPAAm-grafted dish
Neovascularization
growth factor
gene, cell
Mechanical load
Cell sheet
Bioreactor

In Conclusion…

- We have a lot of work to do
- Taking these tissue engineered constructs from benchtop to bedside
- Better understanding the human body and how to manipulate cells