Bio-3D Printing

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Graduate Assistants, Colleagues and Collaborators

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Bio – 3D Printing

Use biomaterials, cells, proteins or other biological compounds as building block to fabricate 3D personalized structures or *in vitro* biological models through Additive Manufacturing processes

Bio-3D Printing

According to the use of biomaterials, we can categorize Bio-3DP into the following 4 level of applications:

Level 1：medical models and medical devices

- **non-biocompatible materials**

Level 2：medical implants

- **biocompatible but not biodegradable**

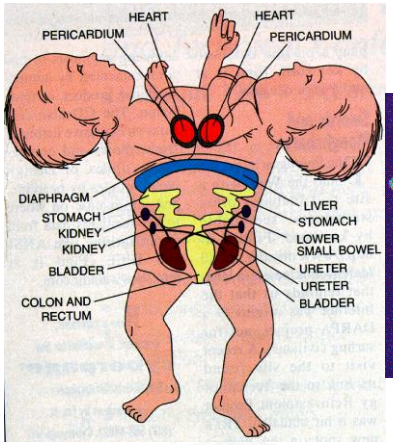
Level 3: tissue scaffolds

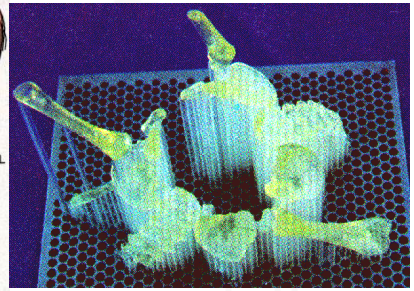
- **biocompatible, biodegradable and bio-absorbable**

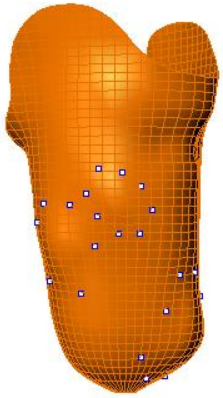
Level 4: in vitro biological models

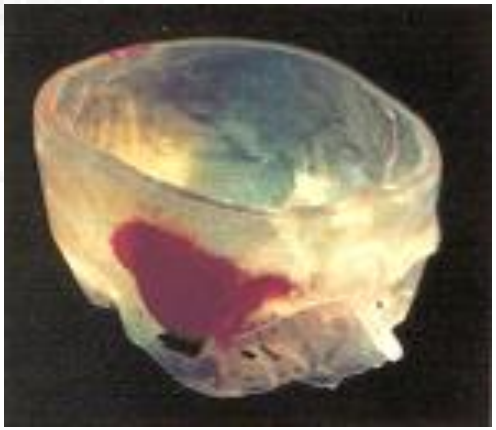
- **cells and living biological compounds as materials**

Bio-3D Printing
Personalized Medical Modeling and Implants



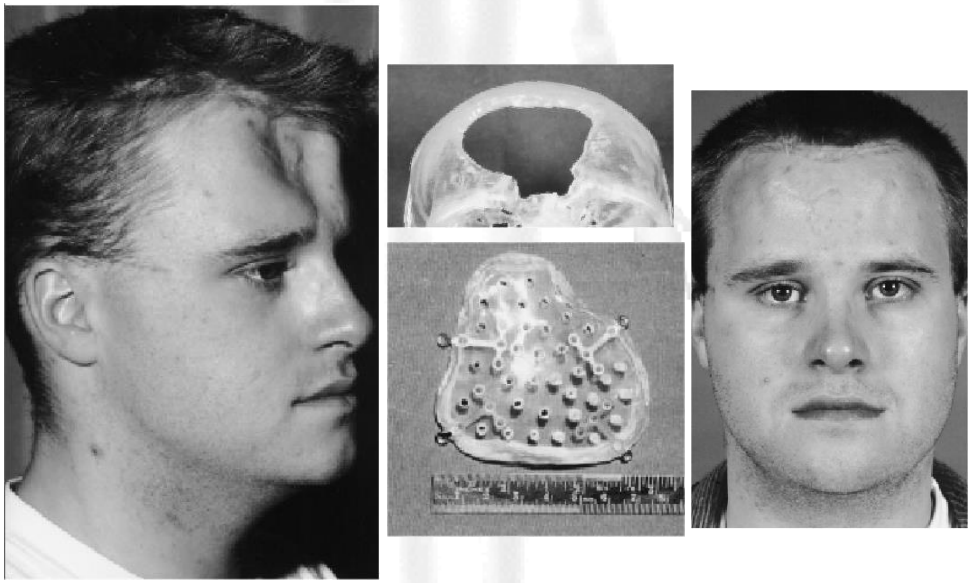






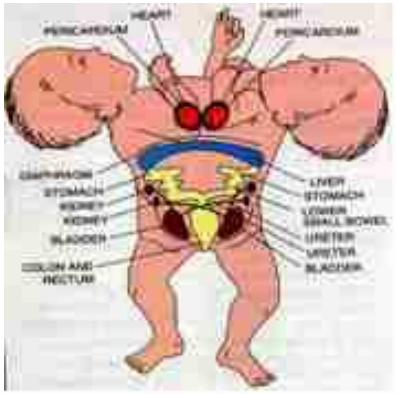
Application： plastic surgery, surgical planning, prosthesis

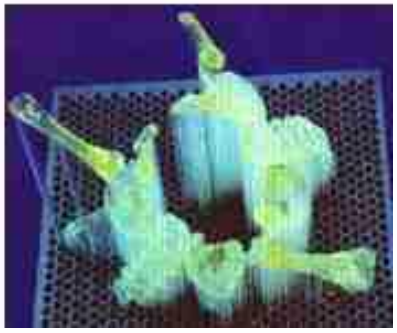
Bio – 3D Printing
Customized Implants



Challenges in 3DP of Medical Modeling, Devices and Implants

Personalization and Customization



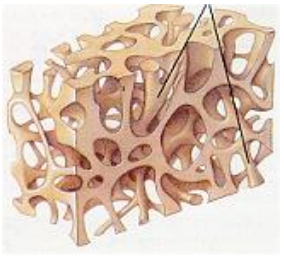


Biomodeling extracts morphological and geometrical information from patient-specific modalities

differs from

conventional CAD design modeling, in terms of both modeling approach and applications.

Process to arrive at a Bio-CAD model from CT/MRI data.



CT/MRI images

2D segmentation

3D Region growing

MedCAD interface

Reverse Engineering interface

STL interface

IGES curves

Point Data

GeoMagics

Surface Generation, rendering and Nurbs surface

Surface rendering and Nurbs surface generation

IGES format

CAD model

Bio-modeling

1) Accuracy

2) Complexity

Challenges for Bio-3DP of Medical Modeling, Devices and Implants

Precision engineering:

- How to precisely manufacturing patient specific geometry

surface engineering:

- How to engineering the surface topography and surface chemistry to enhance cell-surface interaction

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- **cells and living biological compounds as materials**

Scaffold Guided Tissue Engineering
- an application example for craniofacial reconstruction

Bio-3DP of Tissue Scaffolds

CT/MRI

↓

Reverse Engineering
3DR/CAD

↓

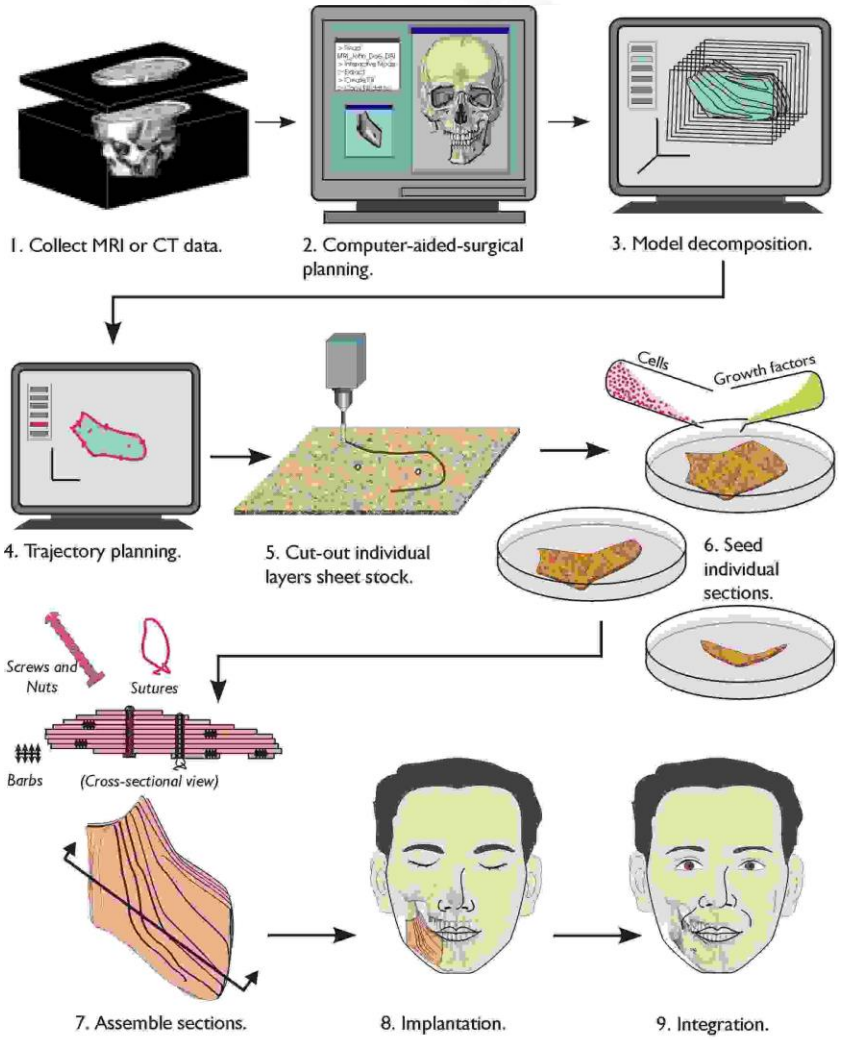
Design/Process

↓

RPM/SFF

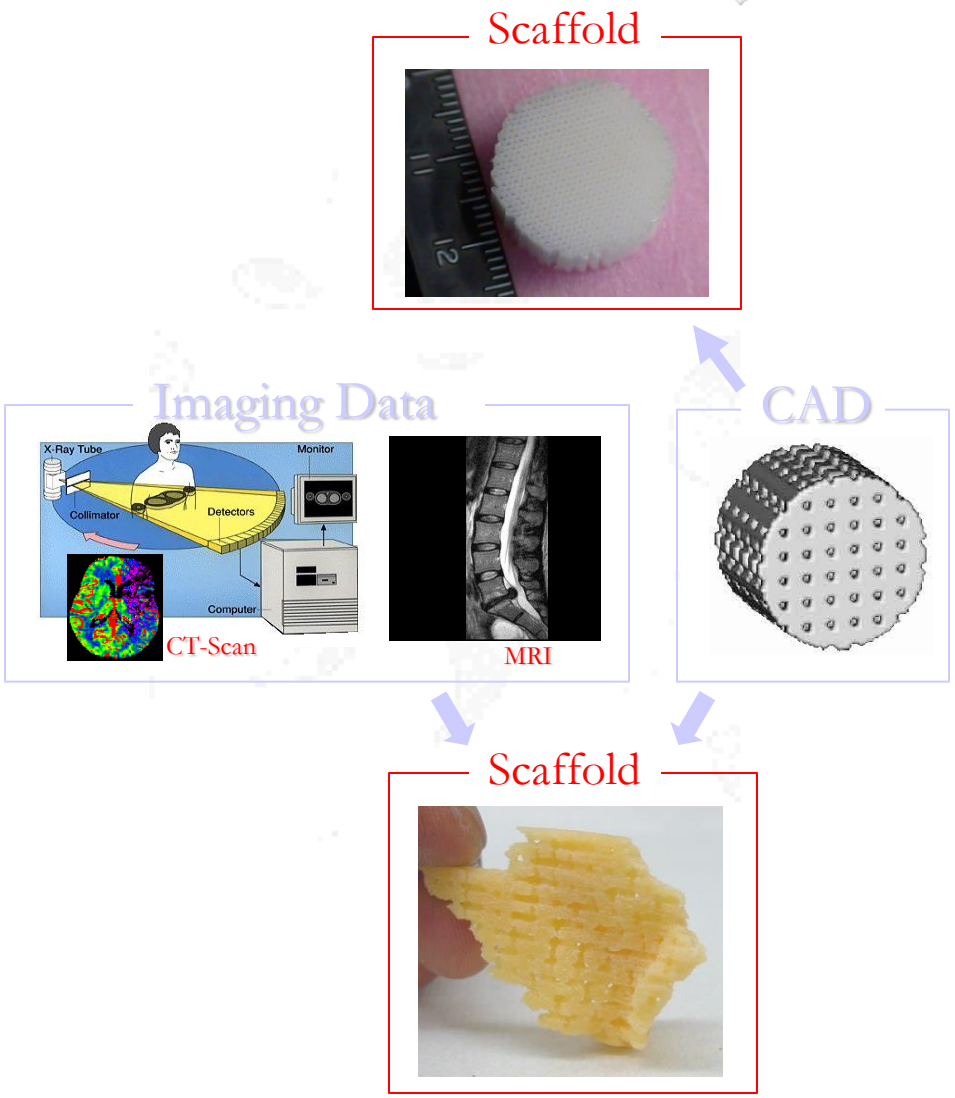
↓

Implantation



CMU – Bone Tissue engineering Website, Dr. L. Weiss

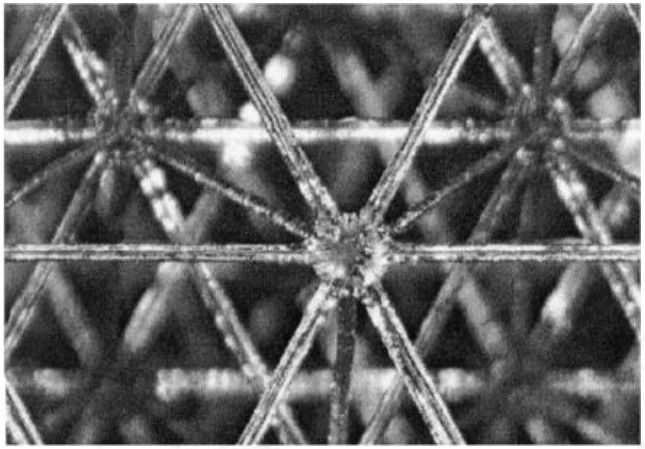
Tissue Scaffold Fabrication - Direct Methods



Additive Manufacturinng

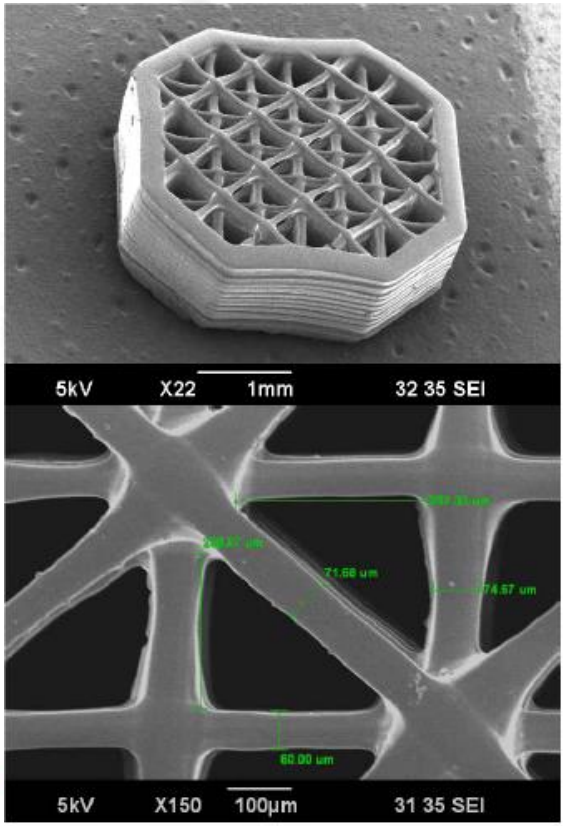
- **CT/MRI – CAD – SFF:**
  - **FDM**
  - **SLS**
  - **3DP – Theriform Process**
- **Advantages:**
  - **No restriction on shape**
  - **High control capability**
  - **Consistent – reproducible**
- **Disadvantages:**
  - **Limited resolution**
  - **Not a cell-friendly environment**
    - **Harsh Heat**
    - **Toxic Solvents**
    - **Non-Sterile**

Scaffolds by Micro-SLA

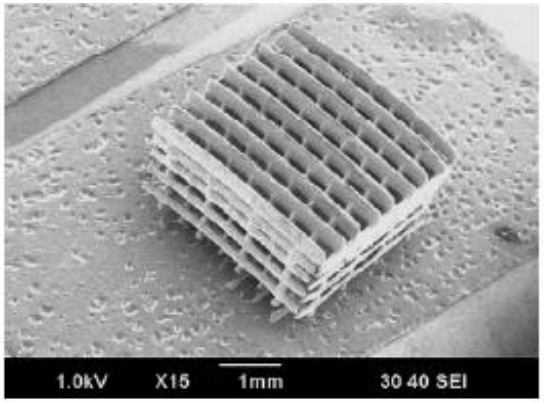


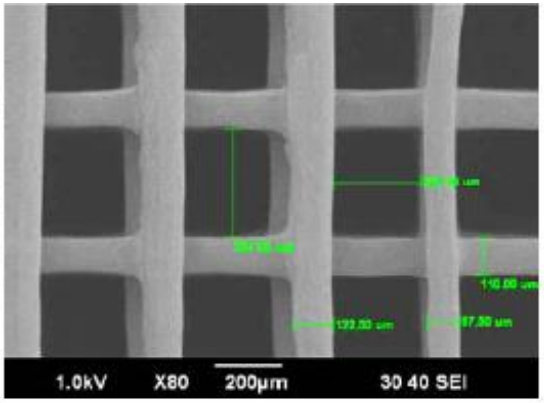
SLA builds concept-verification models of its tensegrity structures

70 μm in diameter.



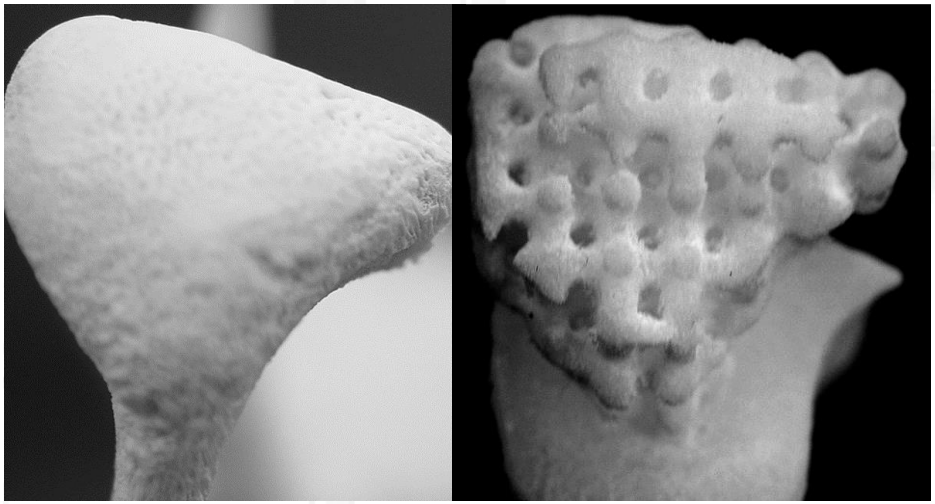
Molecular Geodesics, Inc. Innovation through biological mimicry, www.molecgeodesics.com/contactUs.html





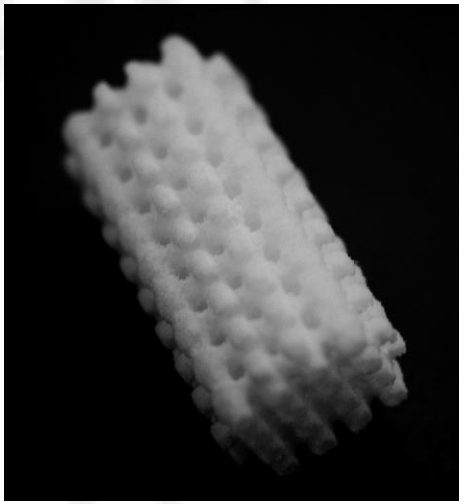
SJ Lee & DW Cho (POSTECH, Korea), Miro-SLA for Tissue Scaffolds, MSEC 2007

Scaffolds by SLS



A B

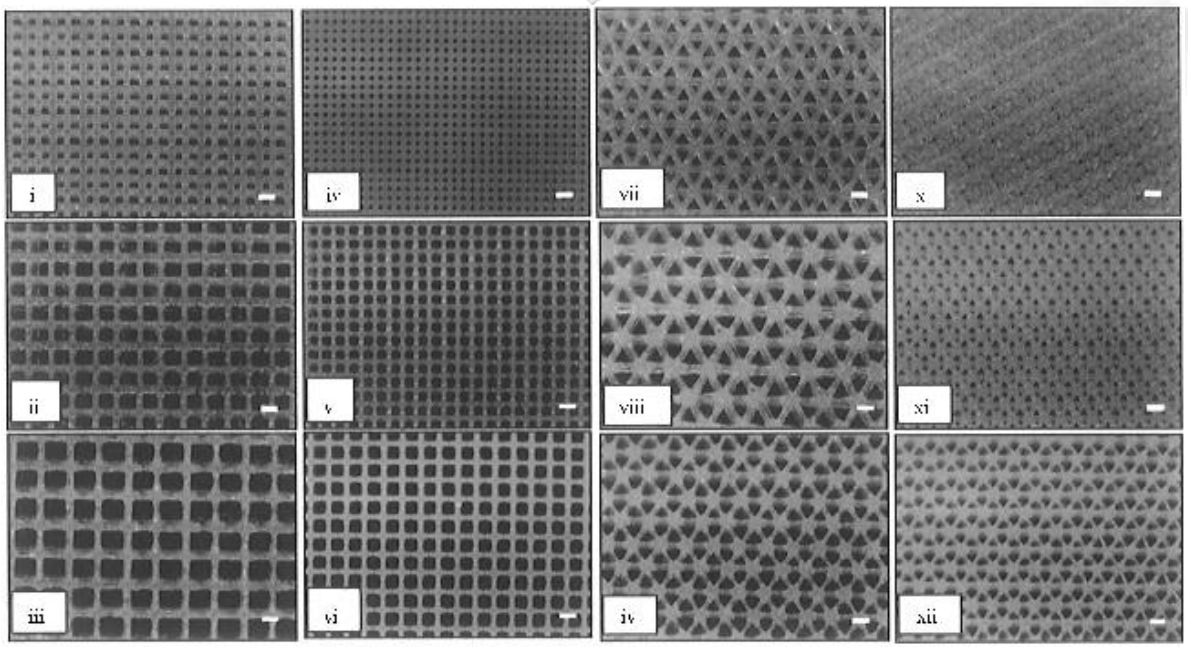
(A) Original Condyle, (B) SLS Fabricated PCL Scaffold

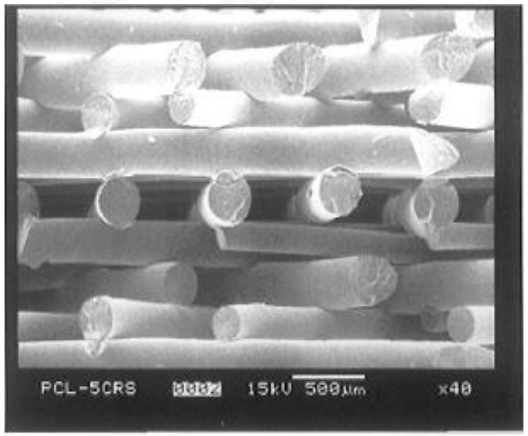


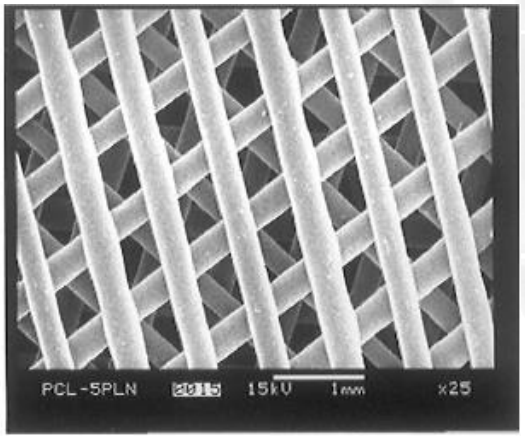
SLS PCL Mechanical Test Scaffold

(Das & Hollister Group, UM)

Scaffolds by FDM







D. Hutchmacher group

TheriForm Process

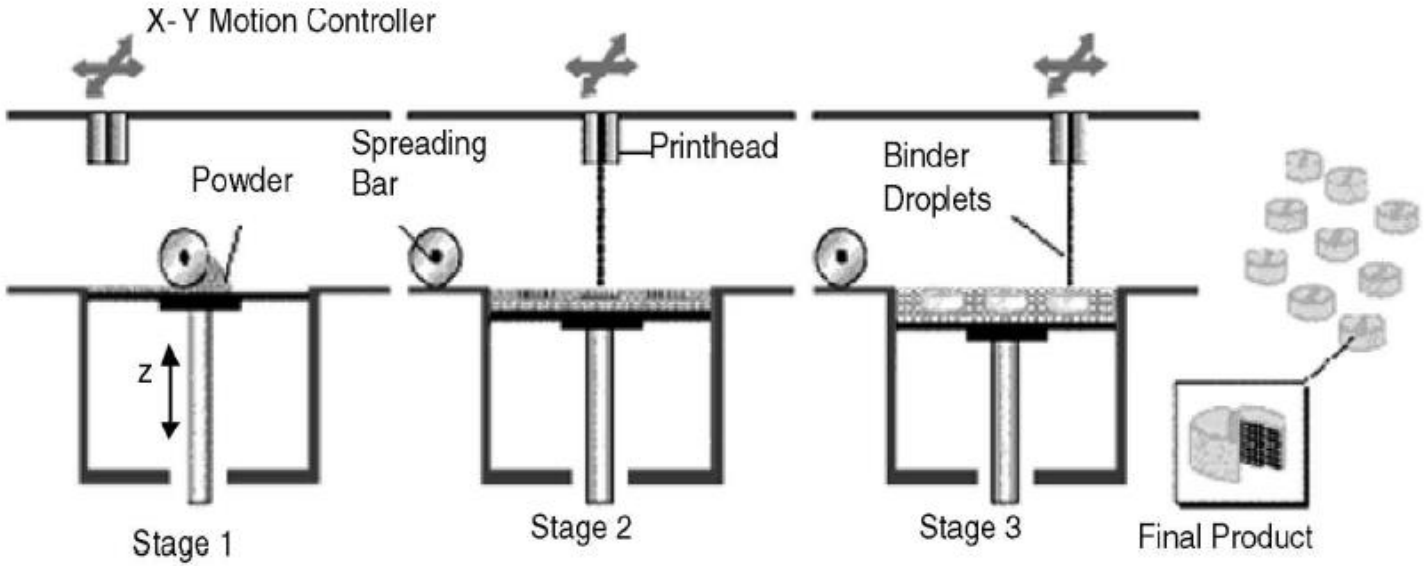


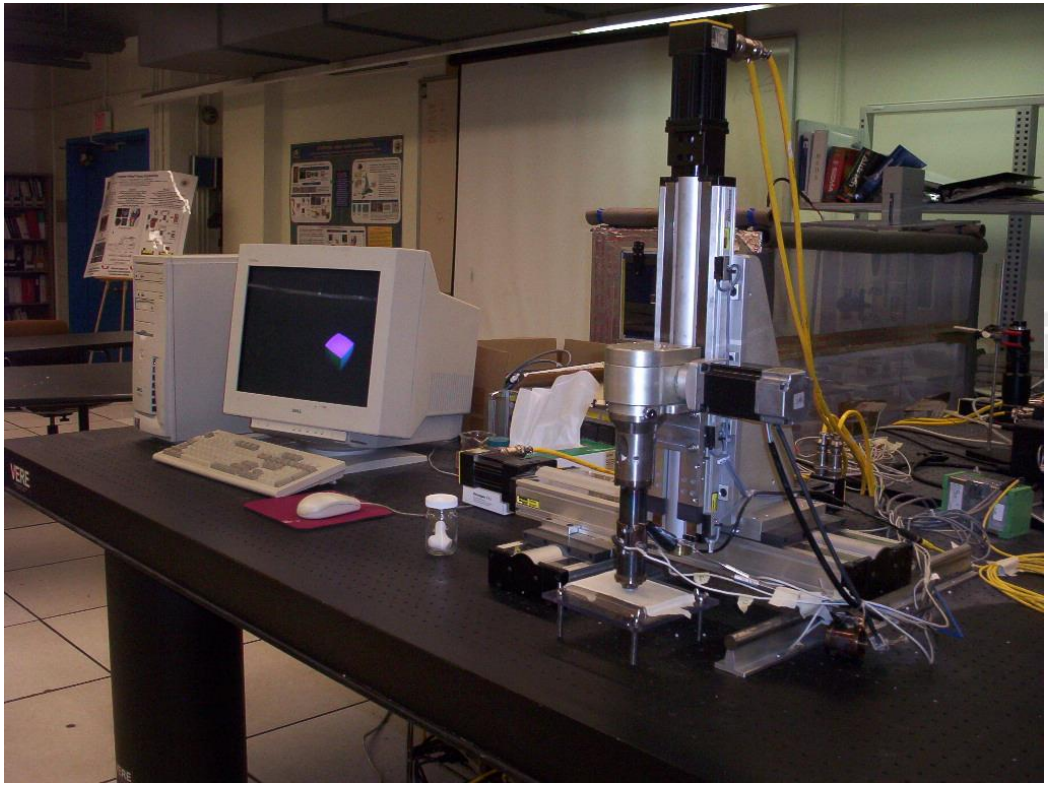
TABLE I. SCAFFOLD FEATURES

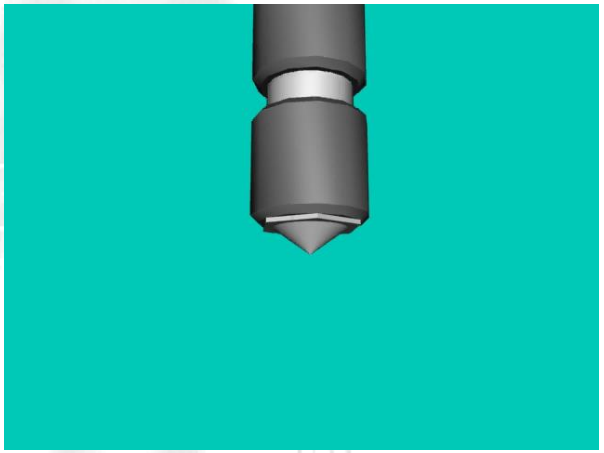
Scaffold composition and architecture			Void fraction estimations					Microcomputer tomography data	
					Scaffold dimensions				
NaCl/polymer ratio	NaCl sieve size (μm)	Polymer sieve size (μm)	Dimensions and polymer density (%)	Weight change upon leaching (%)	Weight (mg)	Thickness (mm)	Diameter (cm)	Calculated void fraction[a] (%)	Average calculated pore size[b] (μm)
90:10	106–150	106–150	90	90	16.0 ± 0.6	1.69 ± 0.04	0.97 ± 0.01	91.1%	121 ± 37
90:10	63–106	63–106	90	90	16.5 ± 0.4	1.79 ± 0.04	0.98 ± 0.01	90.0%	107 ± 31
90:10	38–63	38–63	91	90	14.1 ± 0.3	1.75 ± 0.03	0.98 ± 0.01	91.2%	98 ± 25
90:10	<38	<38	91	90	13.5 ± 0.4	1.63 ± 0.05	0.97 ± 0.01	90.4%	90 ± 24
75:25	106–150	106–150	80	72	48 ± 4	2.33 ± 0.05	1.01 ± 0.01	76.8%	117 ± 48
75:25	63–106	63–106	66	61	59 ± 4	1.76 ± 0.05	0.99 ± 0.01	63.2%	77 ± 31
75:25	38–63	38–63	76	70	44 ± 2	1.86 ± 0.04	0.99 ± 0.01	79.8%	91 ± 31
75:25	<38	63–106	80	72	34 ± 2	1.90 ± 0.10	0.96 ± 0.01	78.7%	101 ± 38

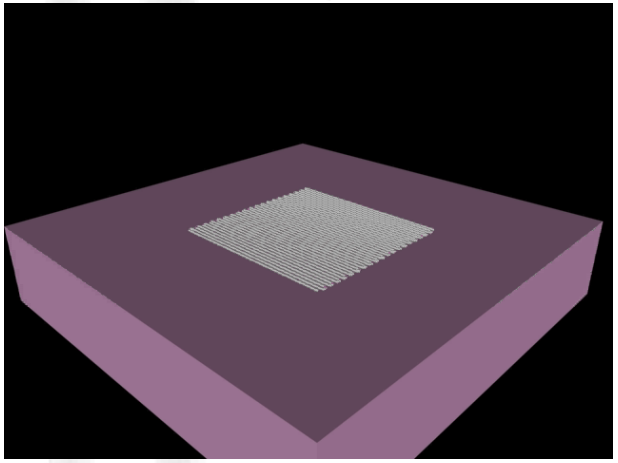
[a]Calculated voids are shown as a % and as μCT subvolume determinations of voids.
[b]Spatial resolution of μCT is 28 μm. The standard deviation of the mean diameter of each pore was 25.5–41.2%.

Precision Extruder Deposition (PED)

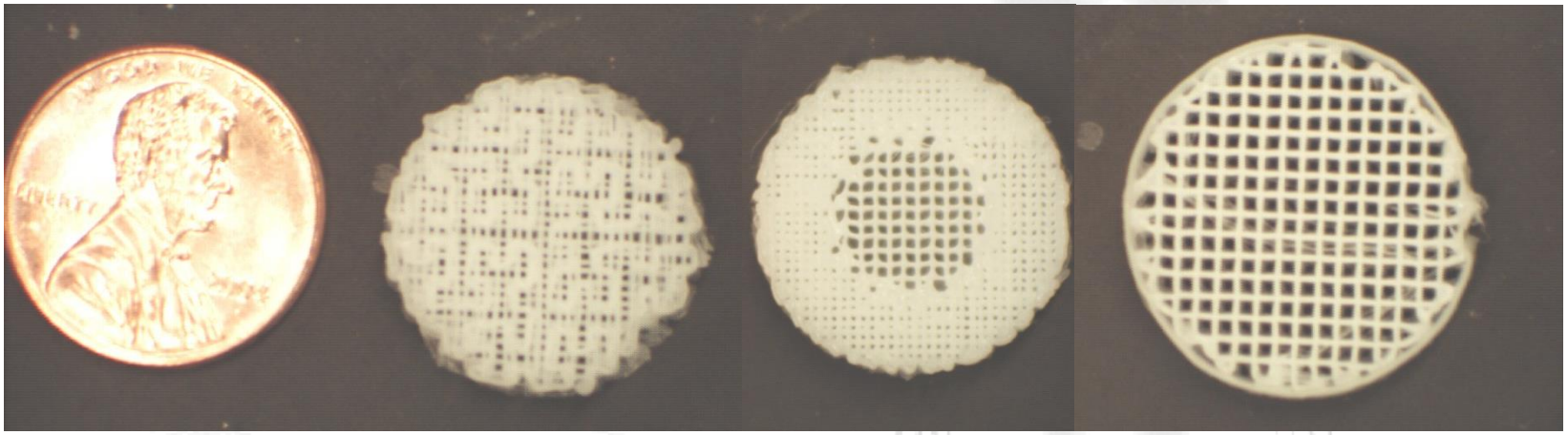
(Drexel University)





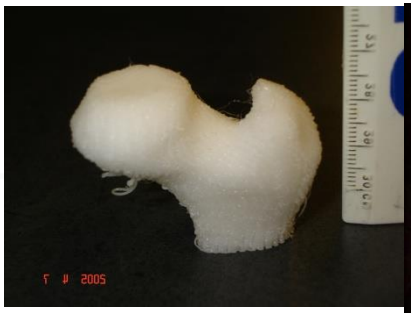


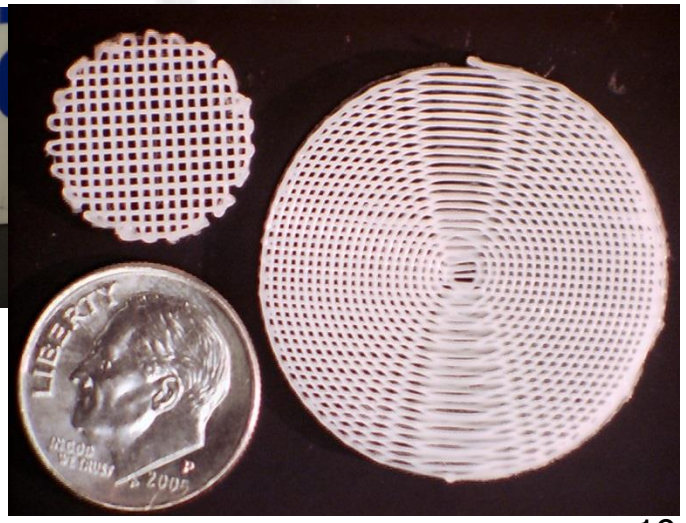
Scaffolds Fabricated by Precision Extrusion Deposition Technique



Material:
Poly-ε-Caprolactone (PCL)

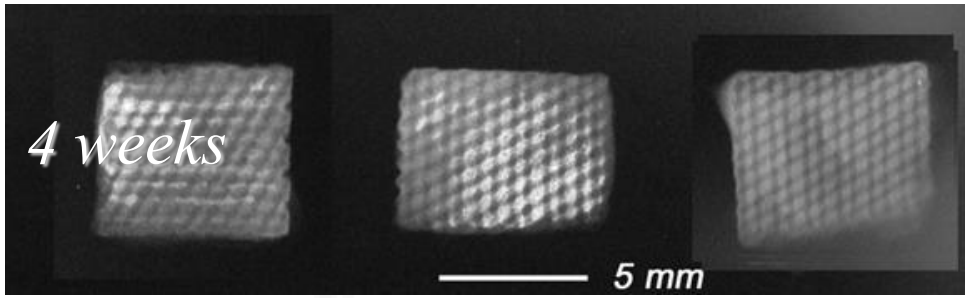
Average pore size:
~ 200 μm
Smallest strut: 100 μm

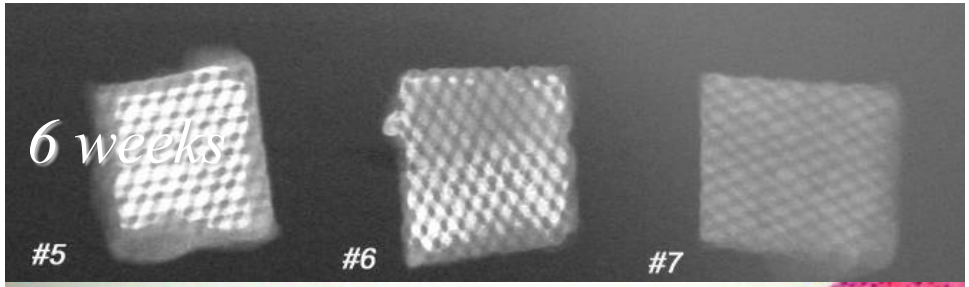


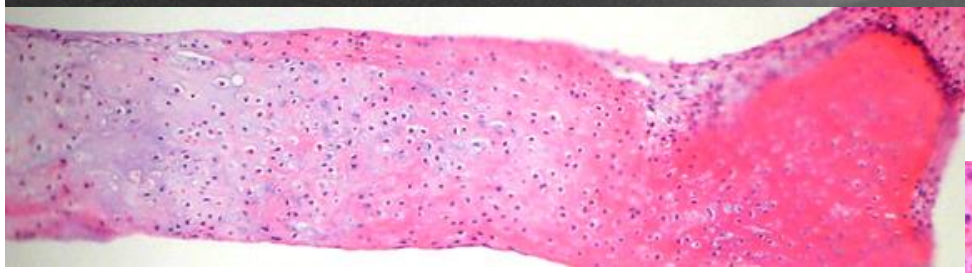


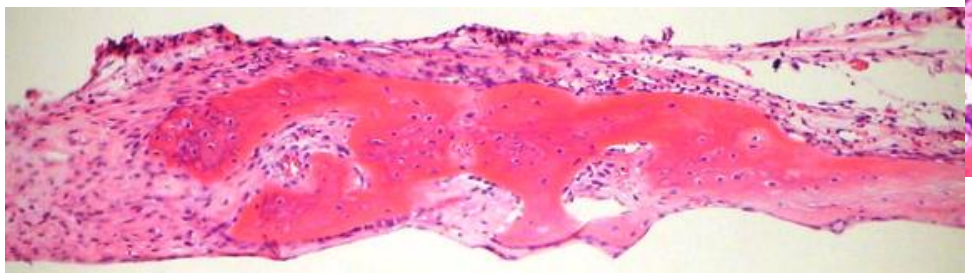
Darling et al, JBMB, 2005
Wang, et al, RPJ, 2005
Starly et al, CAD 2006
Shor et al, Biomaterials, 2007

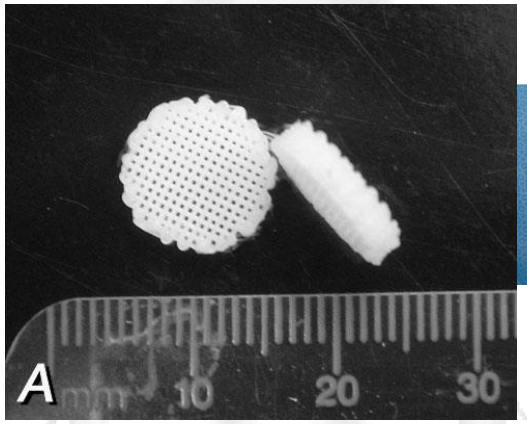
Nude Mouse SC Osteogenesis (collaborate with Dr. H. An, MUSC)

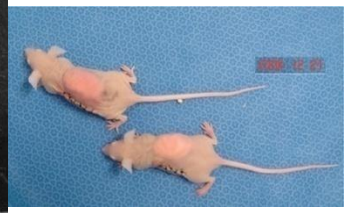






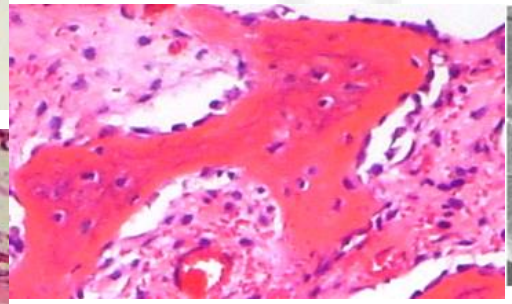


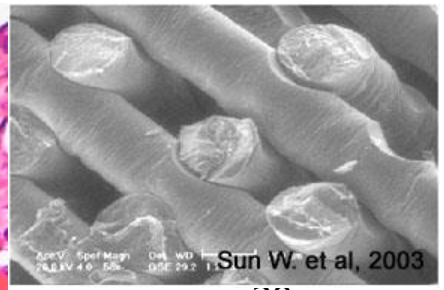




Nude Mouse
Subcutaneous Osteogenesis
Printed poly ε-Caprolactone scaffold

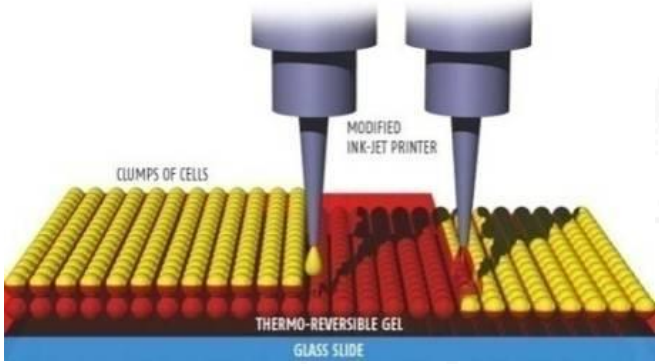
PCL scaffold + bovine osteoblasts

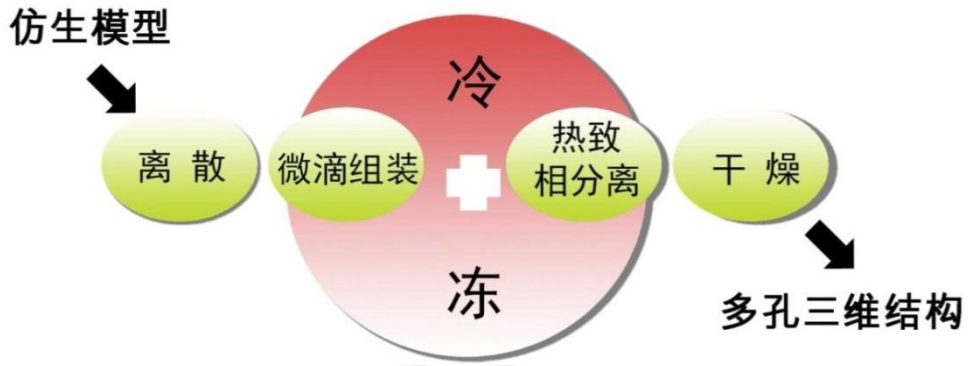




Low-temperature deposition for fabrication of multi-scale pores tissue scaffolds

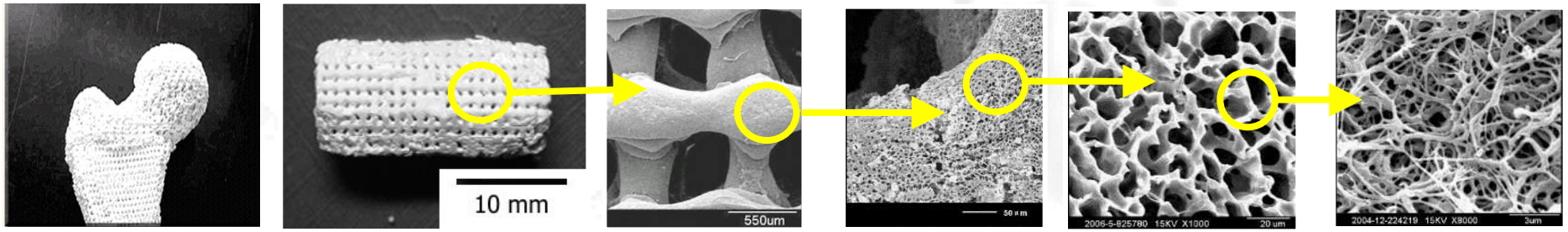
1. double nozzle → multiple materials assemble
2. particle-induced pore → suitable living environment





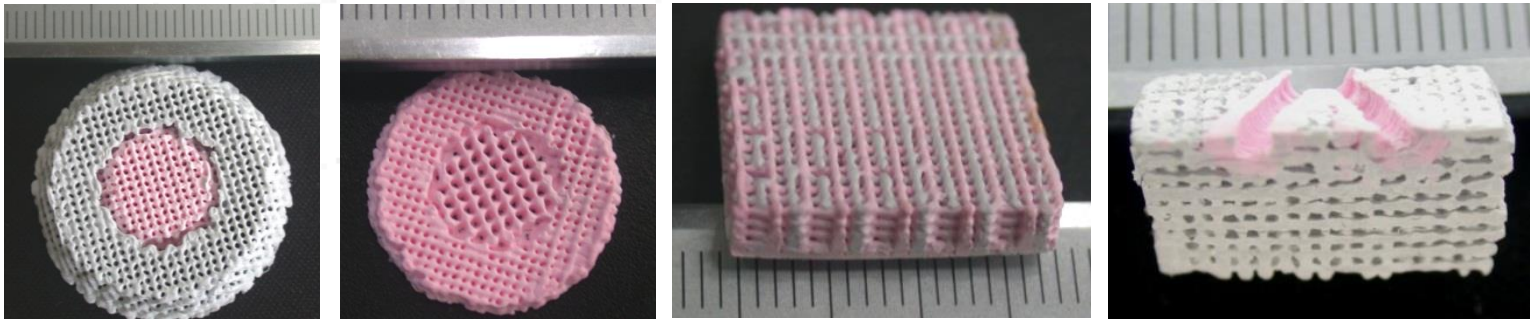
Low-temperature deposition for fabrication of multi-scale pores tissue scaffolds

Gradient Porosity



Microstructure of various levels

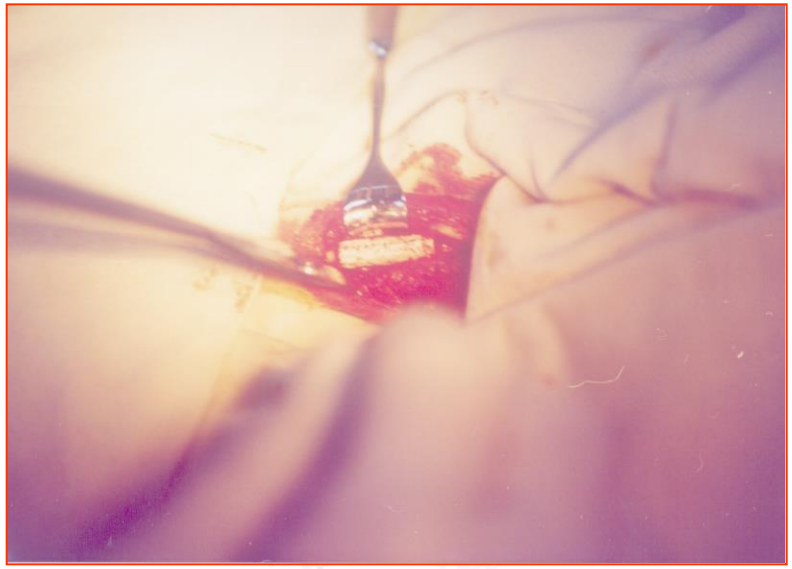
Gradient Structure



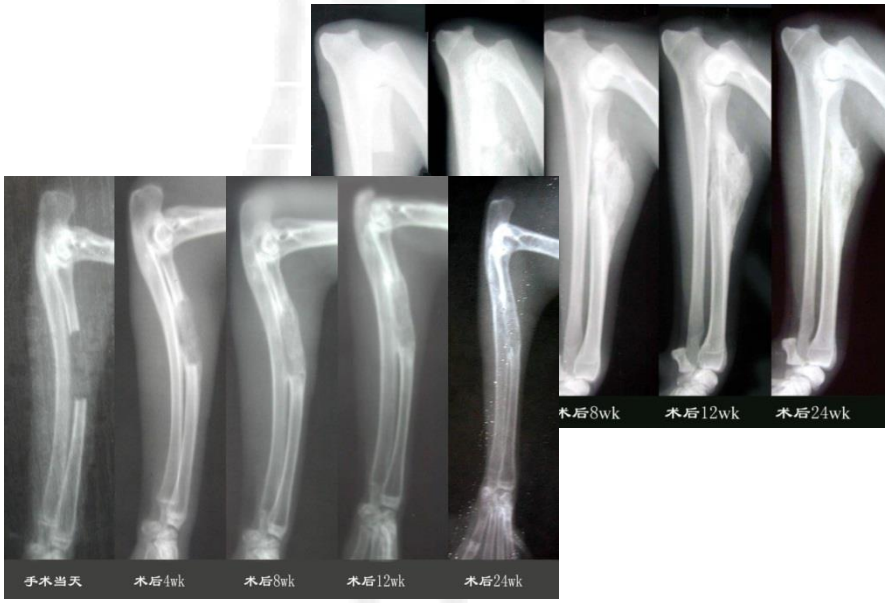
Scaffold:
PLA-TCP

Multi - material : PLLA, PLGA, TCP, Gelatin, Collagen, etc.

Repair of bone defect



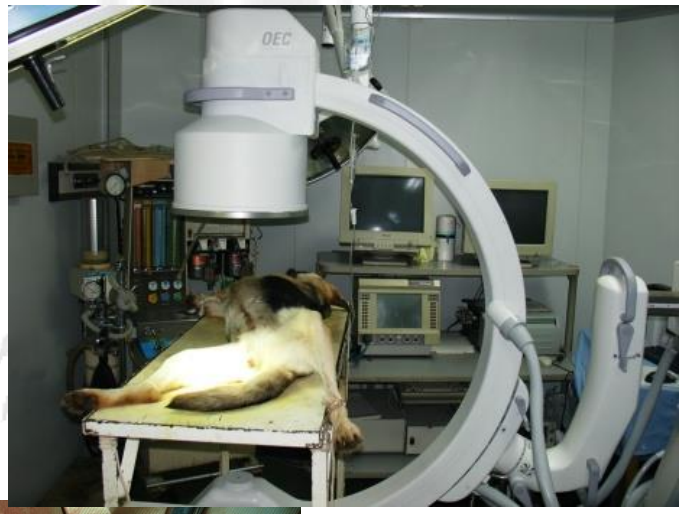
Cooperated with Fourth Military Medical University of PLA and the Institute of Chemistry of Chinese Academy of Science

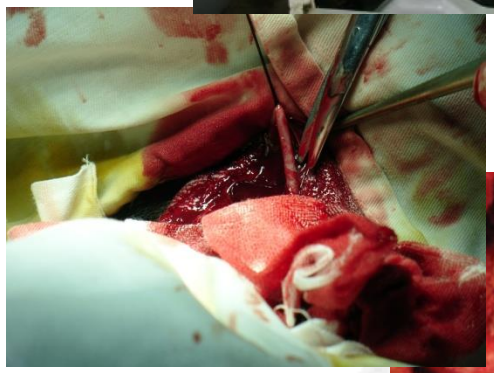


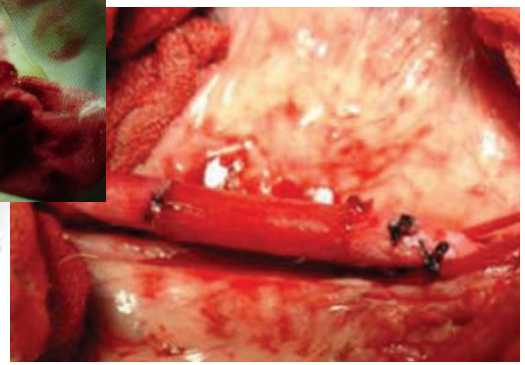
Radiographic images of the rabbit and canine implantation

Engineering of Blood Vessel

(Dr. Zhang L et al)







Animal Models
(Mice and Dog-24 weeks)

Challenges for 3DP of Tissue Scaffolds

Biomaterials
Structure
Topology

Biomaterials for Tissue Scaffolds

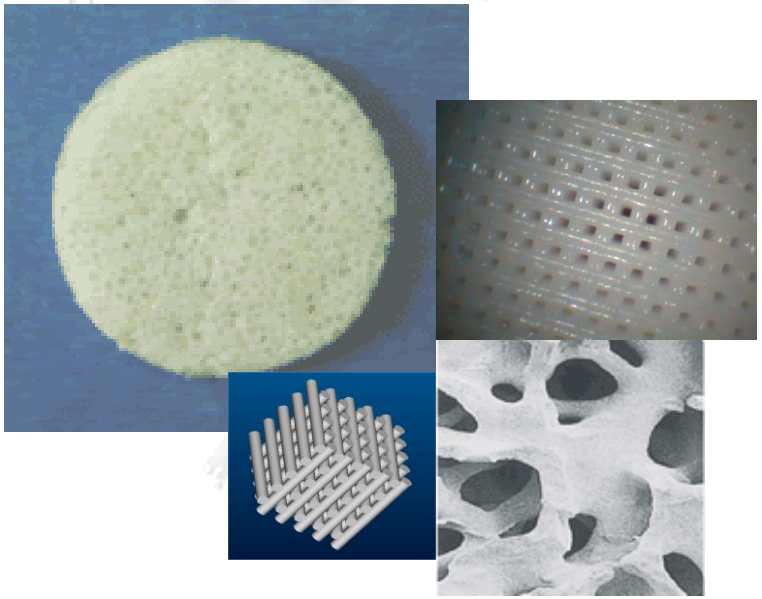
- Topological design for structural cues

Scaffold Materials: biocompatible, biodegradable, bioabsorable,

Scaffold porosity and pore size:

- A large surface area favors cell attachment and growth;
- A large pore volume accommodates and delivers a sufficient number of cells;
- High porosity for easy diffusion of nutrients, transport and vascularization.

5 μm for neovascularization,
5-15 μm for fiberblast ingrowth,
20 μm for the ingrowth of hepatocytes,
20-125 μm for regeneration of adult skin,
40-100 μm for osteoid ingrowth,
100-350 μm for regeneration of bone,
500 μm for fibrovascular tissue



Agrawal, C.M.; Ray, R., . of Biomedical Materials Research, 55(2):141-50, 2001.

Challenges for Biomaterials in Tissue Scaffold - a system design approach

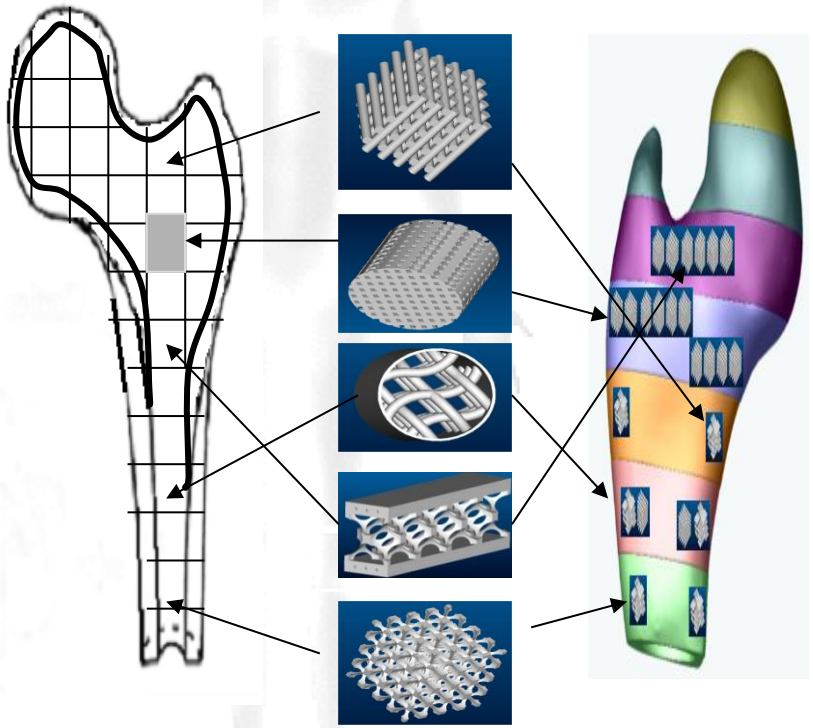
1) Biophysical requirements:
- scaffold structural integrity, strength stability, and degradation;
- cell-specific pore, shape, size, porosity, and inter-architecture

2) Biological requirements:
- cell loading and spatial distributions;
- cell attachment, growth and new tissue formation;

3) Transport
- pore topology and inter-connectivity

4) Anatomical requirements:
- anatomical compatibility;
- geometric fitting

5) Manufacturability requirements:
- process ability (biomaterial availability, printing feasibility etc.)
- process effect (wrapping, distortion, structural integrity, etc.)

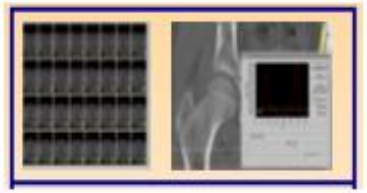


It is a multi-constrained System Design Problem

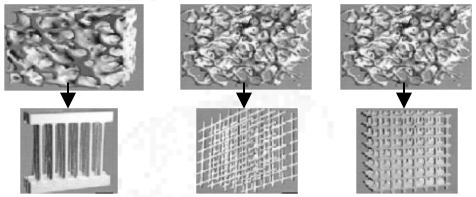
Computer-Aided Tissue Engineering for Load Bearing Scaffold Design and Fabrication

(NSF – 0427216; Sun, Shokoufandeh and Liebschner)

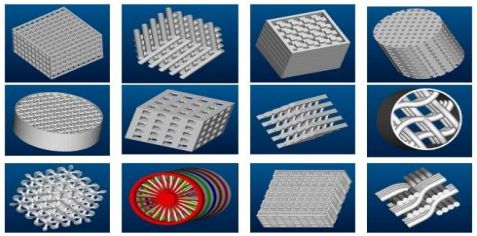
Micro-CT/MRI Image

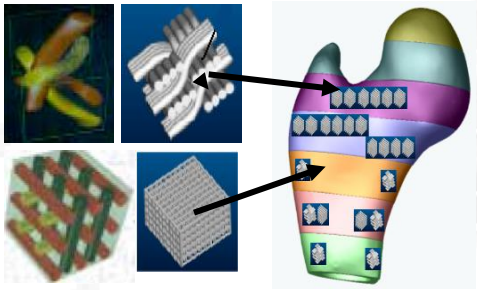


Tissue Primitives

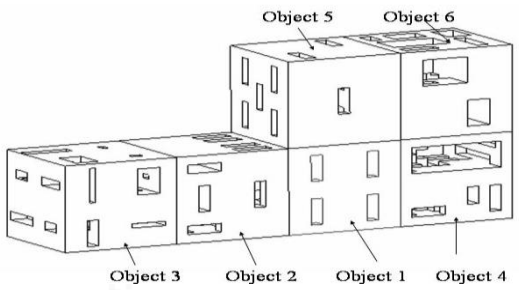


CAD-based Unit Cell Model



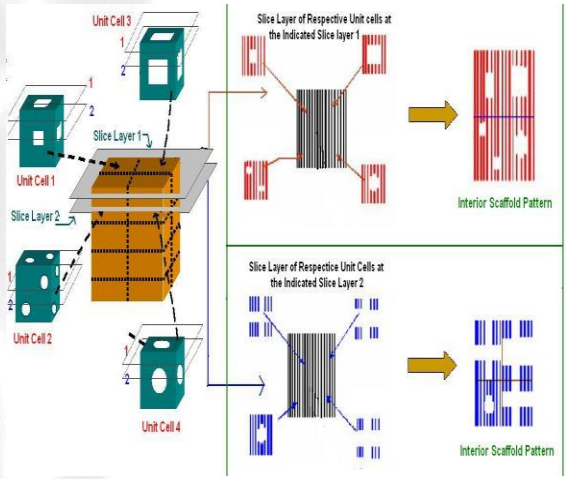


Biomimetic design

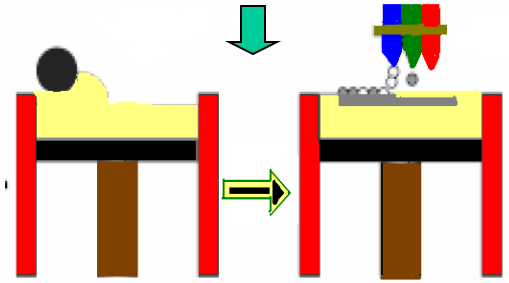


$$\text{Work}(P,Q,F,T) = \sum_{i=1}^{m} \sum_{j=1}^{n} f_{ij} d_{ij}^{T}.$$

Algorithm to determine optimal scaffold transport



Scaffold internal layout pattern



Scaffold layered (TheriForm) freeform fabrication

Computer modeling of bone tissue primitives and micro-structure

Biomimetic design and computational characterization of designed tissue scaffolds

Interface of design and process toolpath for freeform fabrication of tissue scaffolds

Bio-3D Printing

According to the use of biomaterials, we can categorize Bio-3DP into the following 4 level of applications:

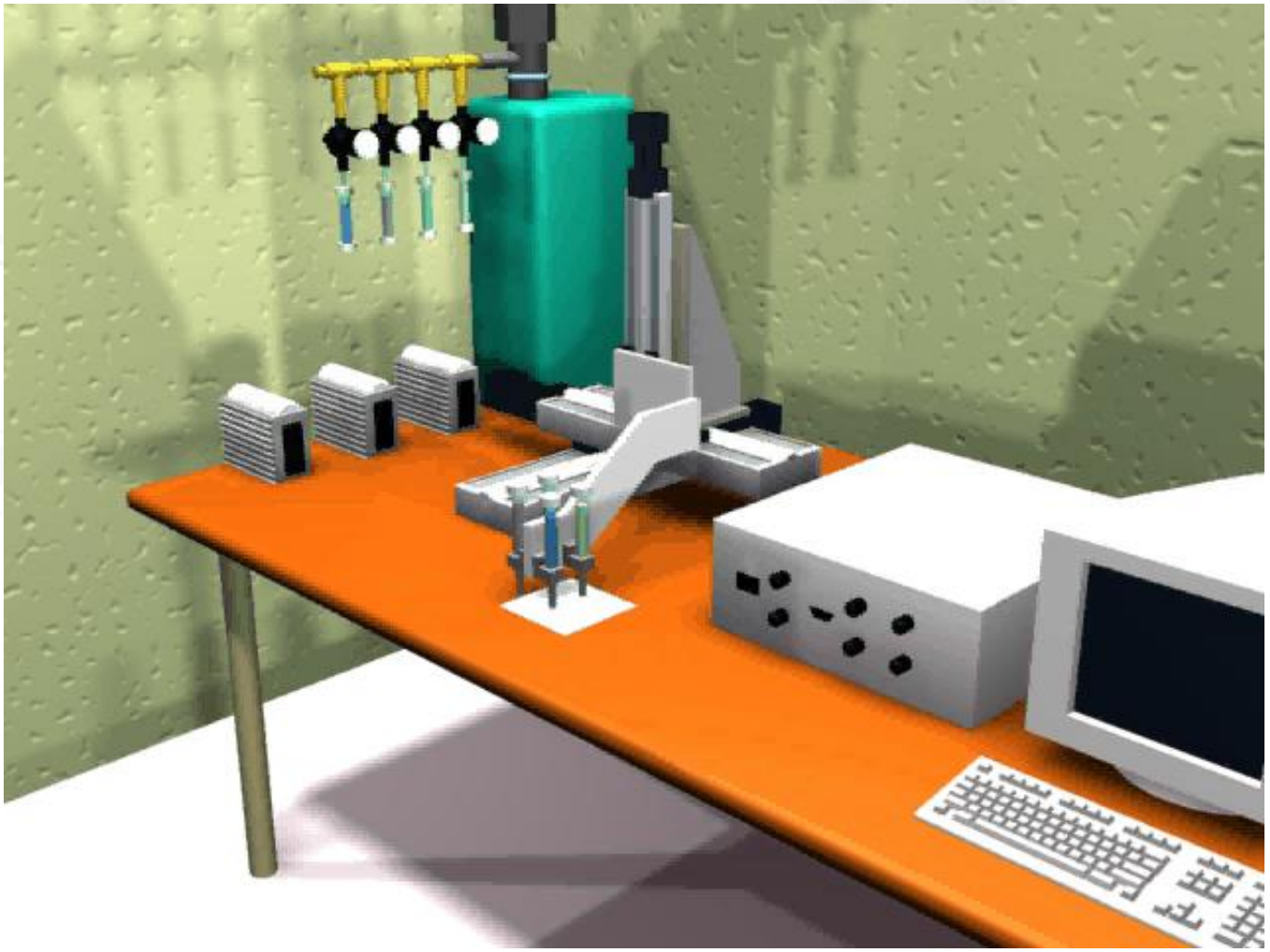
Level 1: medical models and medical devices
- non-biocompatible materials

Level 2: medical implants
- biocompatible but not biodegradable

Level 3: tissue scaffolds
- biocompatible, biodegradable and bio-absorbable

Level 4: in vitro biological models
- **cells and living biological compounds as materials**

Multi-nozzle Direct Cell Deposition



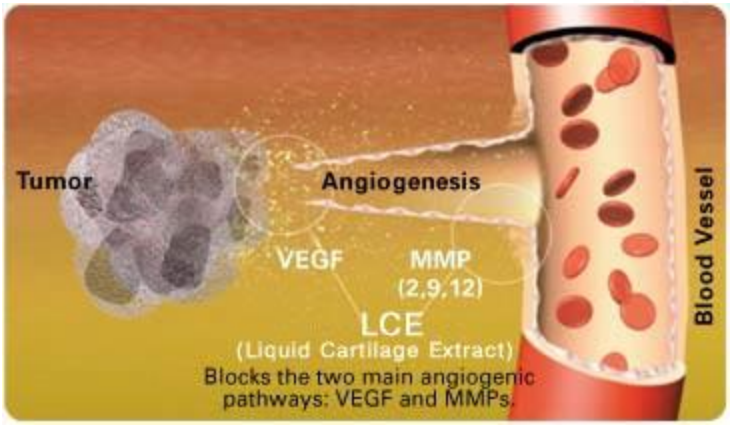
Directly Assembled 3D Biological Model by Cell Printing/Deposition

RGD Modified Surface

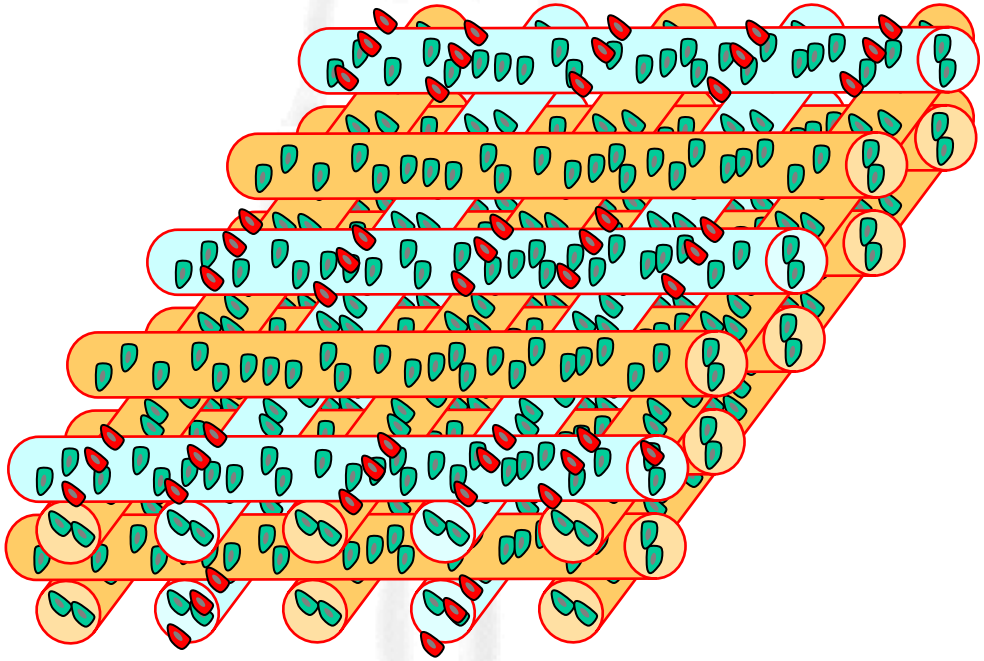
Unmodified Surface

Fibroblasts (Encasulated)

Endothelial (Applied to Surface)



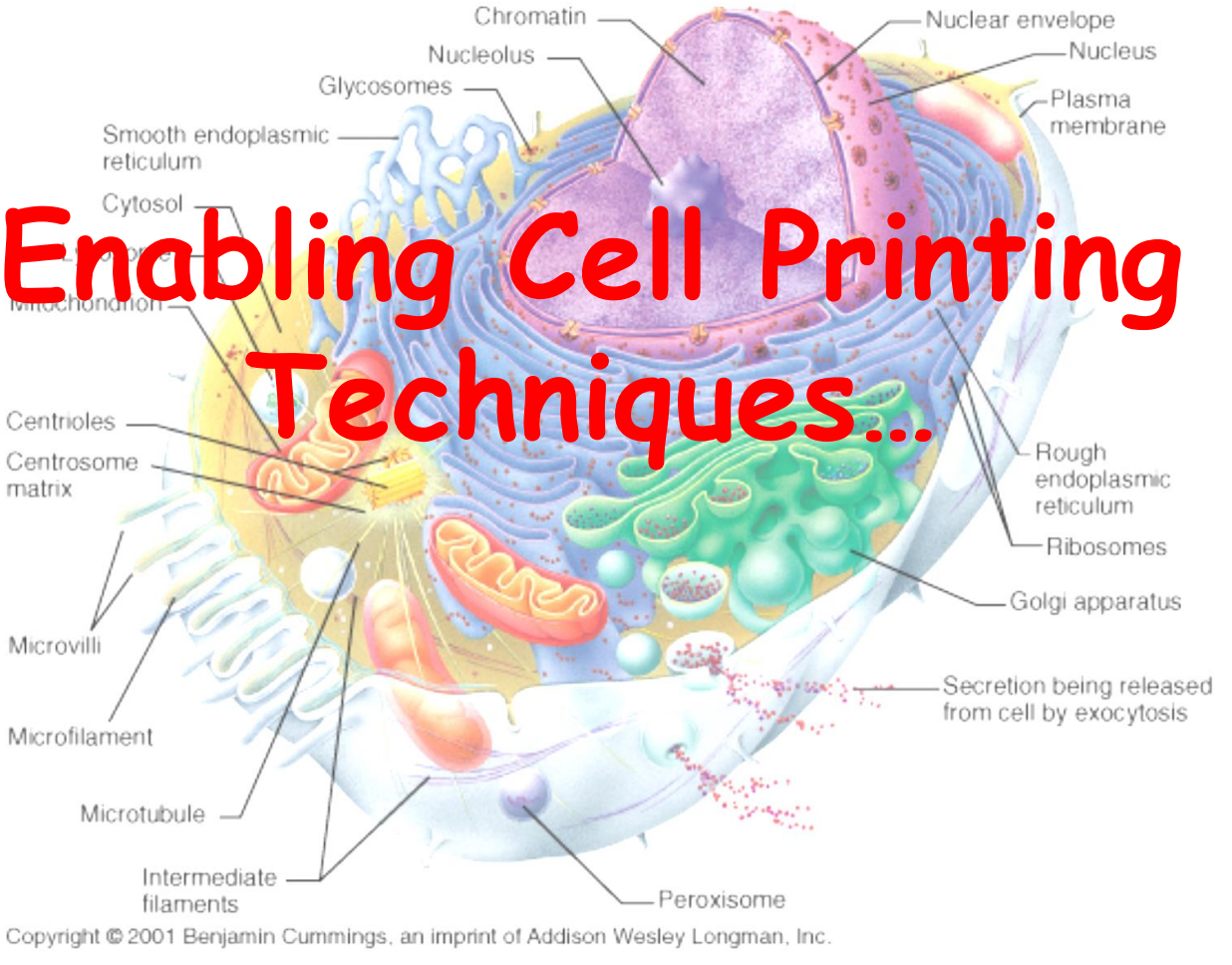
http://www.angioworld.com/angiogenesis.htm



Direct Assembled Biological Model for Angiogenesis

Morss-Clyne & Sun: 2008 Biomaterial Congress; Tissue Engineering, 2010, Biofabrication, 2010

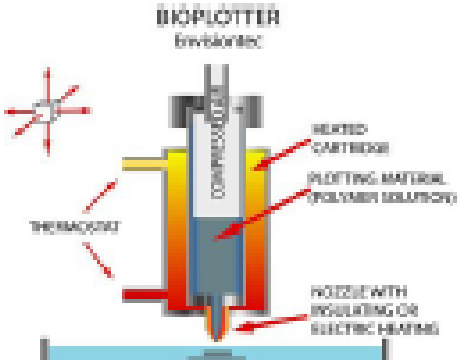
Enabling Cell Printing Techniques…



Enabling Engineering Processes for Cell Printing/Assembly

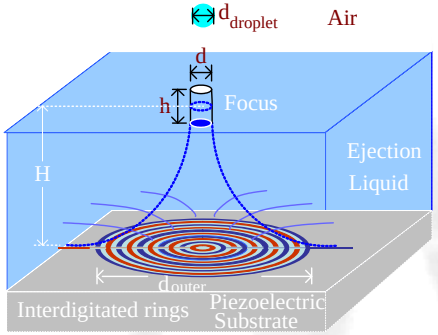
Inkjet

(thermal, piezo)
Dimatix, Clemson
U. Manchester
Epson



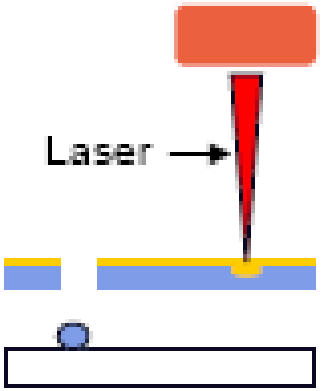
Bio-plotting

(extrusion through syringe)
Envisiontech, Organovo
Tsinghua, Drexel
UIUC(J. Lewis)
Invivo BAT- Sciperio



Acoustic Droplet Ejection

Labcyte
Harvard-MIT
(Demirci)



Laser-Assisting

NRL
INSERM-France
(Guillemot)
LDW-Clemson

Inkjet Cell Printing

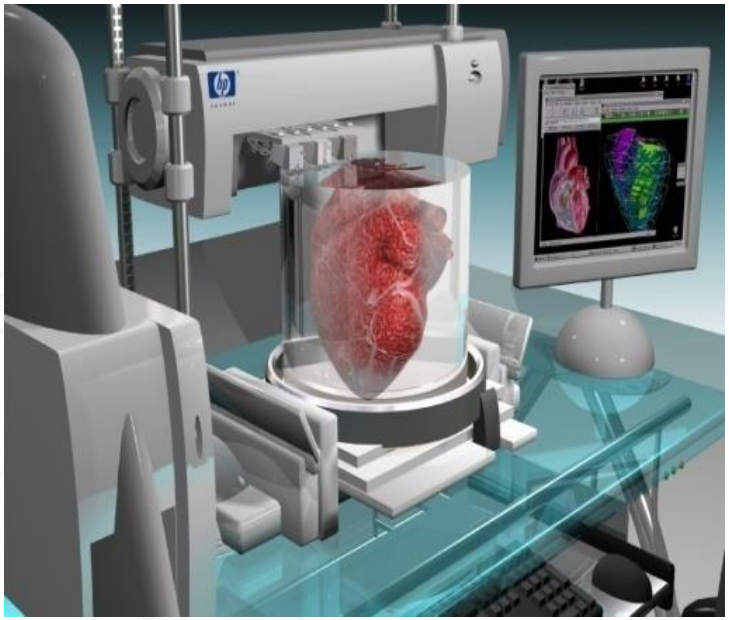
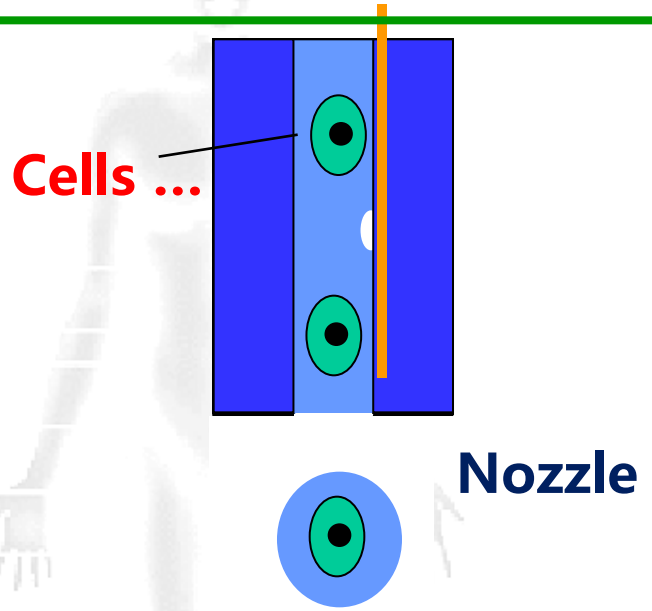
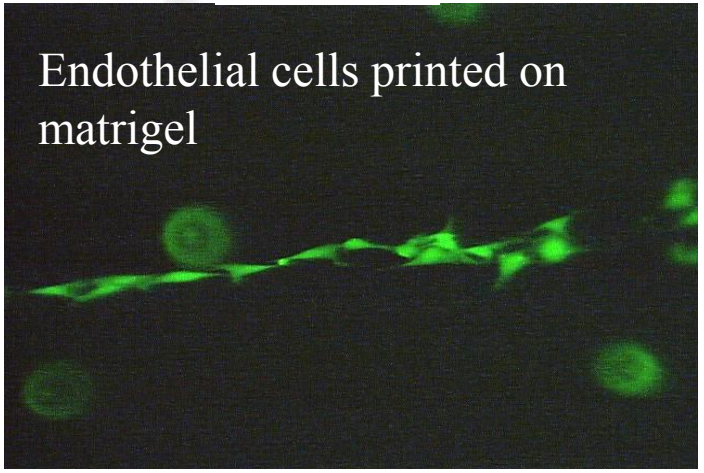


Image courtesy by Dr. T. Boland



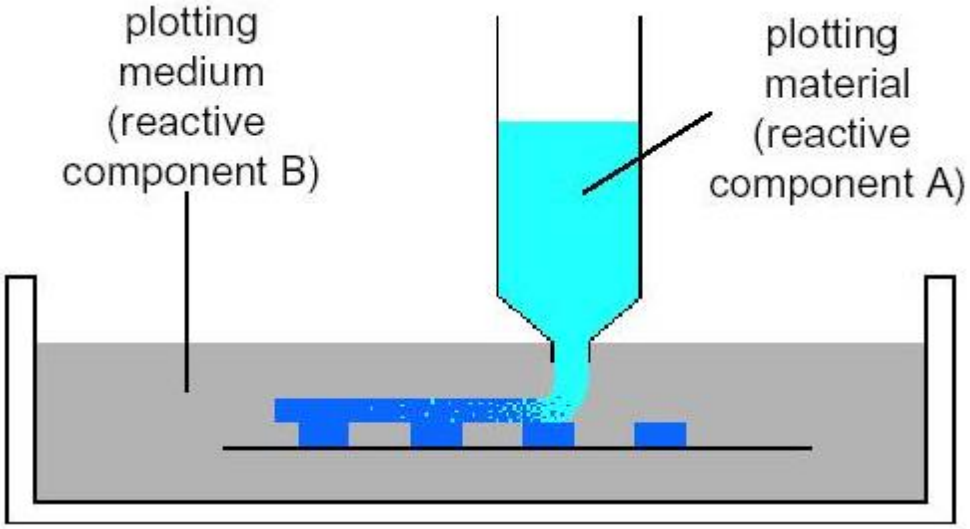


Prof. Thomas Boland (Clemson/UTEP)

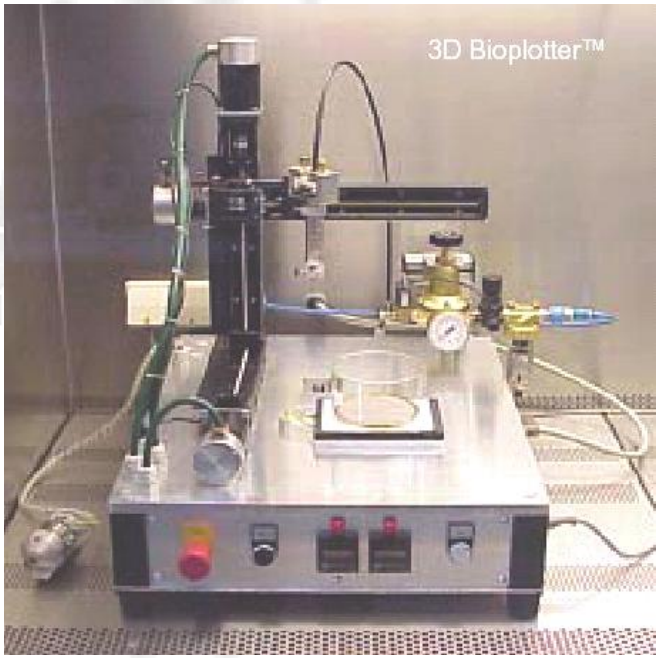
NSF EFRI (2008-2011): Emerging Frontiers in 3-D Breast Cancer Tissue Test Systems

Awarded to: Burg, Boland, Leadbetter and Dreau

Bioplotter - robotic bioprinter



University of Freiburg

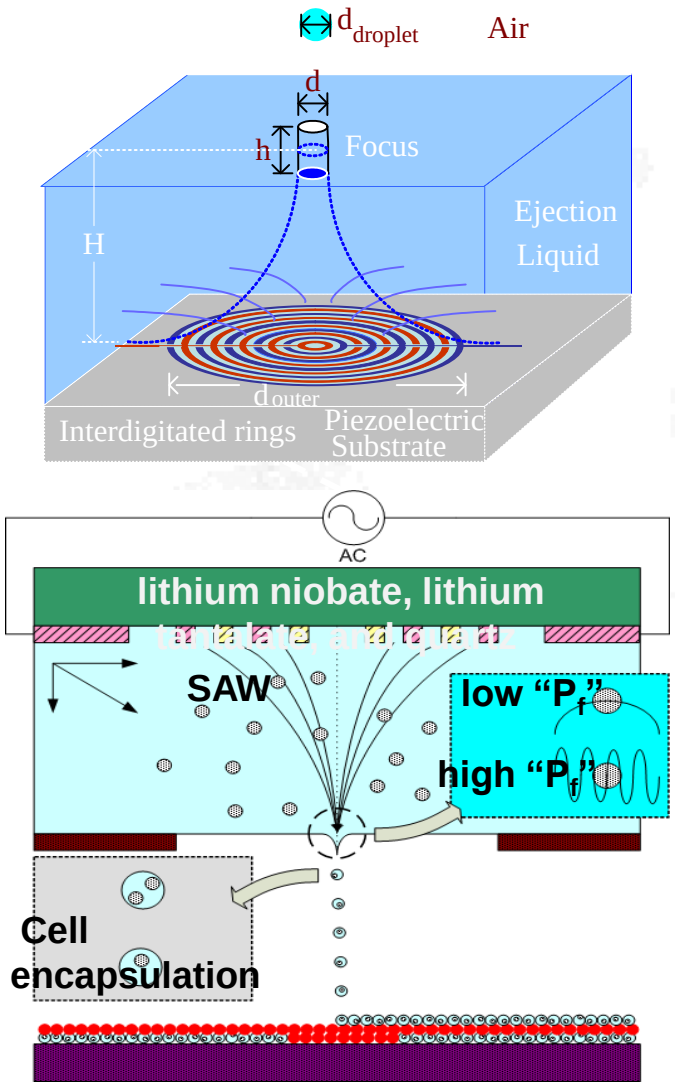


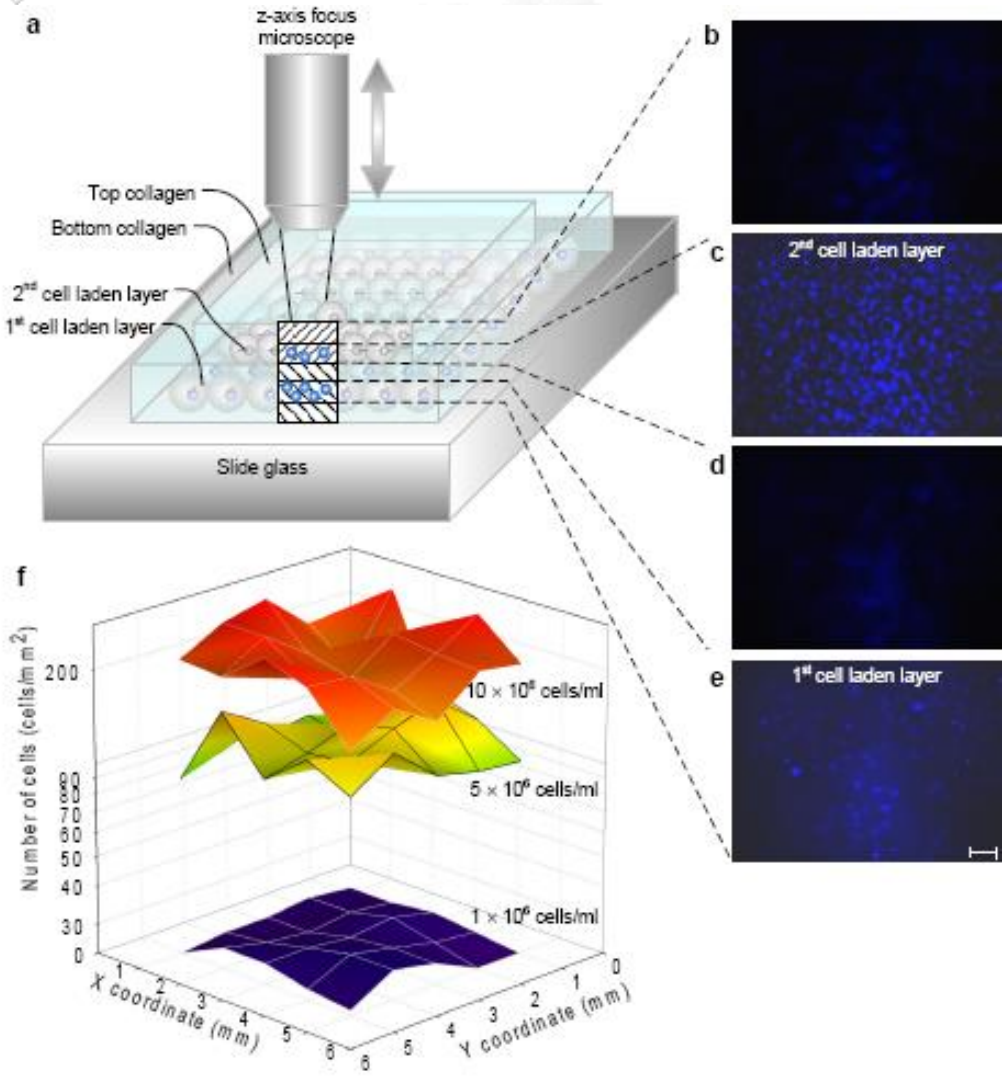
Envisiontec ($100K per system)

Envisiontech: http://www.envisiontec.de

Acoustic Nozzle-Free Droplet Ejection

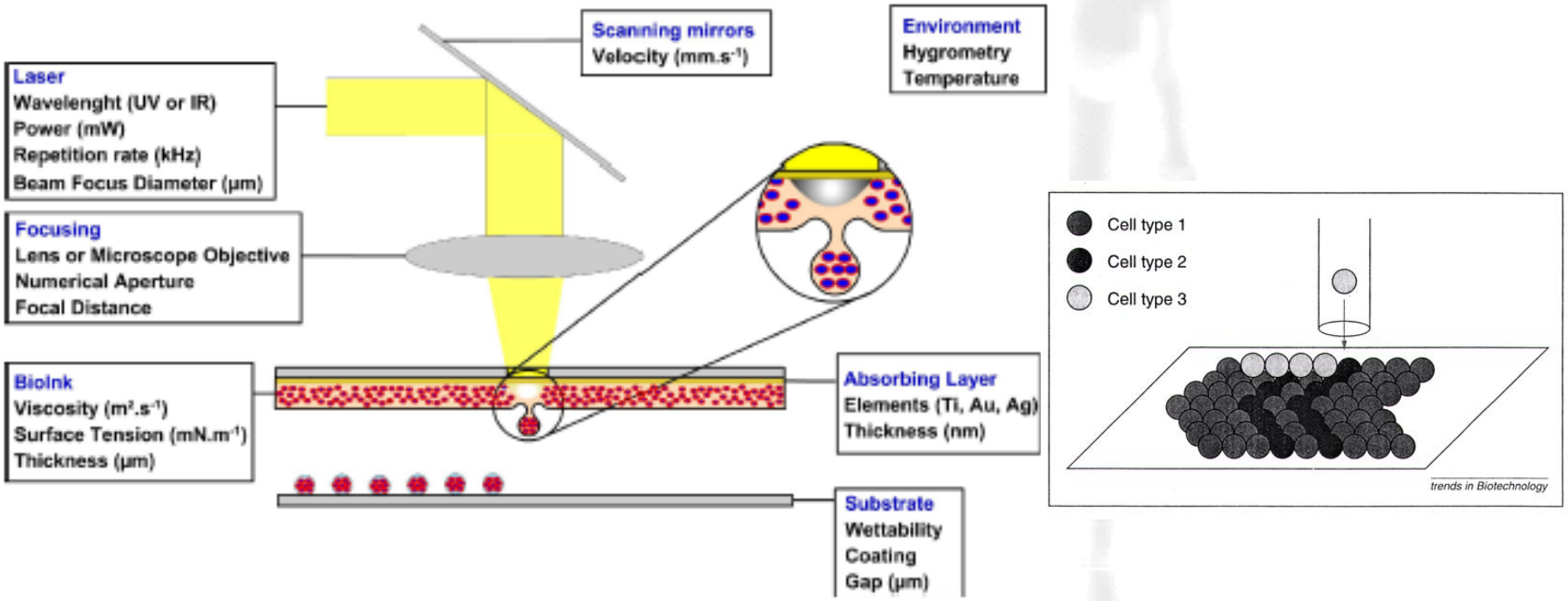
(This slide is by courtesy of Dr. Utkan Demirci. Harvard-MIT)





3D Cell Encapsulating Microgel Printing for Tissue Model

Laser assisted cell printing



BioLP: Biological Laser Printing

MAPLE-DW: Matrix Assisted Pulse Laser Evaporation – Direct Write

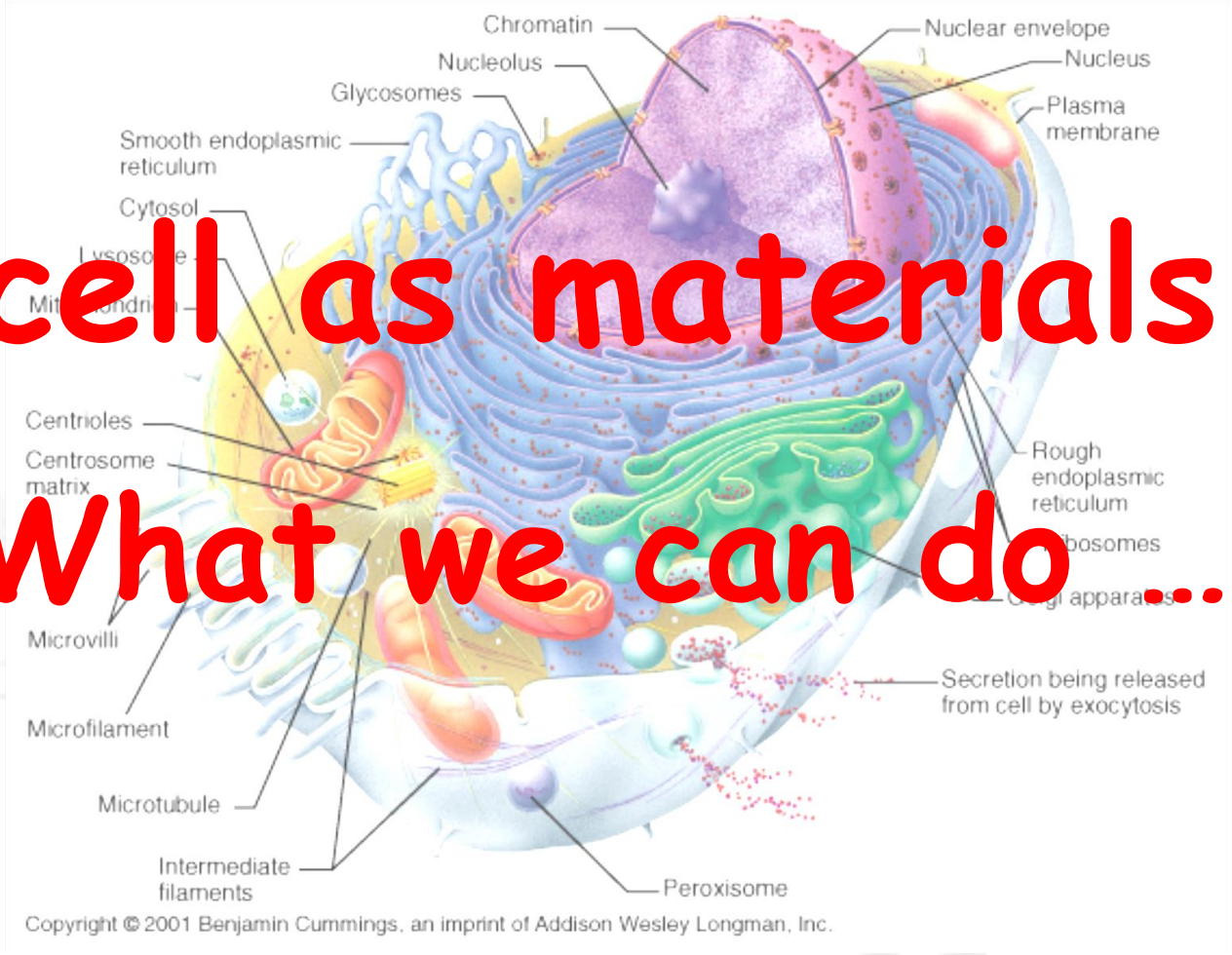
LIFT: Laser-induced Forward Transfer

AFA-LIFT: Absorbing Film Assisted – Laser Induced Forward Transfer

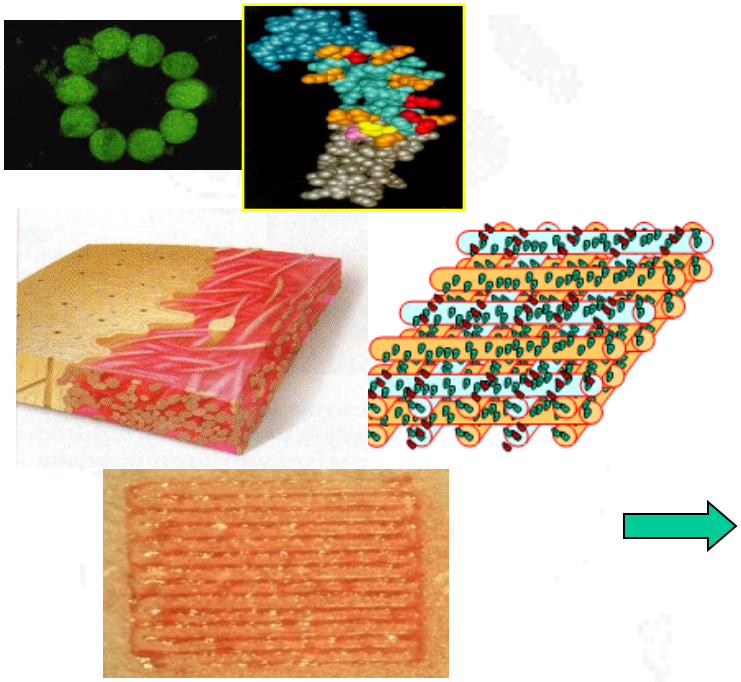
(Courtesy of Dr. Guillemot, INSERM)

cell as materials

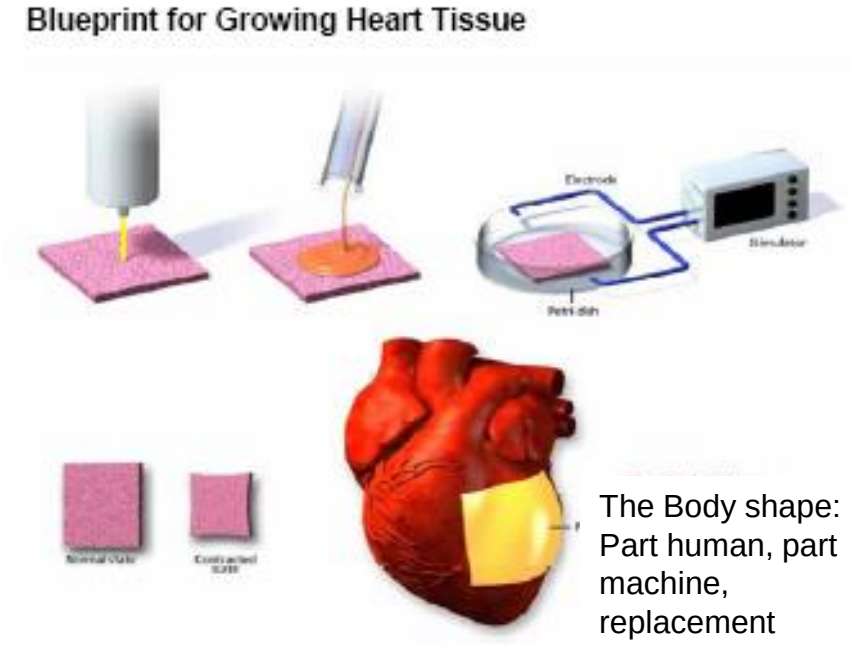
What we can do…



3D Printing of Heart Patch



Cell/Protein 3DP



Radisic, 2004, National Academy of Sciences
美国科学院， 2004

The Body shape: Part human, part machine, replacement maybe one day extend your life

3D Printing of 3D Cell Aggregates as Physiological Model for Disease Study

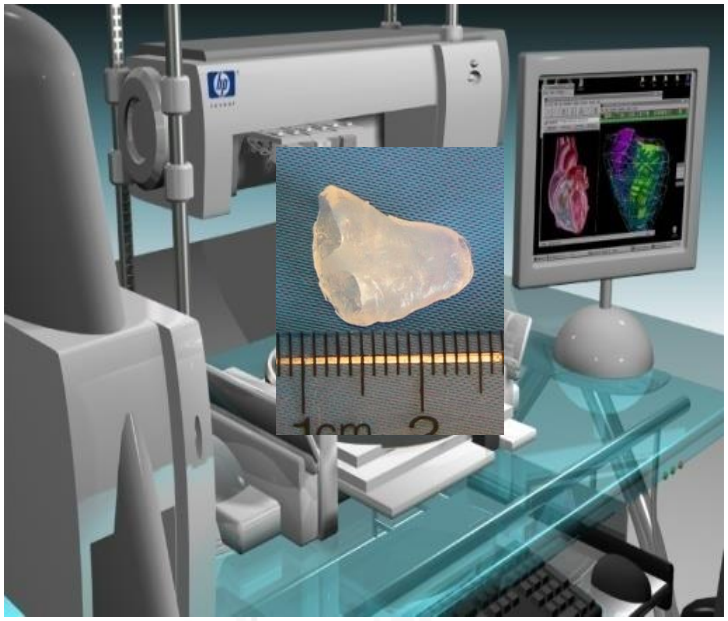
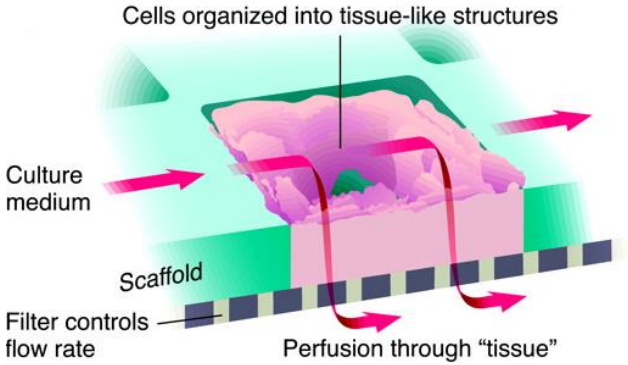


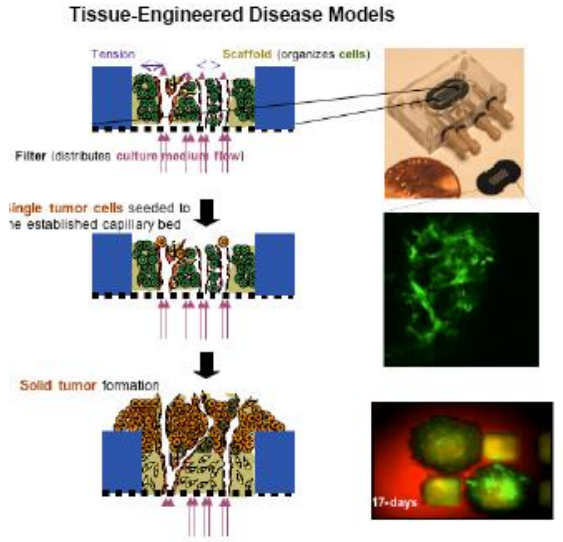
Image courtesy by Dr. T. Boland, Clemson

Funded in part by: NSF EFRI (2008-2011): Emerging Frontiers in 3-D Breast Cancer Tissue Test Systems

Burg, Boland, Leadbetter and Dreau



Griffith L., Naughton, G., Science. 295 (5557), 2002, pp 1009-1014



Griffith & Swartz, Nature Review, 2006

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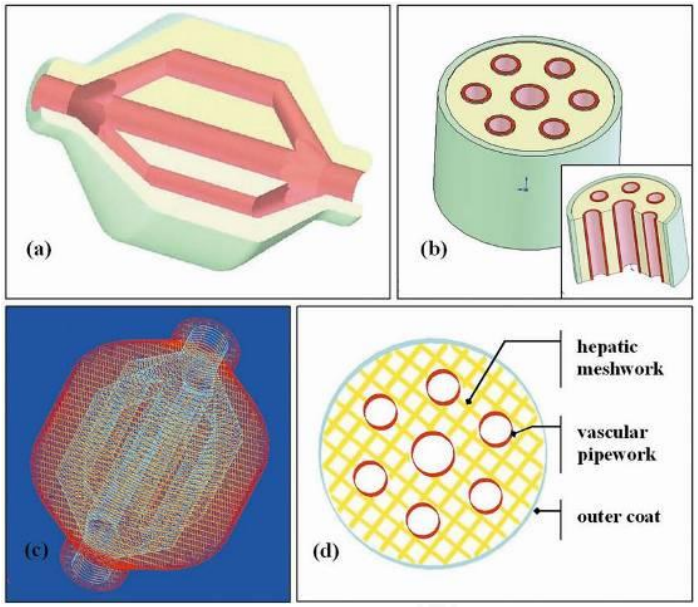
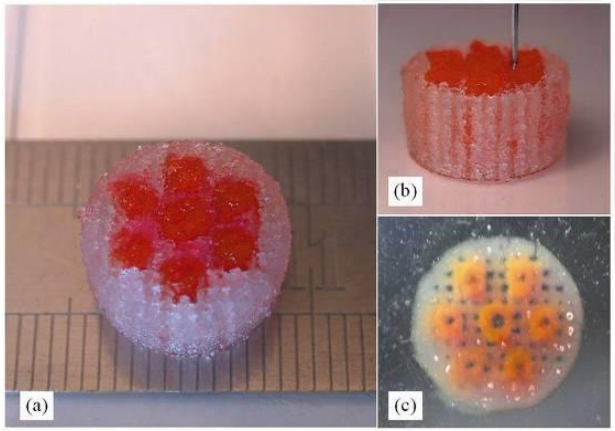
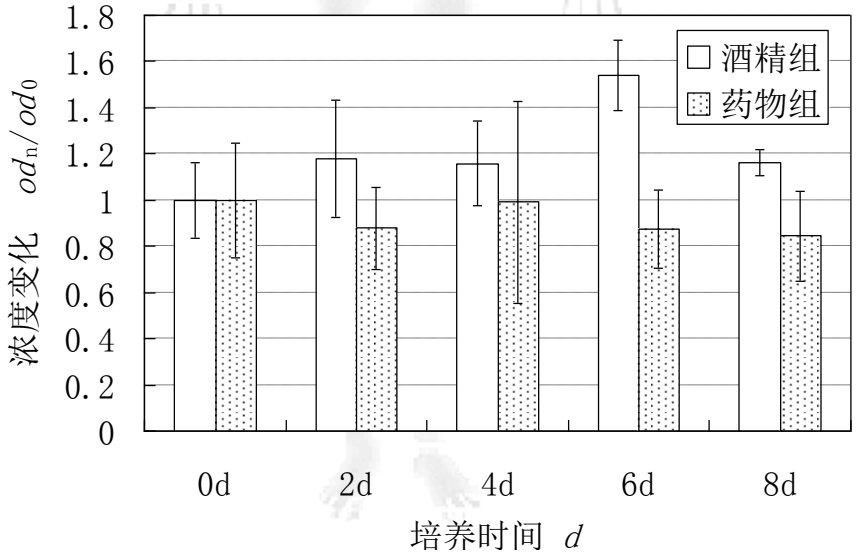
3DP Cells for in vitro Micro-Liver Model

(Tsinghua)



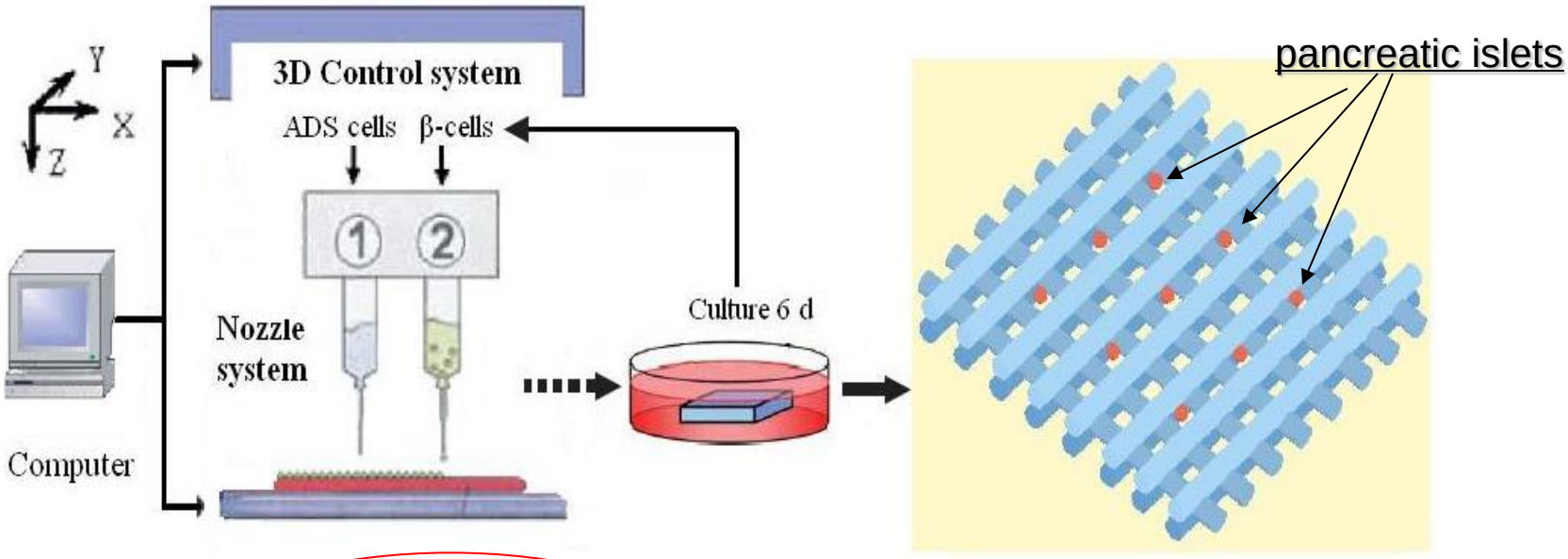


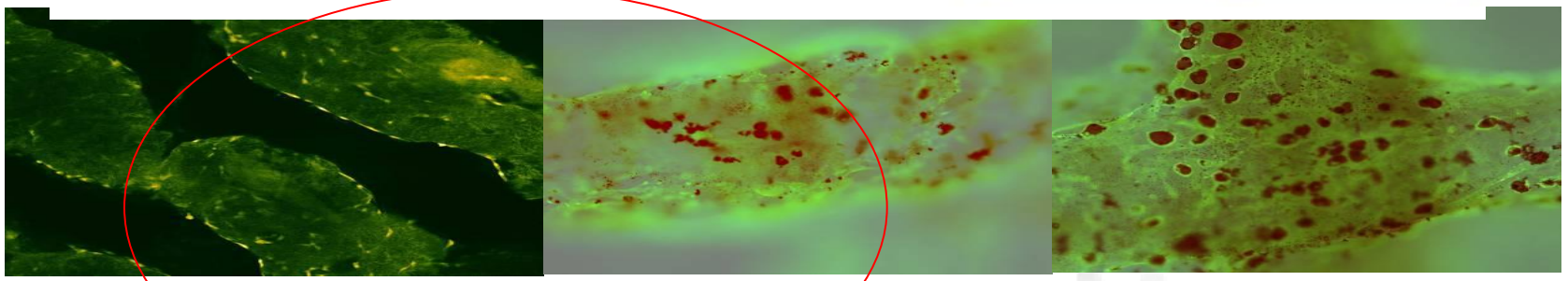


Effect of Alcoholic on Liver Function

Bioprinting Adipose-derived stromal (ADS) Cell and Cell-assembled Drug Model for Metabolic syndrome (Diabetes)

(NSFC-30800248; Tsinghua)





ADSc derived endothelial cells along the edges
A simulated physiological model

Adipocytes cells fill inside
A simulated physiological model

Adipocytes cells Irregularly distributed
false physiological model

Xu et al: Biomaterials, 2010

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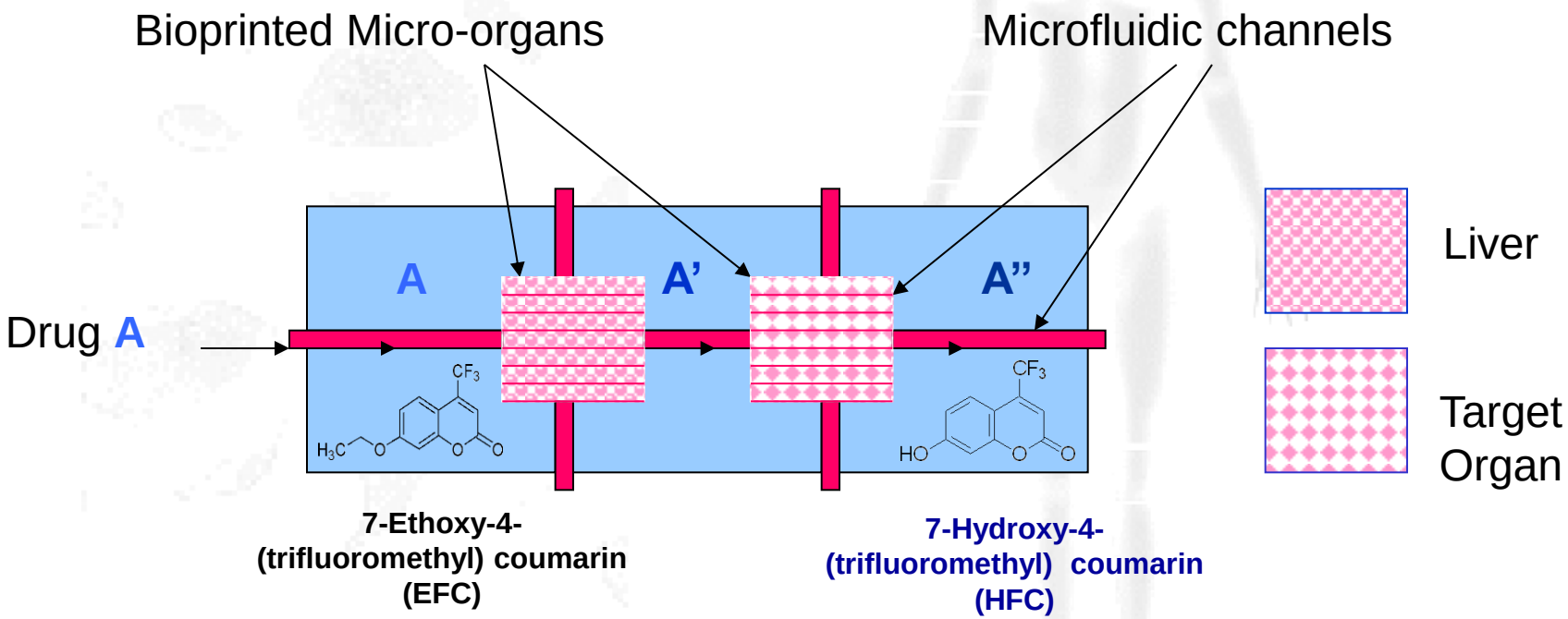
Bioprinting Micro Liver Organ for NASA Pharmacokinetic Study

(NSAS-USRA-09940-008)

NASA's Interest - Safe plenary exploration & Mars Landing

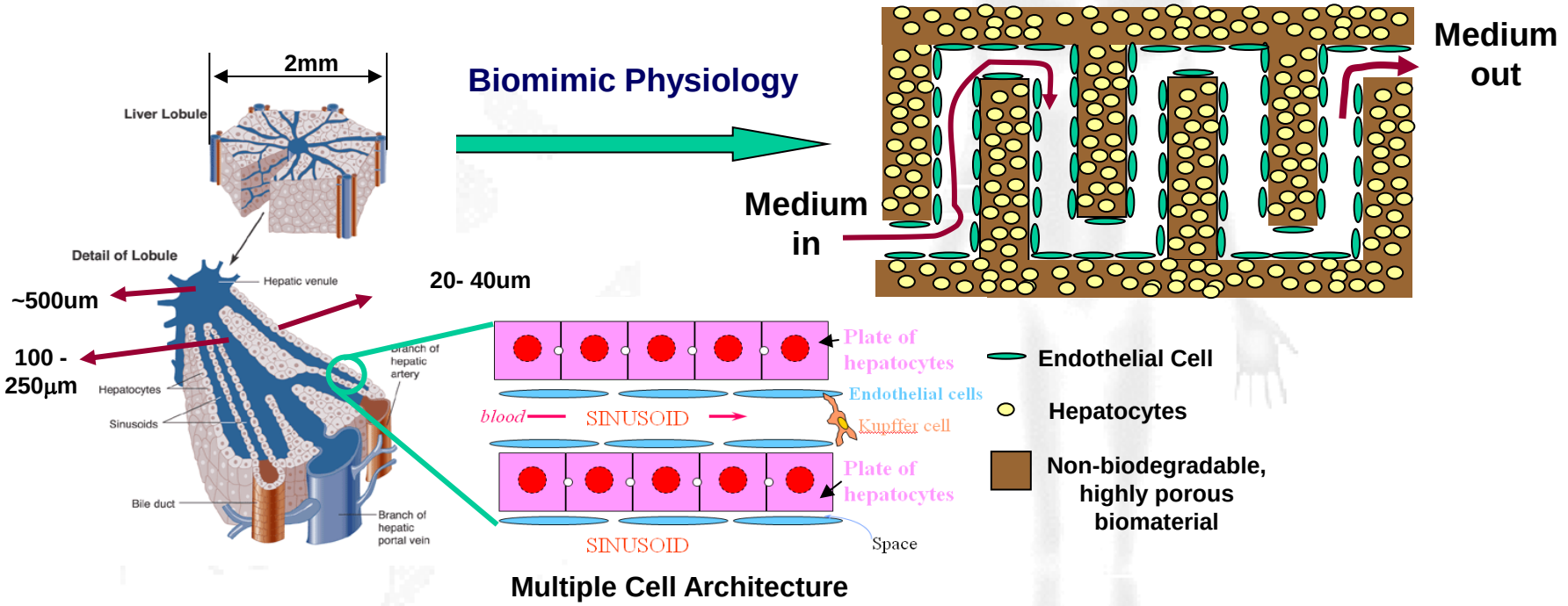


Micro-Organ Device for drug conversion study (**A, A', A"** with multiple micro-organs)

Schematic drug metabolic conversion from EFC → HFC

Sinusoid Flow Pattern Design to Biomimic Liver Physiology

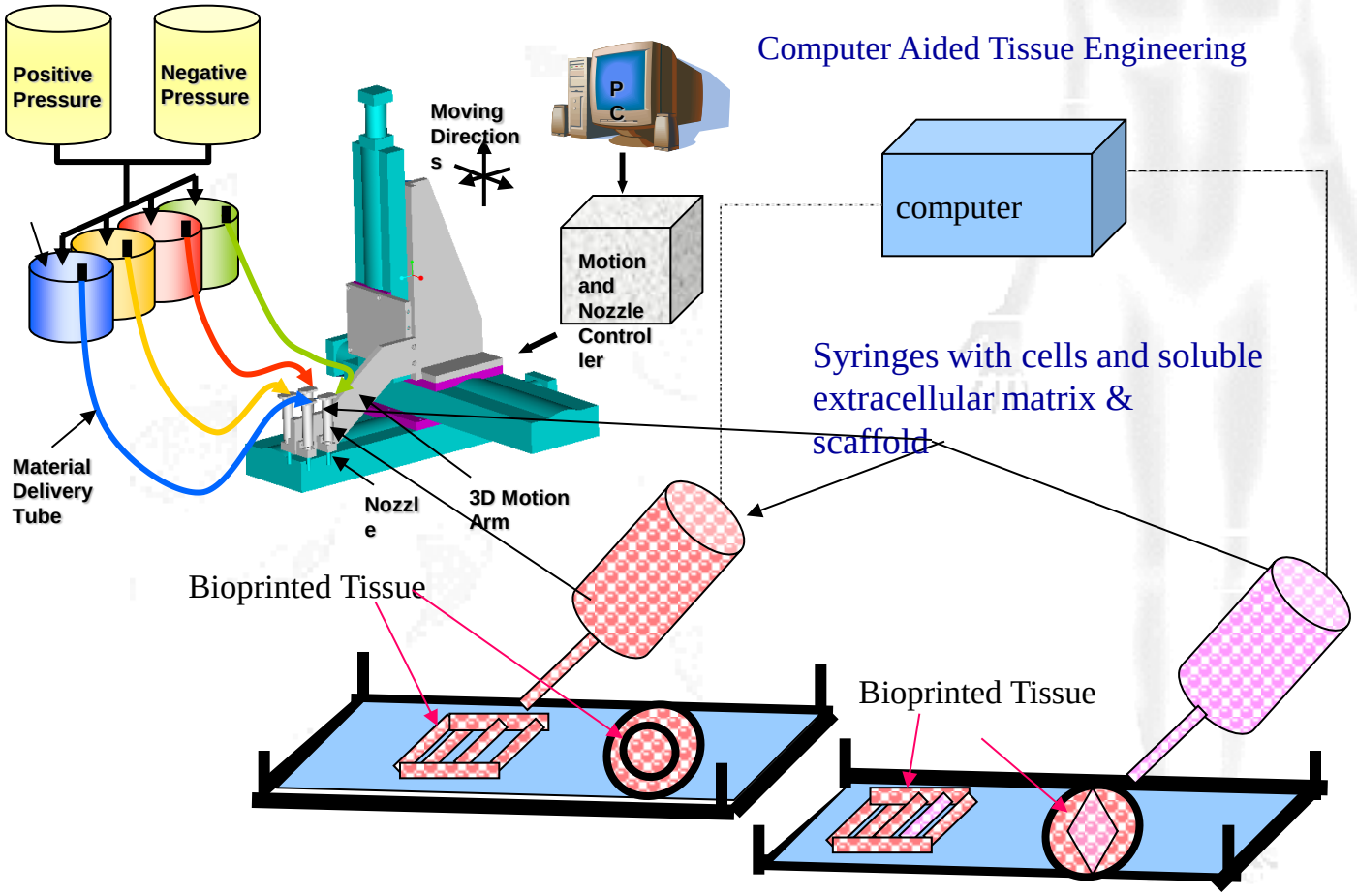
(NSAS-USRA-09940-008)

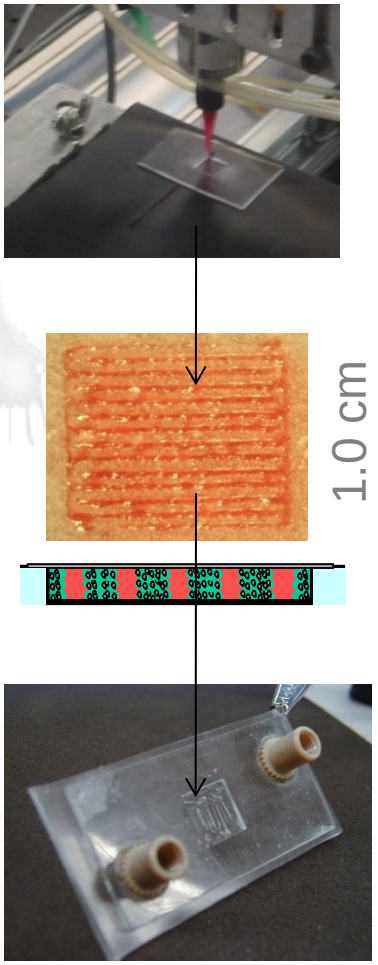


- hepatic vascular system (capillaries) is configured in sinusoidal pattern → design the sinusoidal micro-fluidic channel patterns to biomimic *in vivo* liver microstructure.
- Channel dimensions and strut widths vary from 50mm to 250mm, flow varies from 1ml/min to 5ml/min.

Bioprinting Micro Liver Organ for NASA Pharmacokinetic Study

(NSAS-USRA-09940-008)

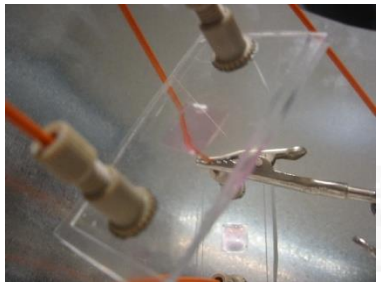


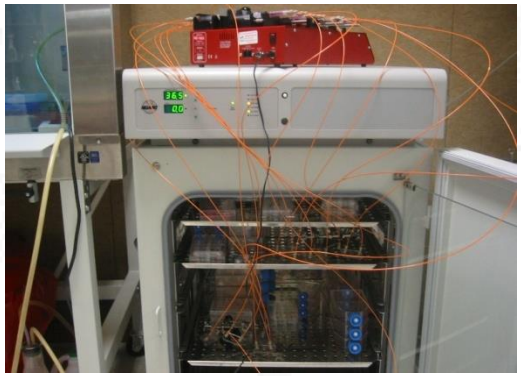


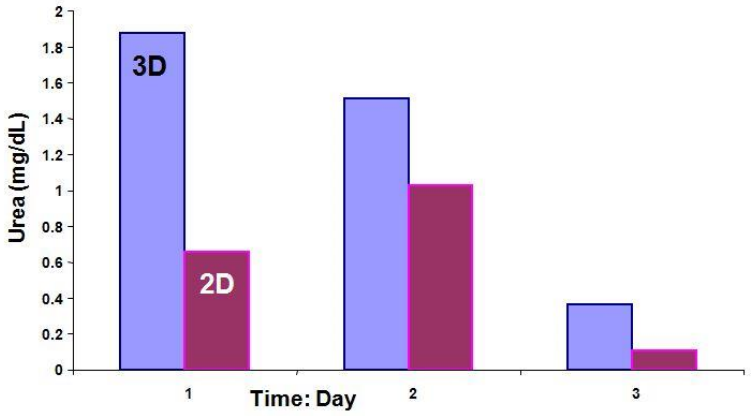
Chang and Sun, Tissue Engineering, 2007 & 2008, Biofabrication, 2010

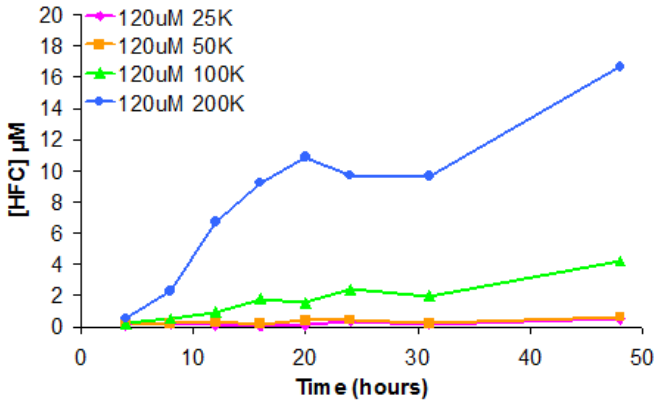
Integration of Bioprinted Liver Chamber with Microfluidic Device

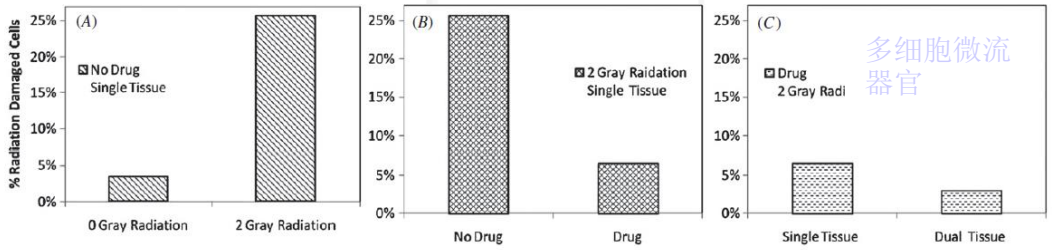
(NSAS-USRA-09940-008)











Chang and Sun, Tissue Engineering, 2007 & 2008, Biofabrication, 2010

Bio – 3D Printing Cells - What we can do ???

- Assemble cells and biomaterials in the right spatial position: accelerated cell migration
- Fabrication in vitro biological model with designed cell micro-environment

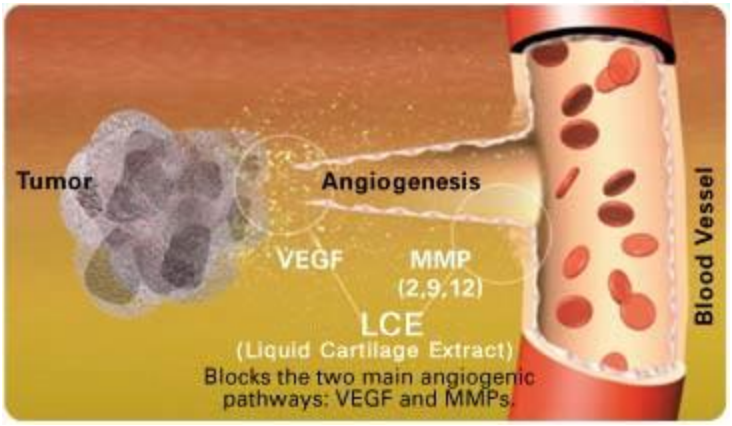
Fabrication in vitro Biological Model with designed Cell Micro-environment by Directly Assembling Cells and Biomaterials

RGD Modified Surface

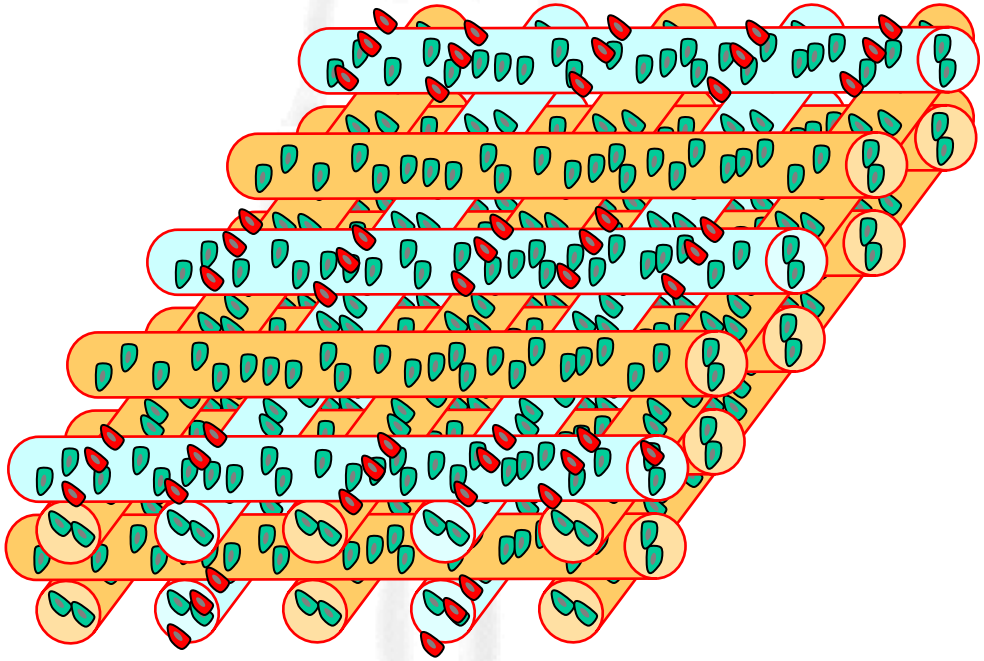
Unmodified Surface

Fibroblasts (Encasulated)

Endothelial (Applied to Surface)



http://www.angioworld.com/angiogenesis.htm

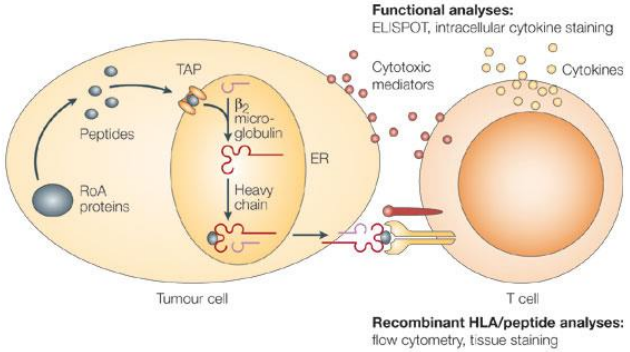


Direct Assembled Biological Model for Angiogenesis

Morss-Clyne & Sun: 2008 Biomaterial Congress; Tissue Engineering, 2010, Biofabrication, 2010

Single Cell Printing/Assembly

Immune responses
(~ 20μm)

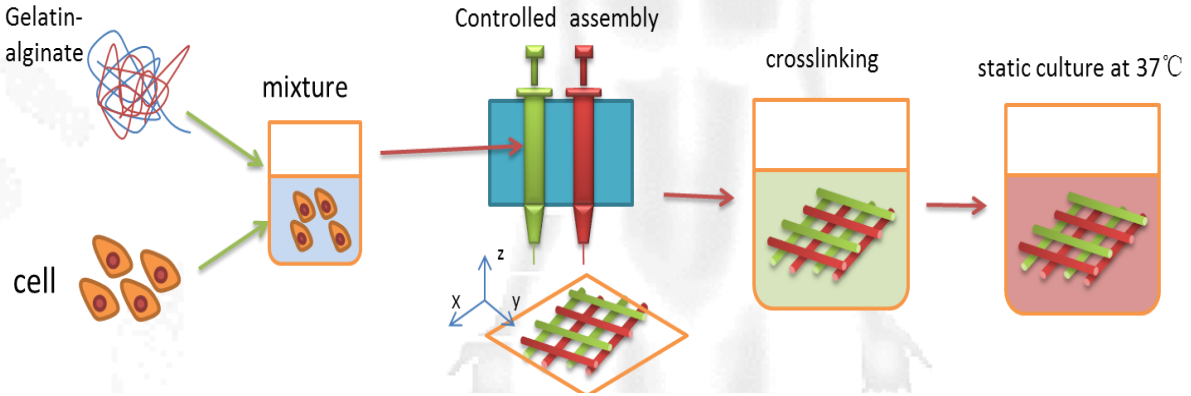


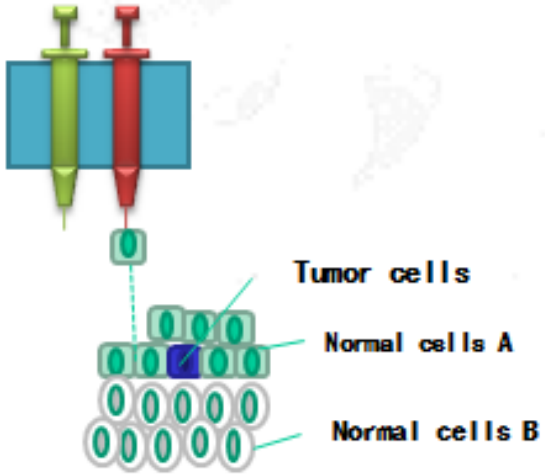
Nature Reviews Drug Discovery 2005; 4, 399-409

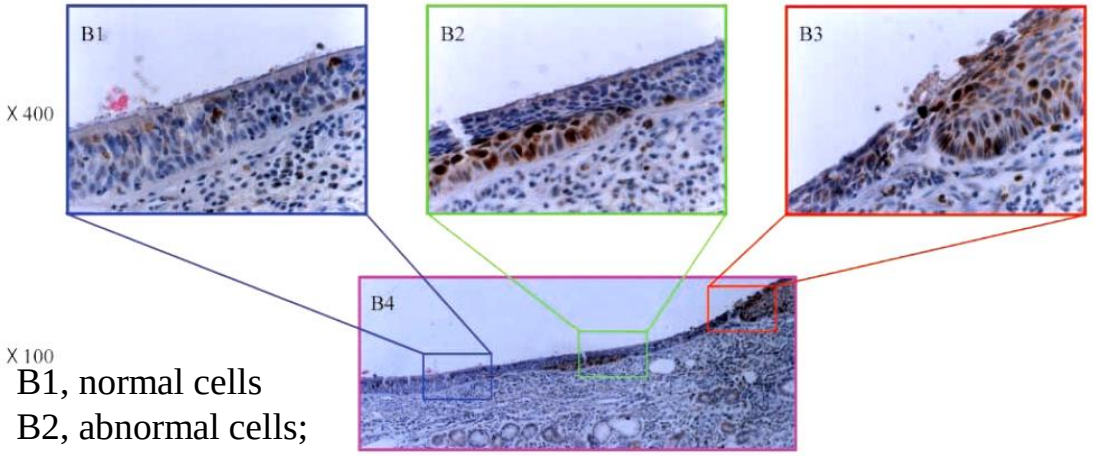
assemble cells together (within 20μm) to study the immune response

Assembly Cancer Cells for In Vitro Tumor Model

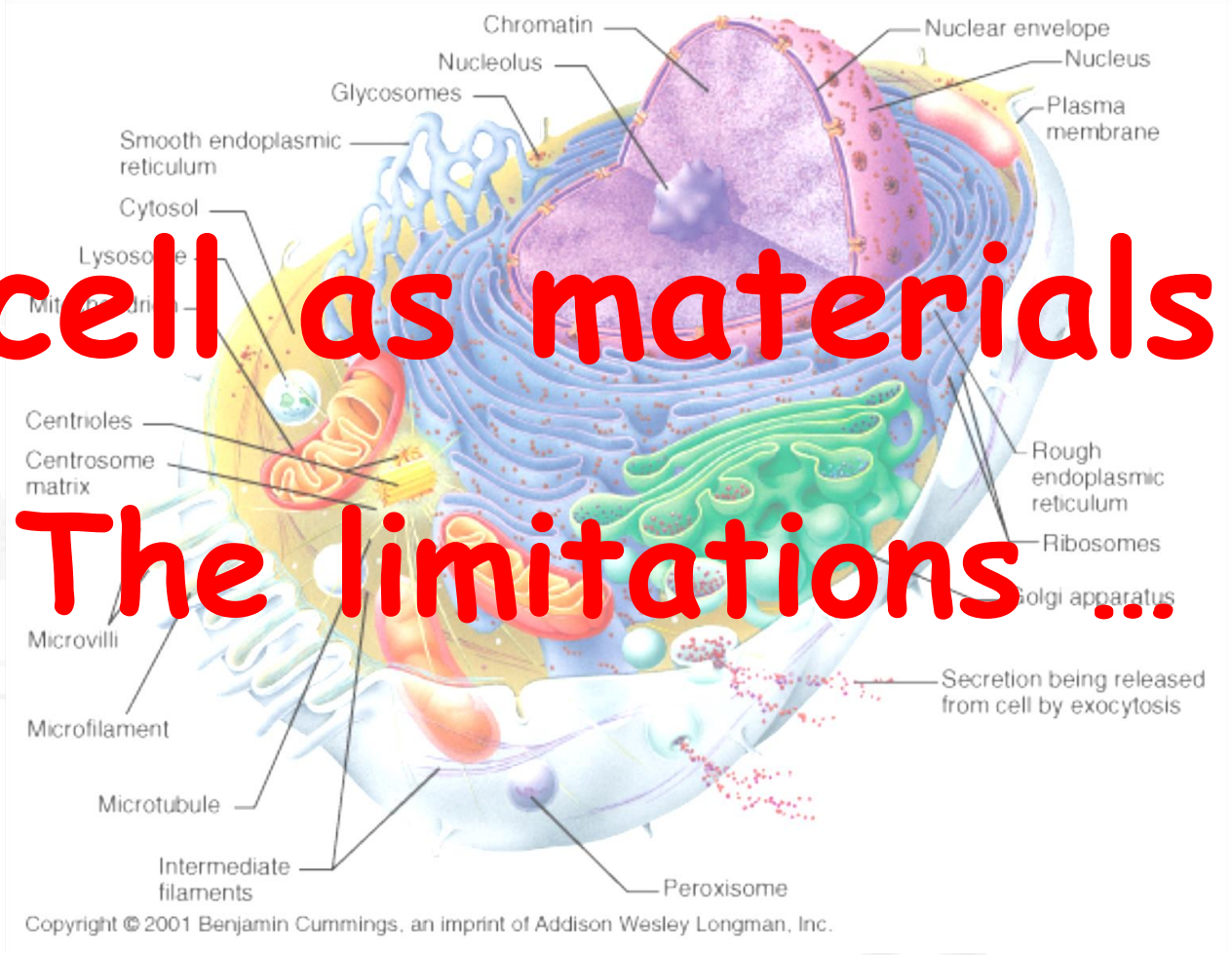
(NSFC 2012 E05 Key Research Project; Tsinghua)







B1, normal cells
B2, abnormal cells;
B3, cancer cells;
Clinic Cancer Res 2006; 12(4): 1121.



cell as materials

The limitations…

Printing Cells - 3DP Process

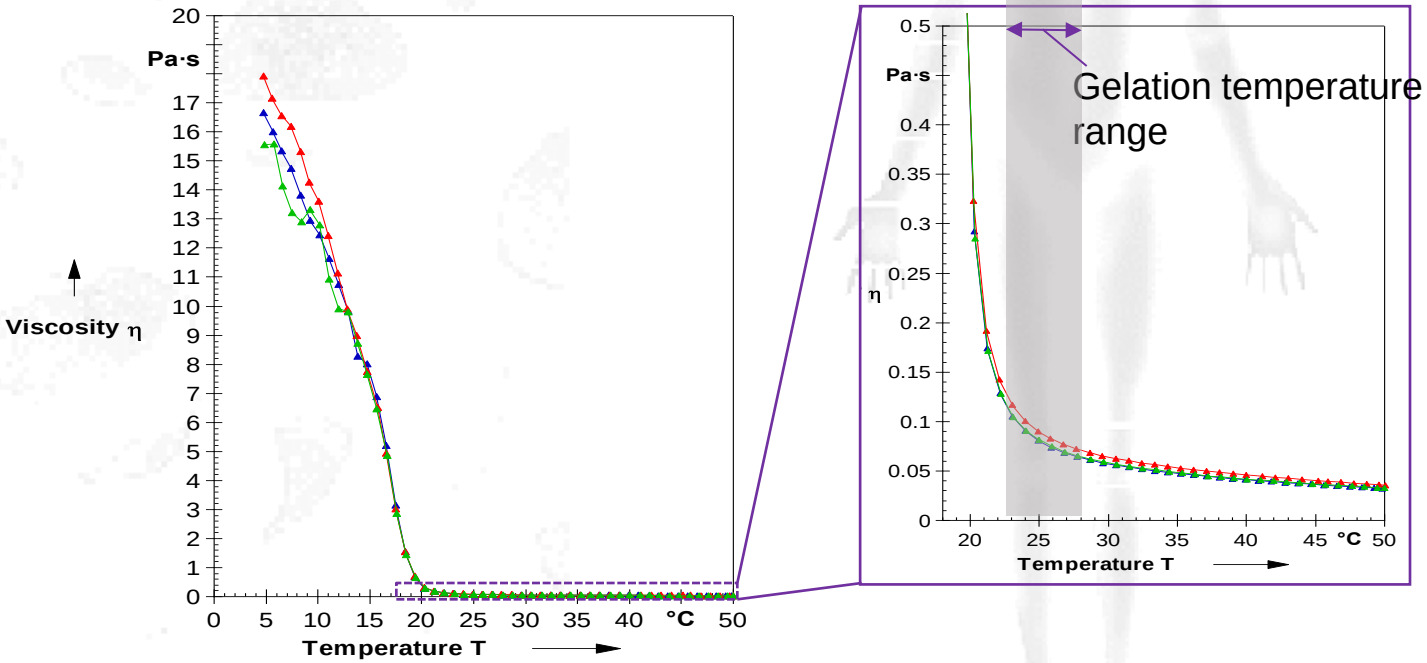
- Prepare cells and cell delivery medium
  - Bioink
- Printing cells
  - 3D assemble at temperature controlled environment
- Post printing
  – bioreactor for 3D culture

Printing Cells - 3DP Process

- Prepare cells and cell delivery medium
  - Limited selection: Hydrogel, Alginate, Collagens, MetraGel etc
- Printing cells
  - cell injury
- Post printing
  – structure integrity, strength and stability
  - 3D co-culture to simulate human physiology

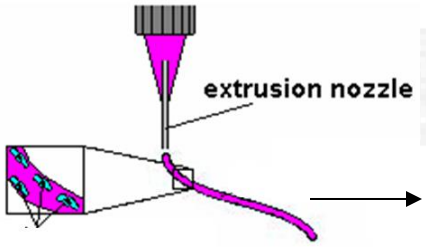
Cell delivery medium viscosity changes with temperature

We have very limited cell delivery medium and they are temperature sensitive



Viscosity changes with temperature for Gelatin/Alginate hybrid materials. Concentration for Gelatin is 10% (w/v) and for Alginate is 1% (w/v). The uprush region means the gelation temperature range, which is sensitive to temperature.

Cell will injury when printing



Bio-deposition of cell-hydrogel thread

Mechanical Disturbances by Cell Deposition Process

Deposition Pressure
Deposition Speed
Nozzle Diameter
Nozzle Length
Hydrogel Properties

Healthy cell with desired phenotype

Normal nucleus

Injured

Recovery

Altered phenotype

Apoptosis

Dead

Karyolysis

Fragmentation on an dissolution of nucleus

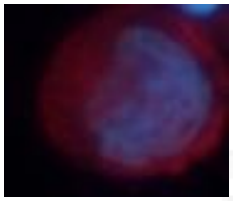
Pyknosis

Contraction of nuclear chromatin followed by nuclear condensation

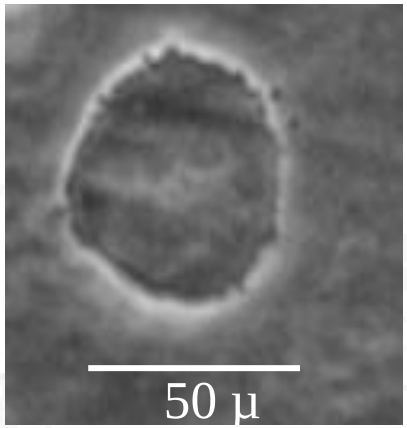
Optical Microscopy Image for Single Cell Injury

Constructs counterstained with DNA stain Hoechst 33342 and
cell-impermeant Alexa Fluor ® 594 wheat germ agglutinin (WGA)

Before printing

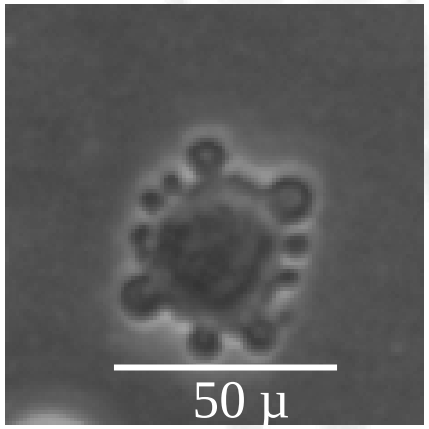


Fluorescent Microscopy showing normal cell

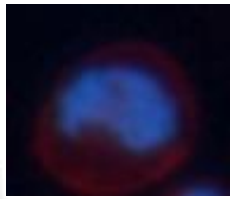


Optical Microscopy

Printing at 150 µ nozzle and p=5psi



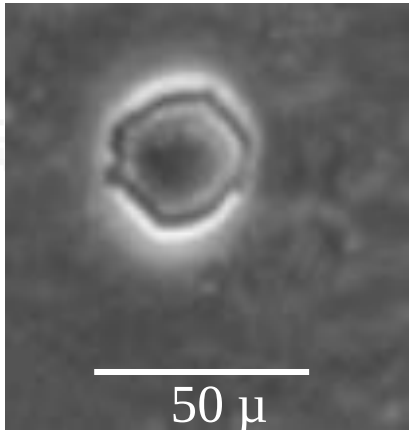
Optical Microscopy



Fluorescent Microscopy showing condensed nucleus suggesting possible reversible injury

Blue: nucleus
Red: cell membrane

Printing at 150 µ nozzle and p=40psi

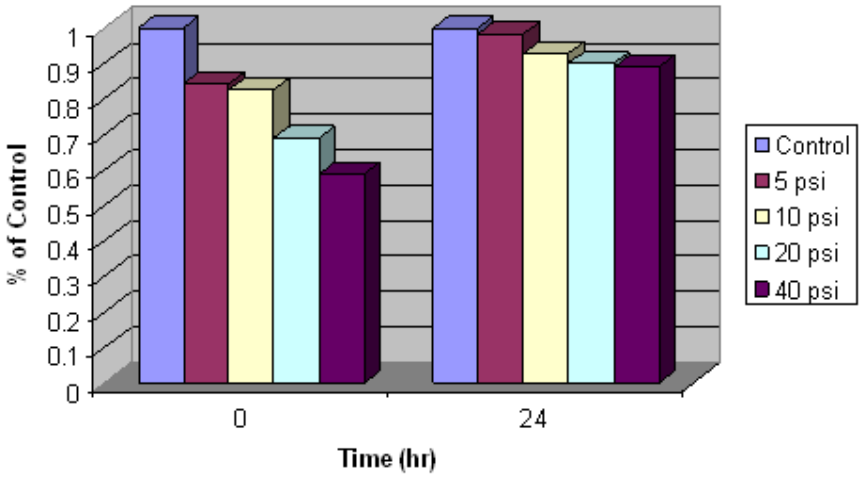


Optical Microscopy

Fluorescent Microscopy showing disintegrated nucleus suggesting irreversible injury and cell death

56

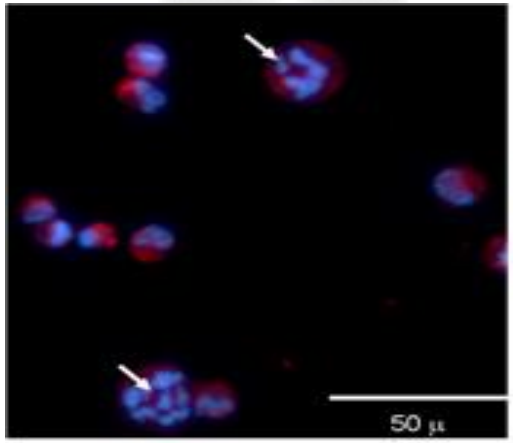
Bio-deposition Induced Effect on Living Cells
(NSF-0700405)



Cell viability and recovery as function of deposition pressure

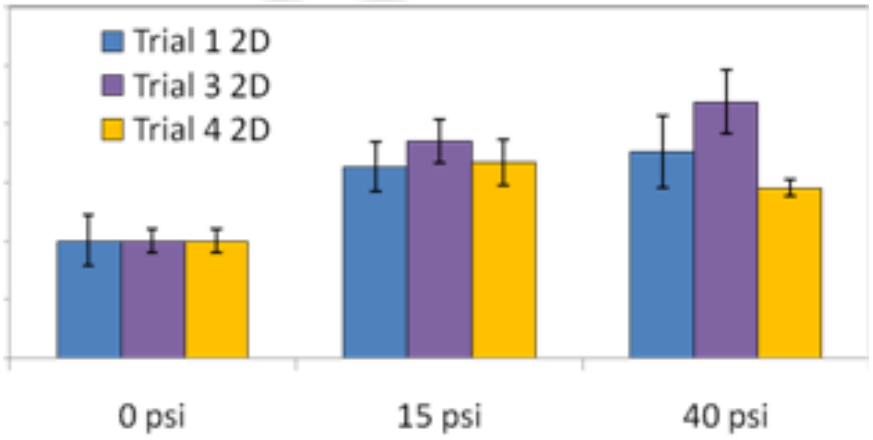
Cell images for Hepatocytes in 3% Alginate (1 million cells/ml) deposited at 40 psi pressure with 100 μ diameter nozzles

Chang, et al: Tissue Engineering 2007, Tissue Engineering 2008

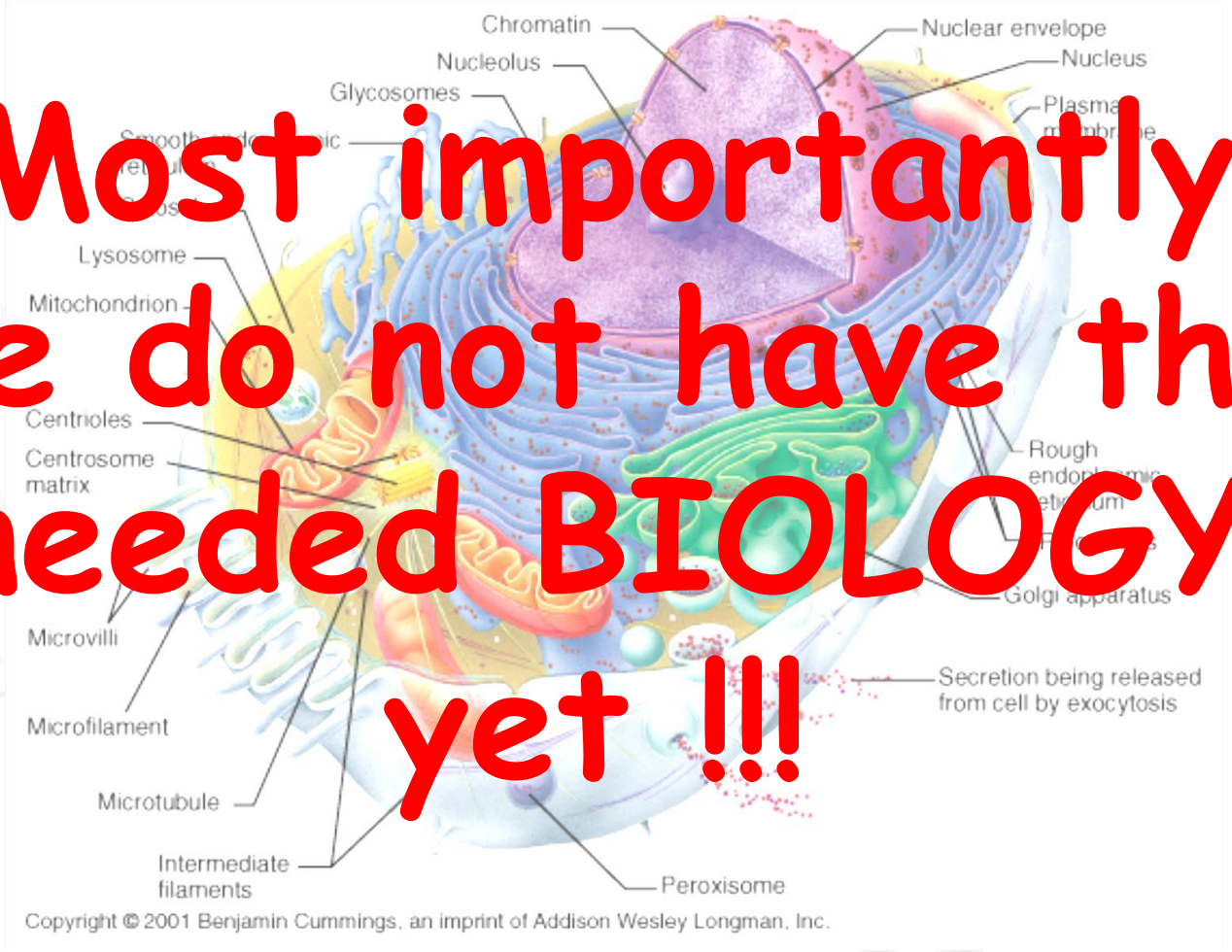


Cell apoptosis after printing (40psi)

Nair, et al: Biotechnology Journal, 2009



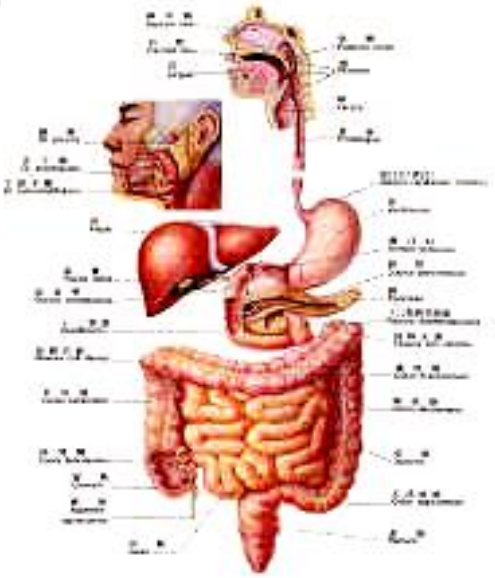
Stem Cell expedited differentiation after printing



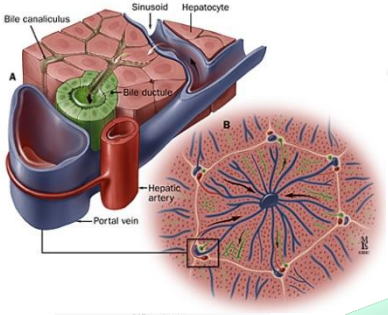
Most importantly we do not have the needed BIOLOGY yet !!!

尺度单位：m

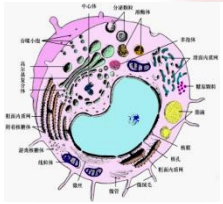
10^{-1}



10^{-3}



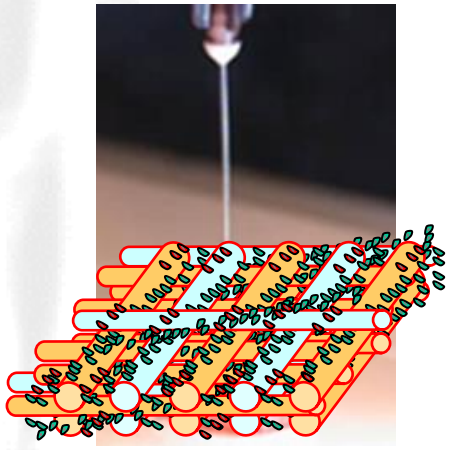
10^{-4}



10^{-6}

10^{-9}

Cell/Tissue Printing for 3D in vitro Biological Model



In vitro Biological Model

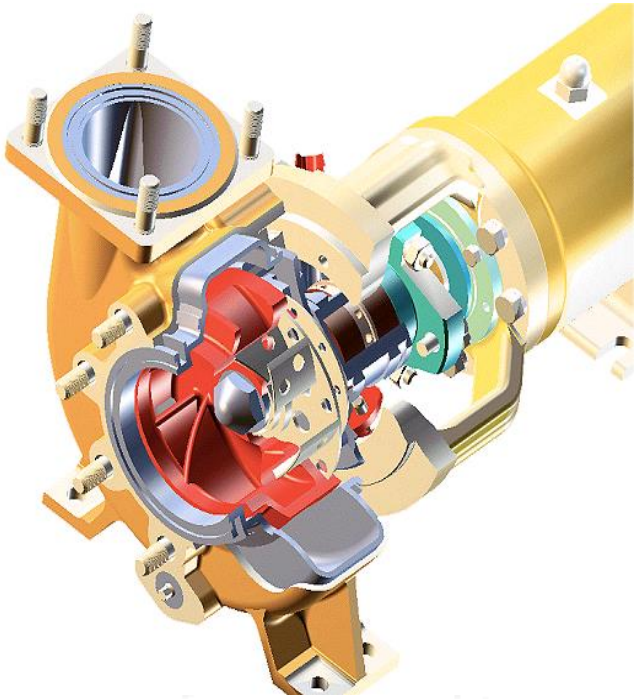
Cell Printing

Difference in Engineering and Biology

System

Assemblies

Parts



Organs

Tissues

Cells

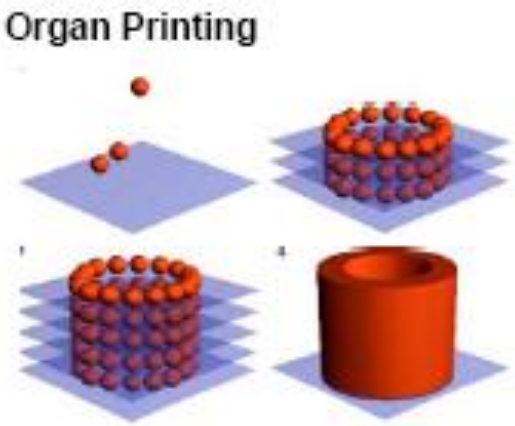
If it looks like an engine,
it probably is an engine.
Form-based Engineering Design
(Functionality is designed through Form and Material)

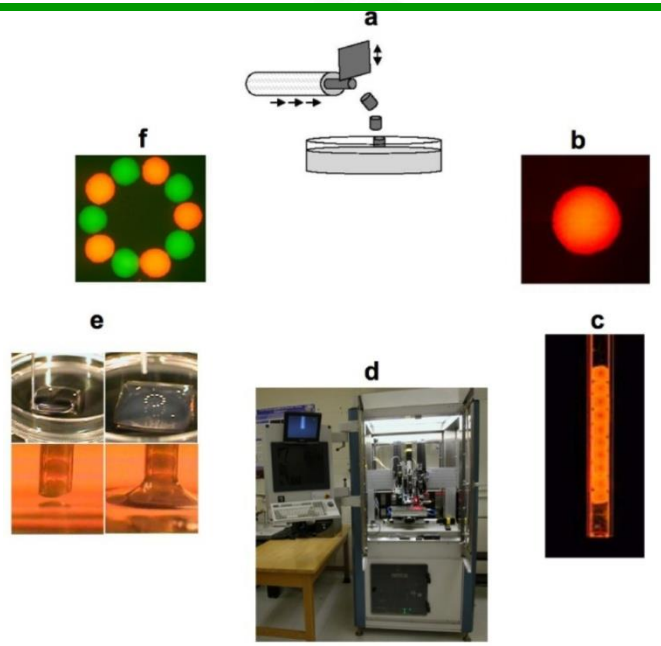
It looks like a heart,
but it does not have the function
Time-based Cellular Squences
(Functional regeneration through cellular tissue engineering process)

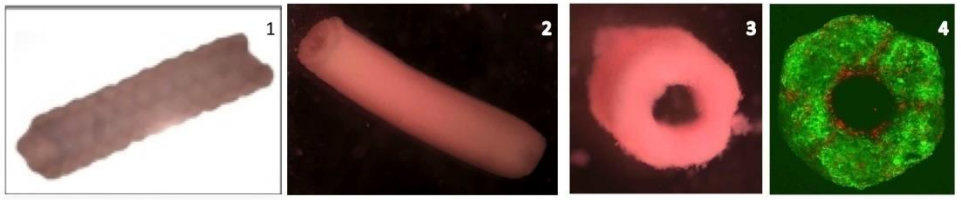
3D Printing of Blood Vessels

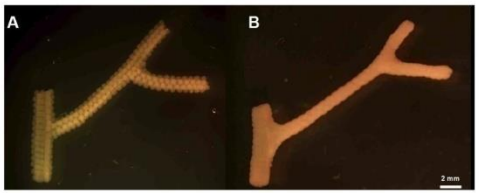
NSF-FIBR: Frontiers of Integrative Biological Research; 2007-2012
"Understanding Cell Assembly"

Gabor Forgacs, U. of Missouri



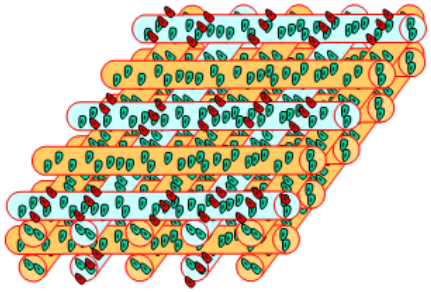






Knowledge Gap

"Classical Biology is based on the understanding of developmental physiology, i.e., growth from cells in Petri dishes. What if biologists are given cell printing 3D cellular biological models"



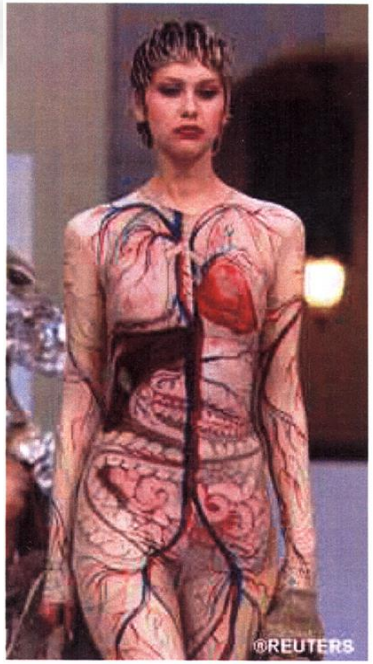
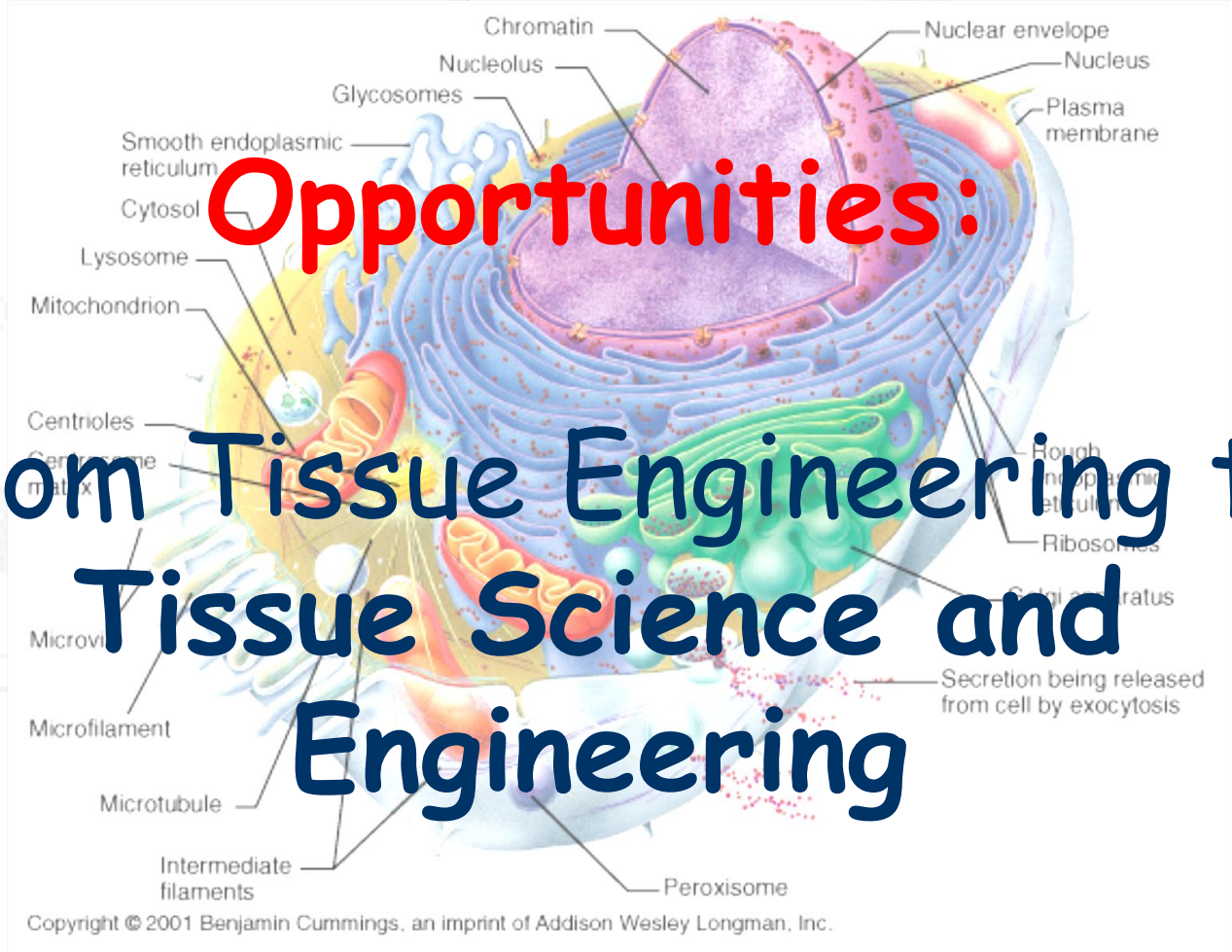


Image courtesy by Dr. V. Mironov, MUSC

We do not have enough BIOLOGY!!!

Opportunities:

From Tissue Engineering to Tissue Science and Engineering



Evolving of Tissue Engineering …

NSF definition of Tissue Engineering (1989):

"Tissue engineering is the application of principles and methods of engineering and life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve tissue function"

New for Tissue Science & Engineering*(2007)

"**The use of physical, chemical, biological, and engineering processes to control and direct the aggregate behavior of cells**"

** Advancing Tissue Science & Engineering: A multi-angency strategic plan, June 2007*

From Tissue Engineering to Tissue Science and Engineering

- Regenerative Medicine
  - more on cells, particularly on Stem Cells
- 3D Physiological or Disease Models
  - For better study disease pathogenesis and for developing molecular therapeutics
- Pharmacokinetic Models to replace animal testing
  - For drug screening and testing
- Cell/Tissue on Chip
  - For detection of bio/chemical threat agents

** Advancing Tissue Science & Engineering: A multi-angency strategic plan, June 2007*

Fabrication of In Vitro 3D Tissue Constructs as Drug Testing Models

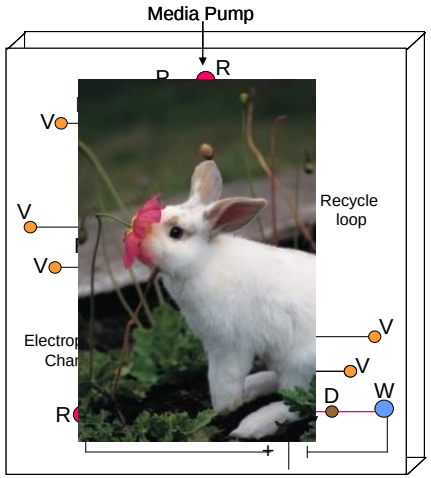
Introduce test molecules

Tissue Chamber

Metabolism of primary chemical compounds

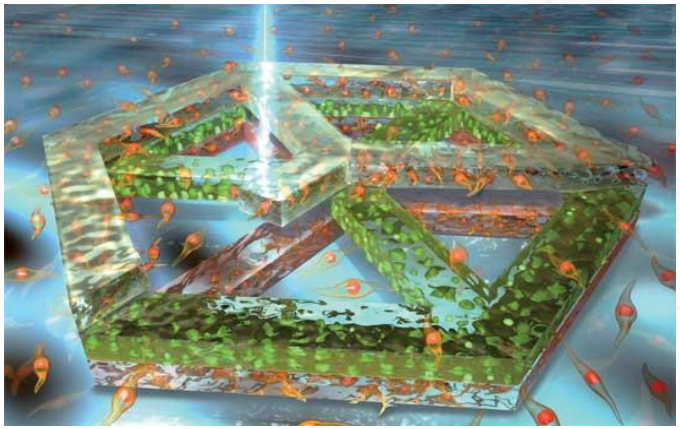
Tissue-on-Chip

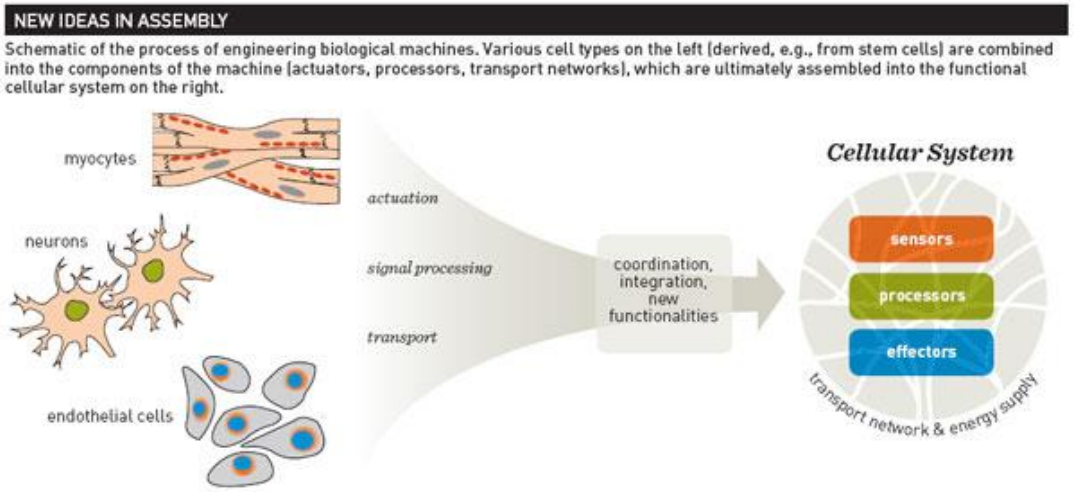
Animal on-Chip



Manufacturing Cellular Machines

By creating the building blocks — component cell types of biological machines to produce integrated cellular systems, such as biosensors, cell-on-chips, bio-robots, etc



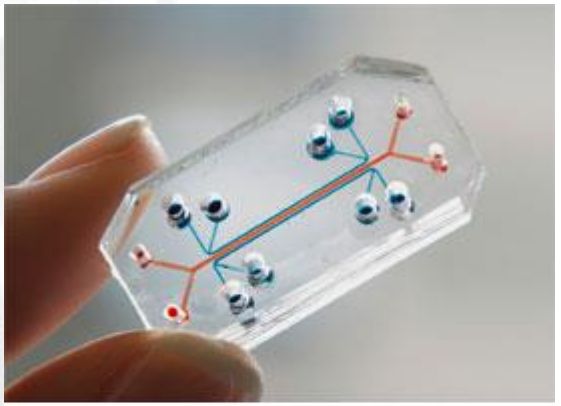


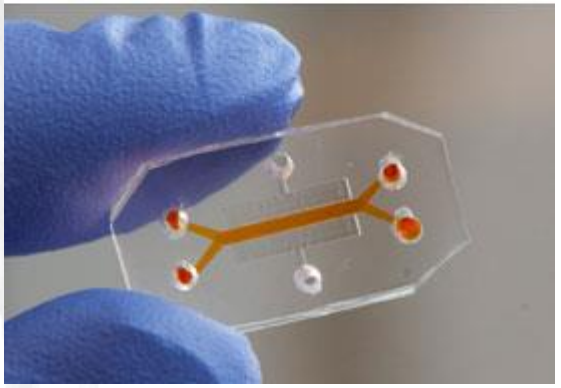
NSF Research Center - Emergent Behaviors of Integrated Cellular Systems (MIT, GT, UIUC)

Mechanical Engineering Magazine, Nov. 2010

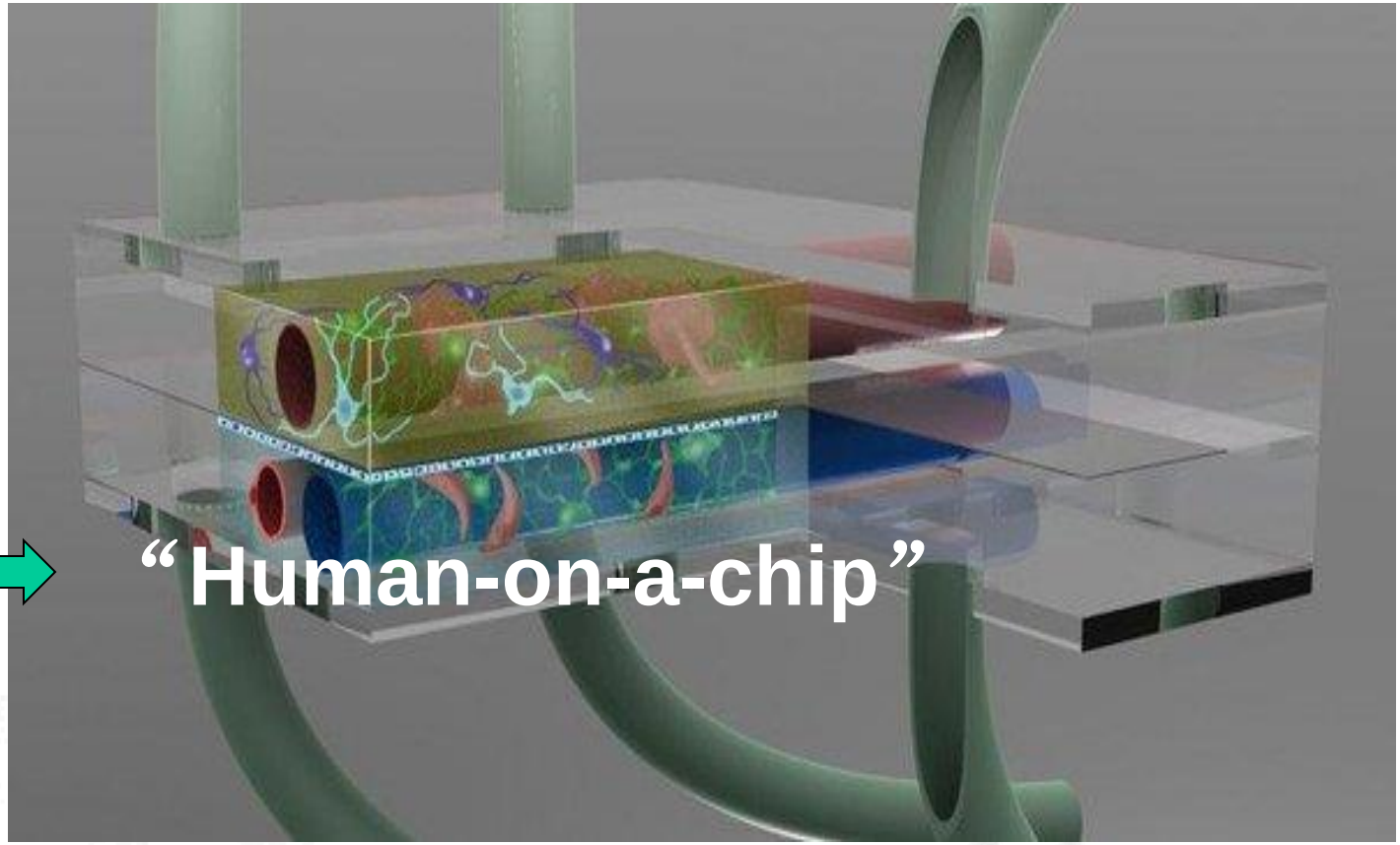
DARPA/NIH Joint Program – $150M/year for 5 years

A 5 year plan to develop an in vitro platform of engineering 3D human tissue constructs that accurately predicts the safety, efficacy, and pharmacokinetics of drug/vaccine candidates prior to their first use in man





Broad Agency Announcement
Microphysiological Systems
DSO
DARPA-BAA-11-73, Sept. 15, 2011

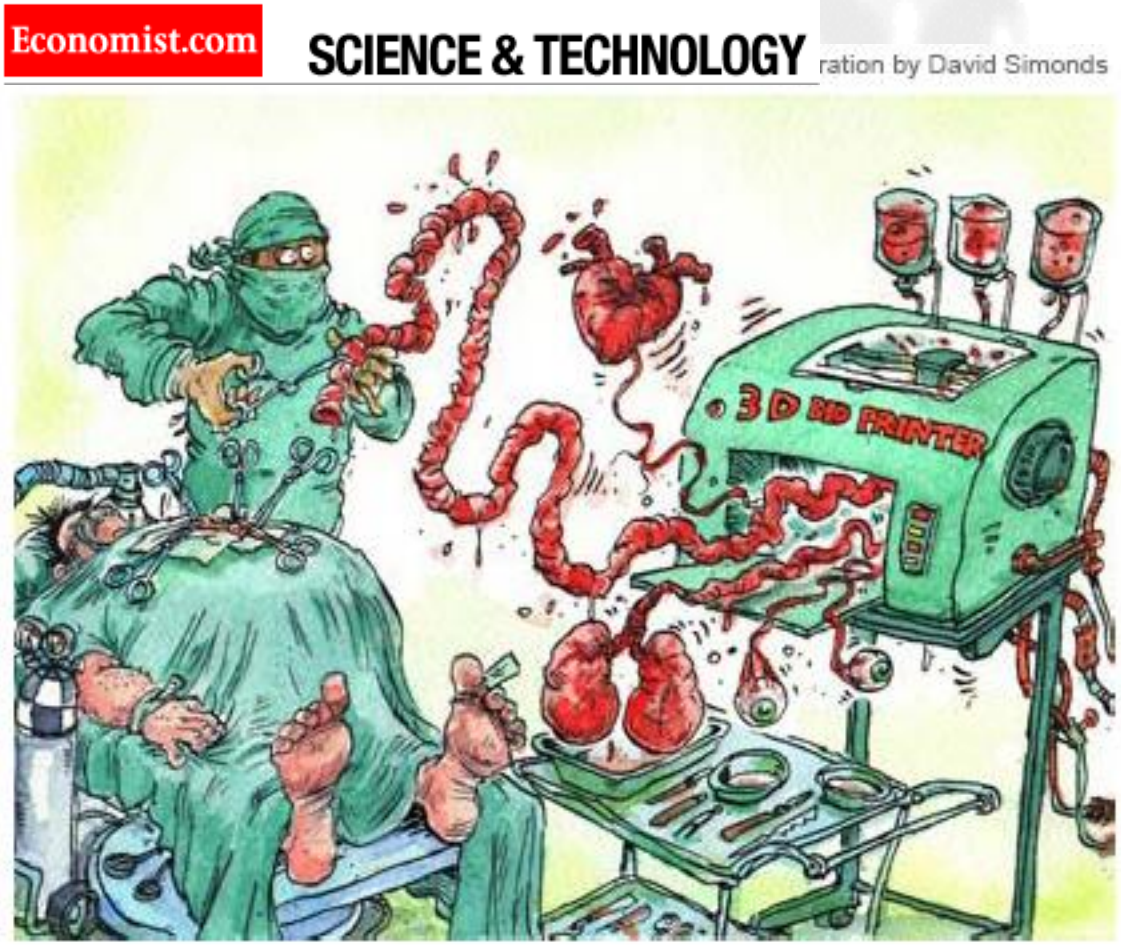


Wyss Institute to Receive up to $37 Million from DARPA to Integrate Multiple Organ-on-Chip Systems to Mimic the Whole Human Body

http://wyss.harvard.edu/viewpressrelease/91/wyss-institute-to-receive-up-to-37-million-from-darpa-to-integrate-multiple-organonchip-systems-to-mimic-the-whole-human-body

Cell Printing + Novel Biomaterials + Micro-fluidic technology will provide a vital tool to this development.

Printing Body Parts



A machine that prints organs is coming to market
Feb 18th 2010, The Economist print edition

Frontier Research - What We Need …

- **A new generation of biomaterials - Bio-Ink: go with cells (structure as cell delivery medium), grow with cells (support as cell ECM) and function with cells (as biomolecules);**
- **Developmental Engineering (vs Developmental Biology) to fill the biological knowledge gap;**
- **Bio-3DP manufacturing tools: viable, reliable and reproducible, and capable of making heterogeneous structures;**
- **4-D 3DP model: embedded time into Bio-3DP model: printing Stem Cells with control released molecules for complex tissues, Organs, Cellular Machines and Human-on-a-Chip devices**

Thank you!