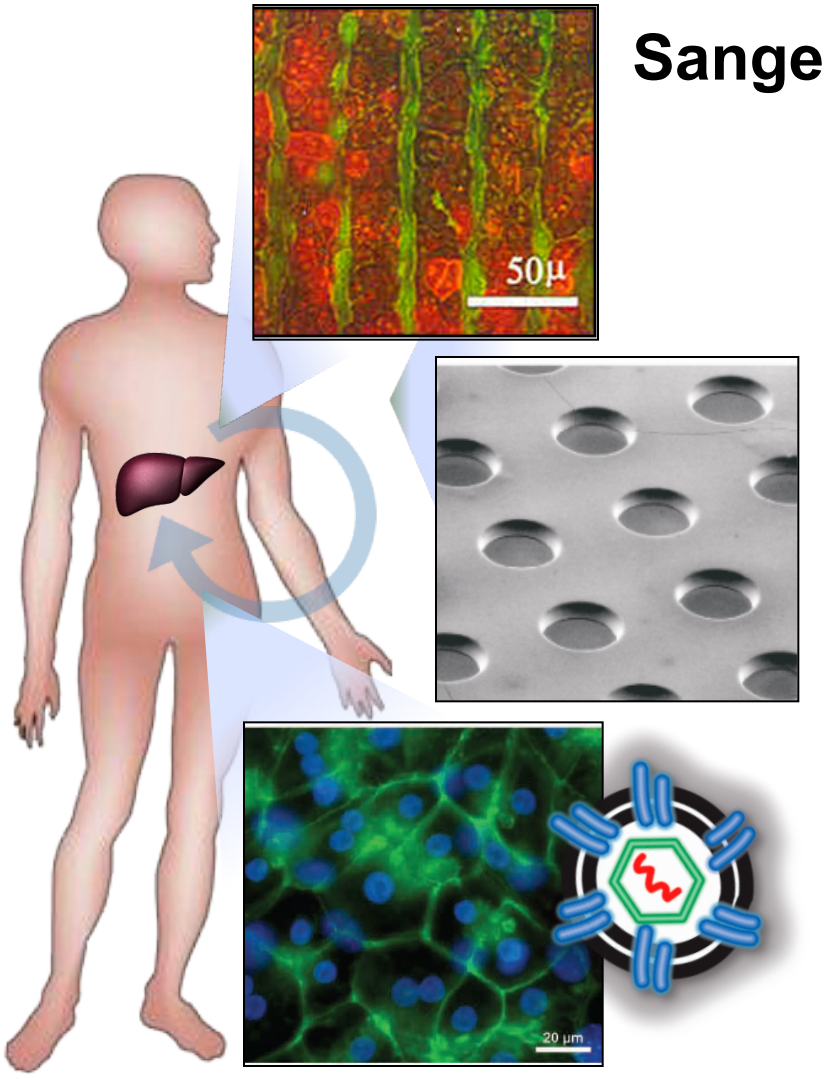
Tissue Engineering

Part 2 Microscale Liver Tissue Engineering



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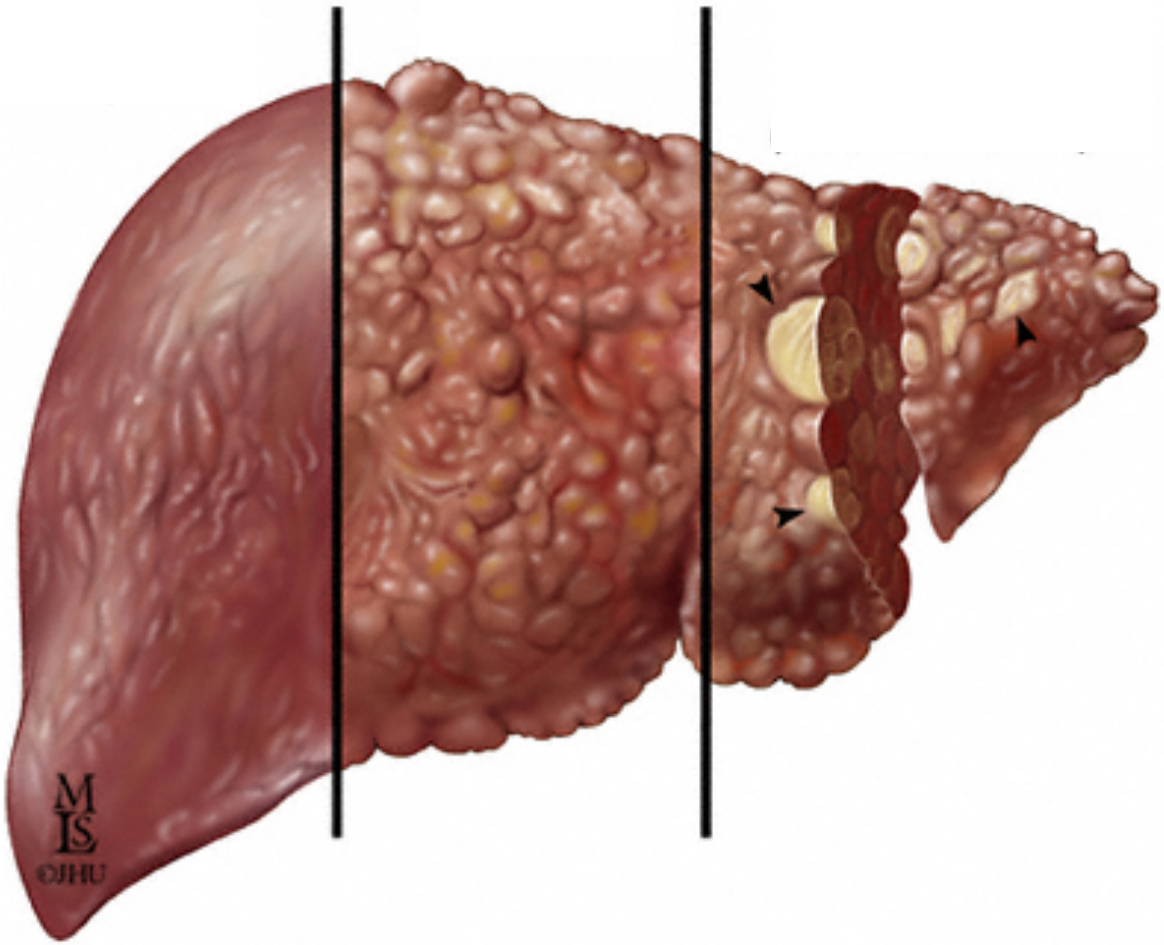
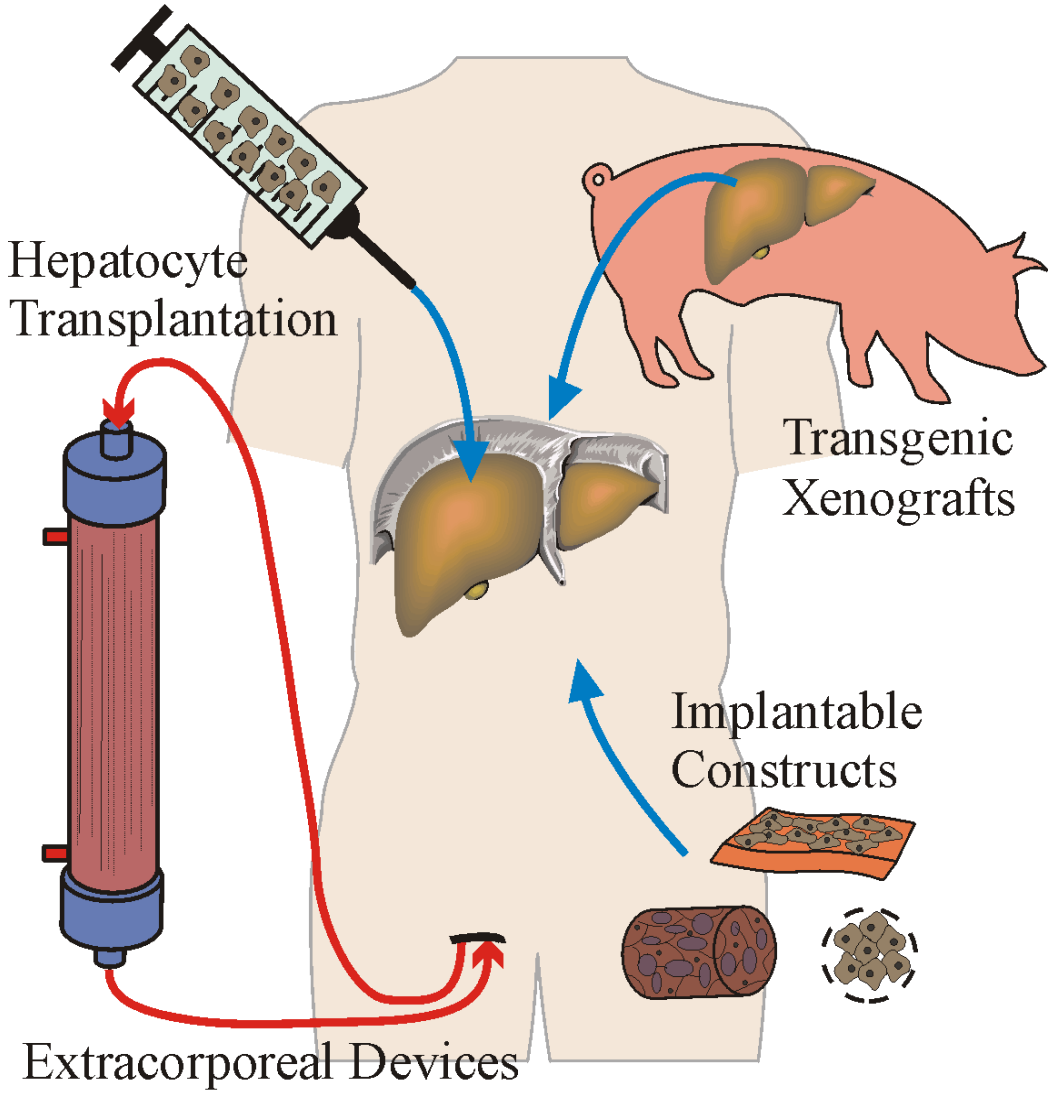
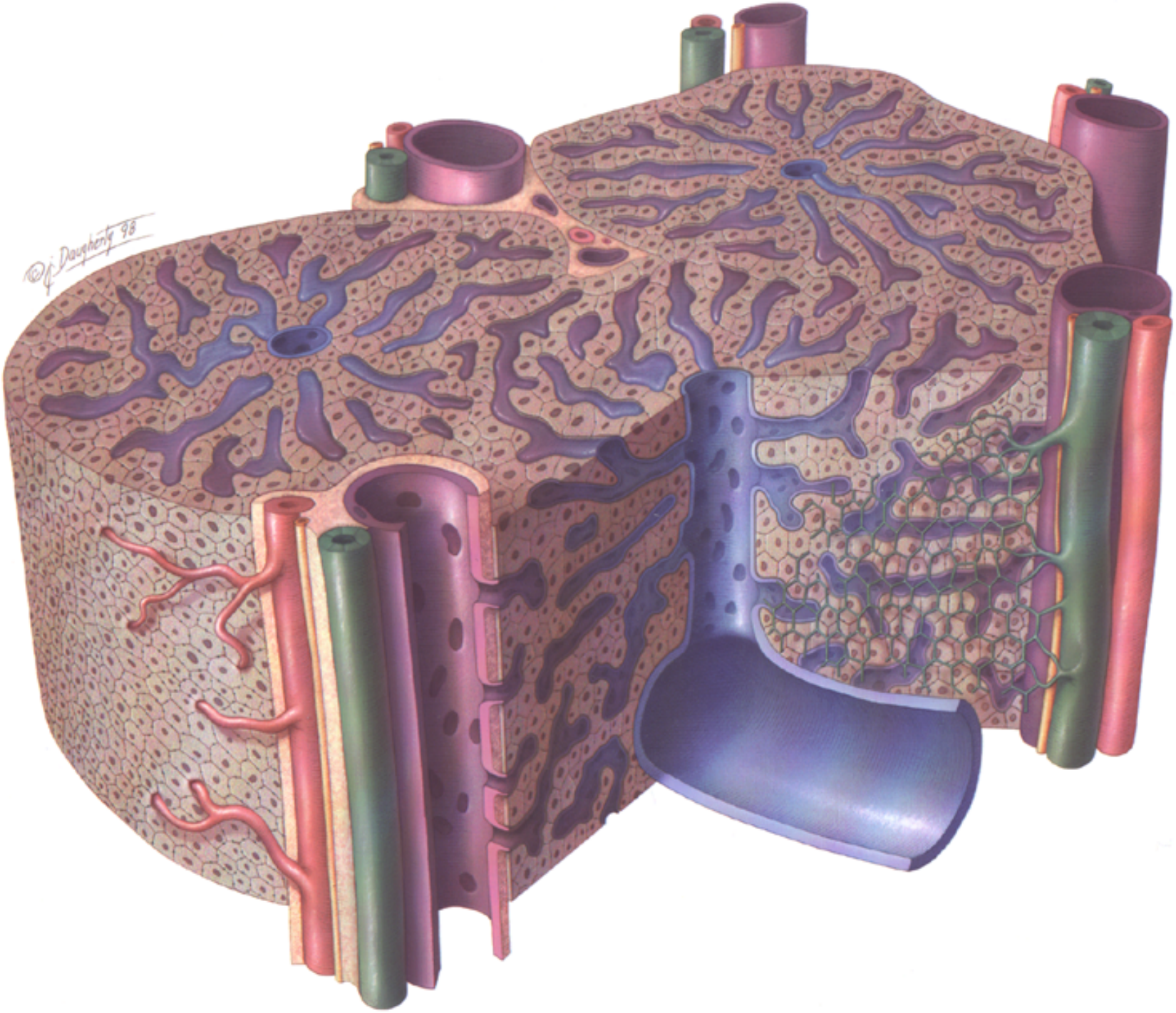
HHMI
HOWARD HUGHES MEDICAL INSTITUTE

Liver Disease



Living Cells Needed to Provide Support

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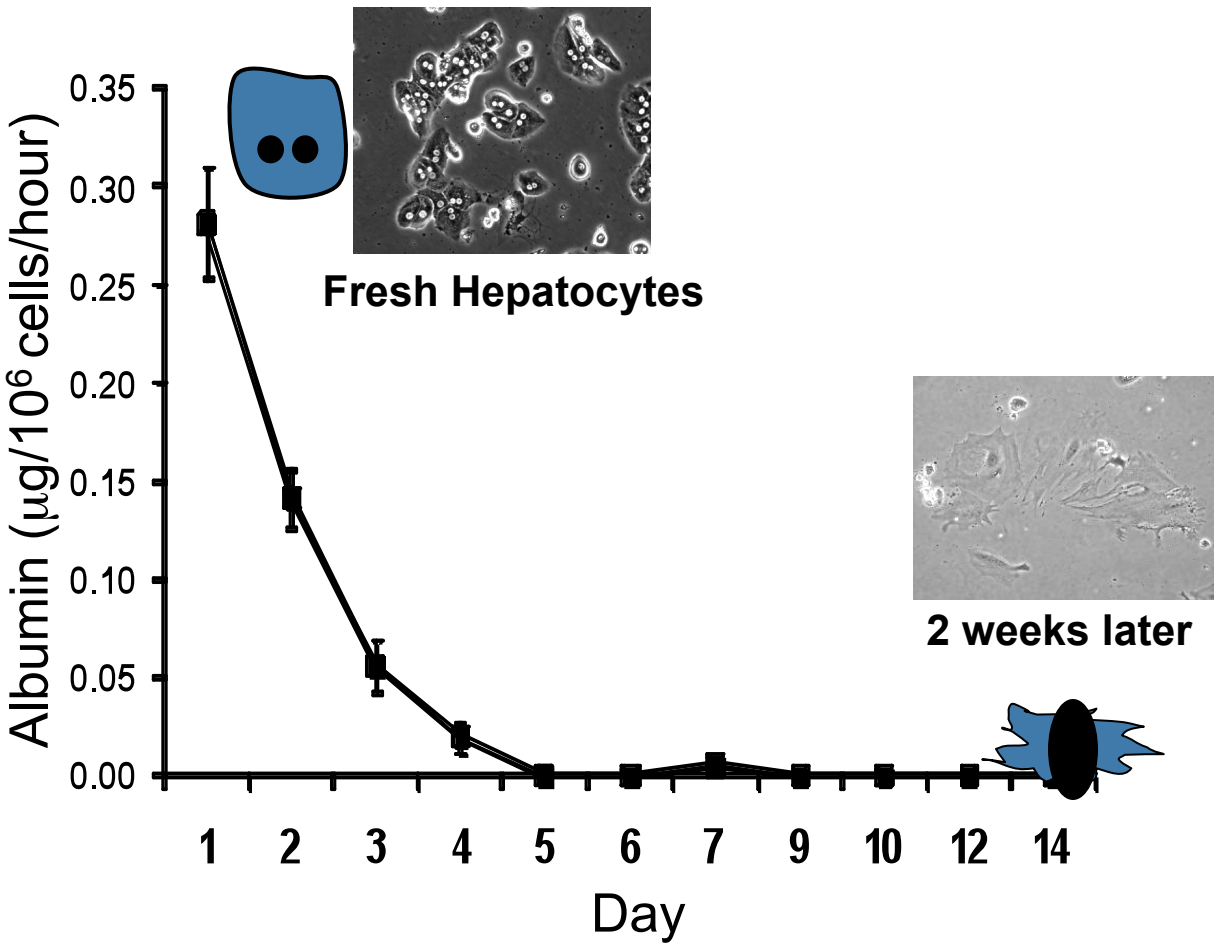
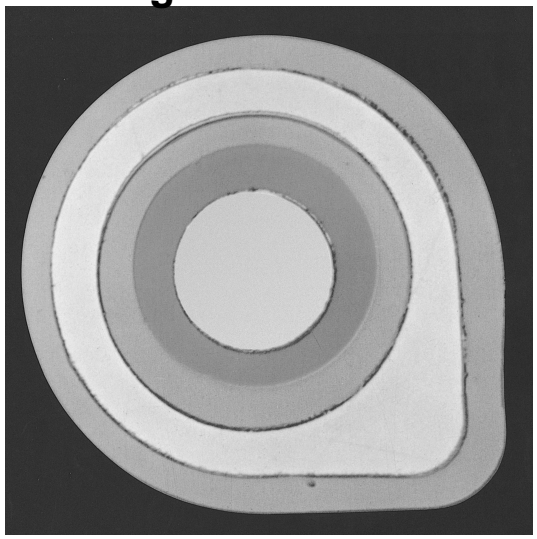
Loss of Phenotype in Culture



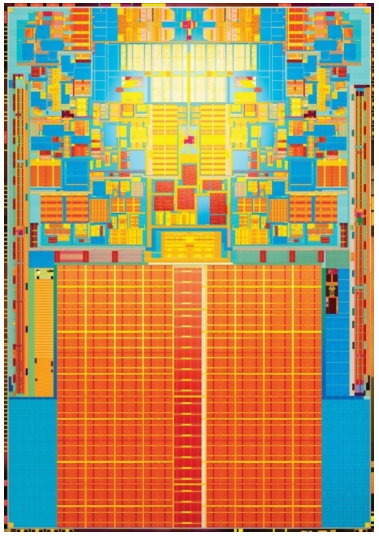
Guguen-Guillouzo+ *Exp Cell Res* (1983), Bhatia+ *FASEB* (1999), Khetani+ *Hepatology* (2004)

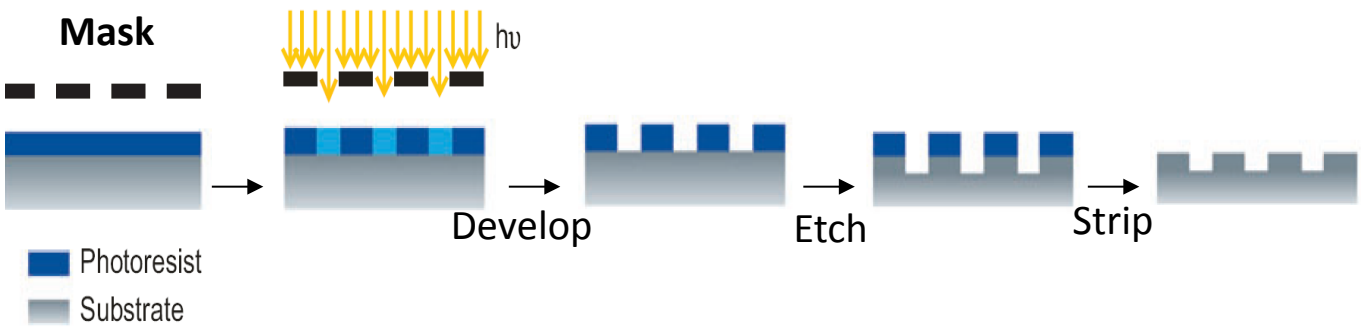
Building with Tiny Technology

Single Transistor [1]



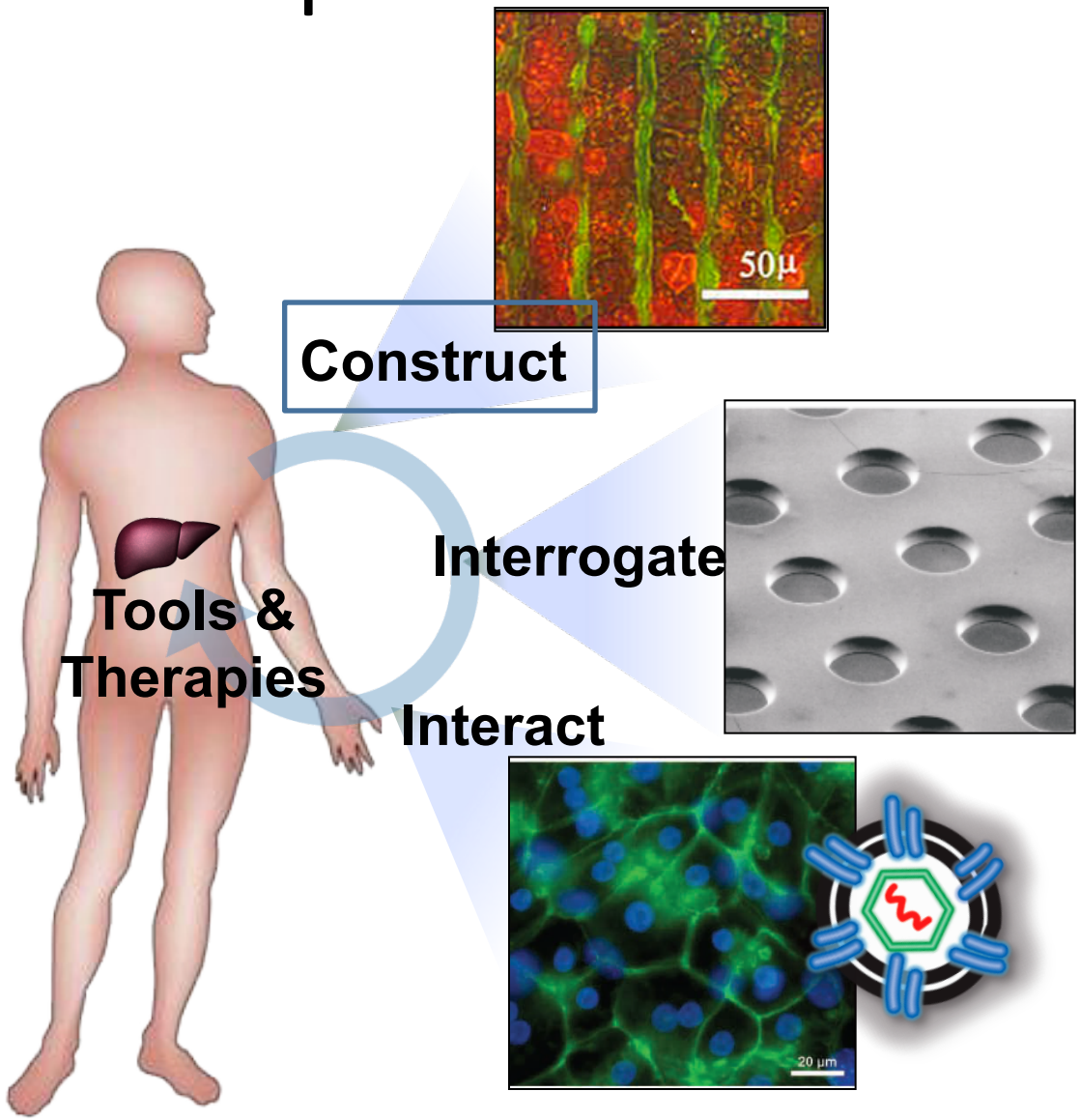
100 million Transistors [2]



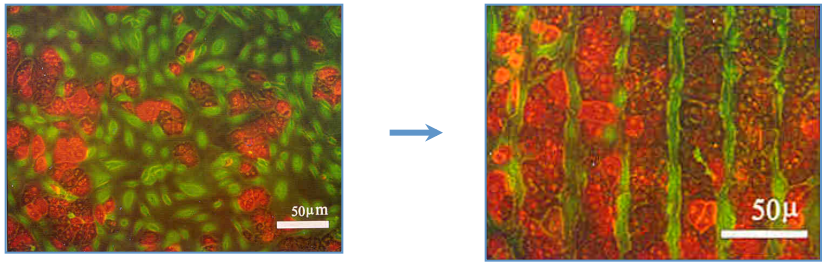


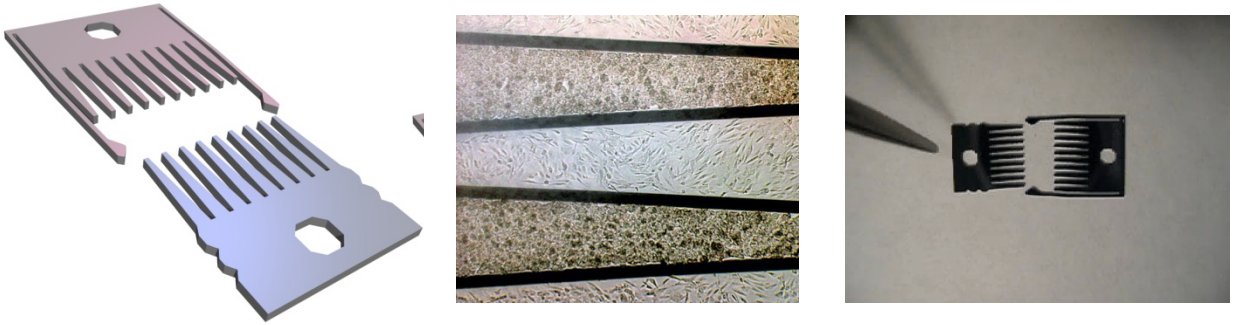
[1] Technology Review, [2]Intel, [3] Torres+ *Annual Rev. Biophys. 2008*

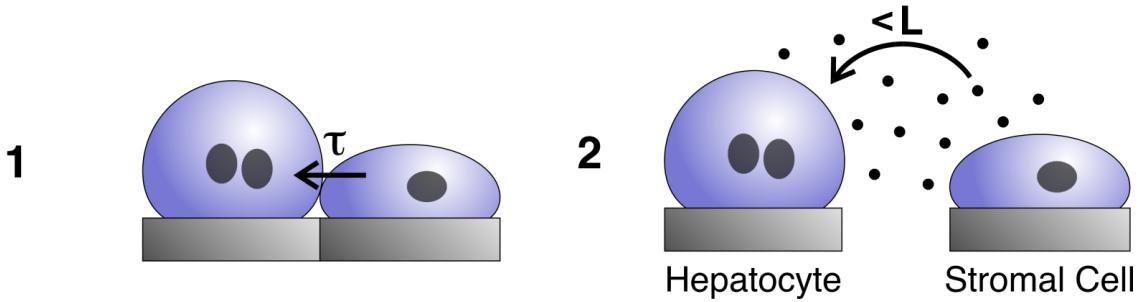
Engineering Human Hepatic Tissues



Photolithography to Control Cell-Cell Interaction

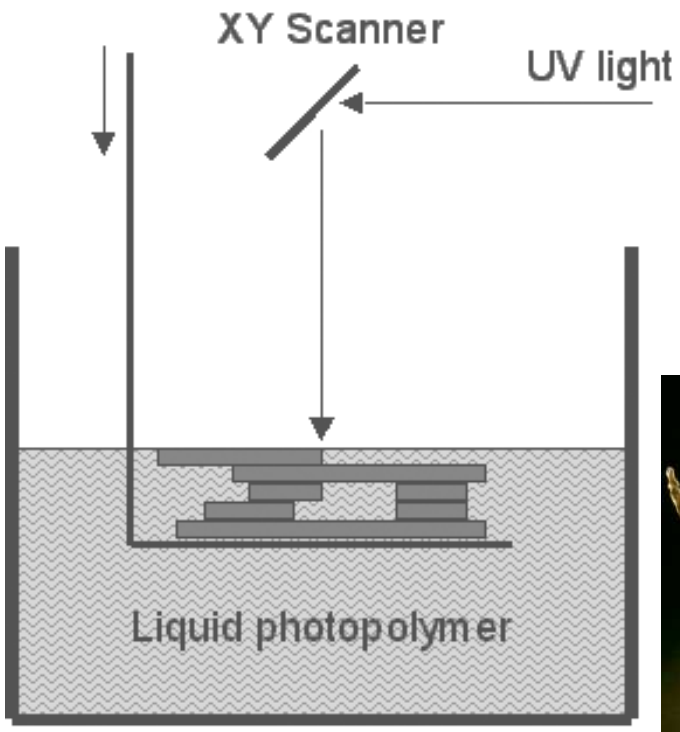




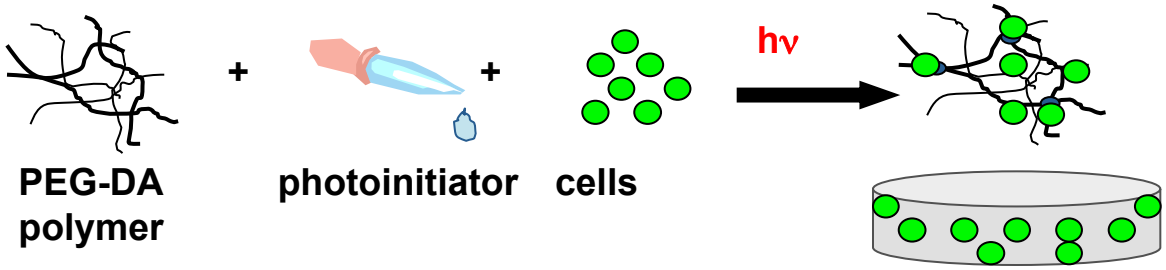


Bhatia+ *J Biomed Mat Res.* 1997; Bhatia+, *J of Biom Science*. 1998; Bhatia+ *Biotech Prog.* 1998; Bhatia +, *FASEB J.* 1999; Hui & Bhatia, *PNAS* 2007; Khetani+ *Hepatology*, 2004; Khetani+ *Nature Biotech*, 2008; Khetani+ *Hepatology*, 2008; March+ *FASEB J*, 2009

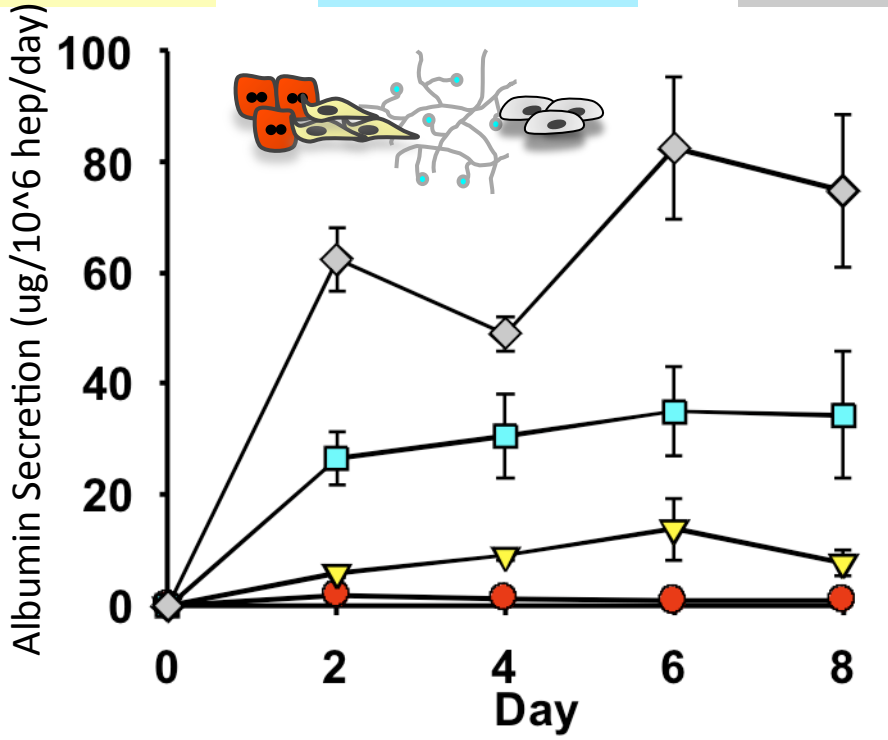
Making 3D Parts with Light



3D Hydrogels For Hepatocytes

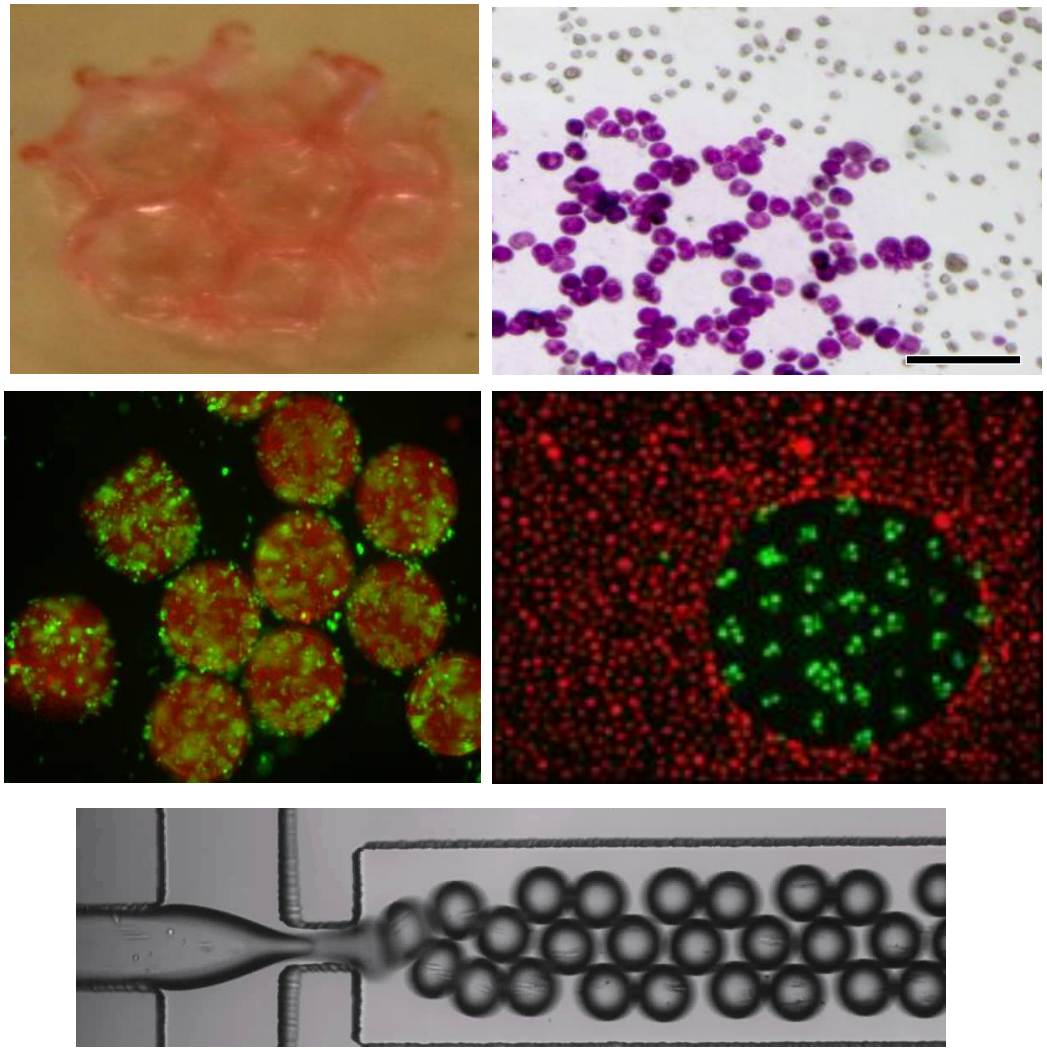


Cell-Cell Interactions[3-5] → **Cell-Matrix Interactions**[4,5] → **Soluble Factors**[5]



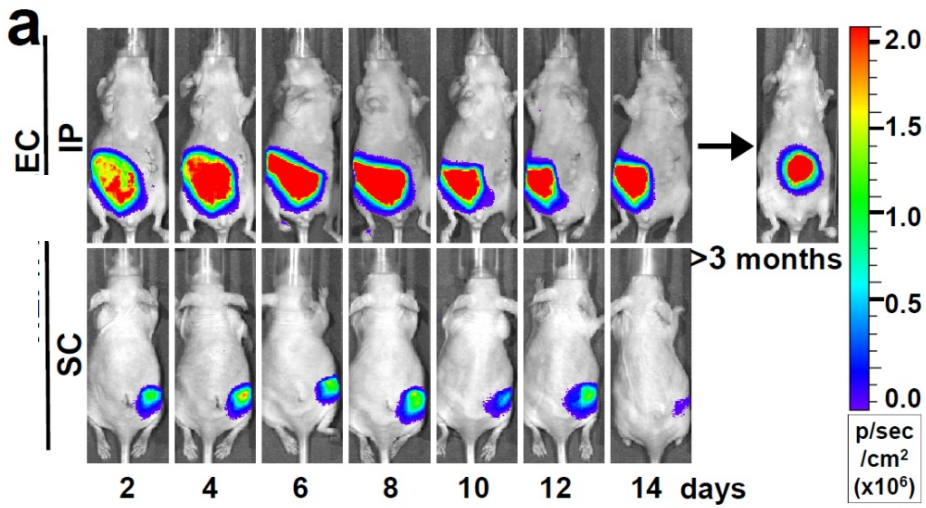
[3]Khetani+ *FASEB J* (2008) [4]Underhill/Chen+ *Biomaterials* (2007) [5]Chen+ (Submitted)

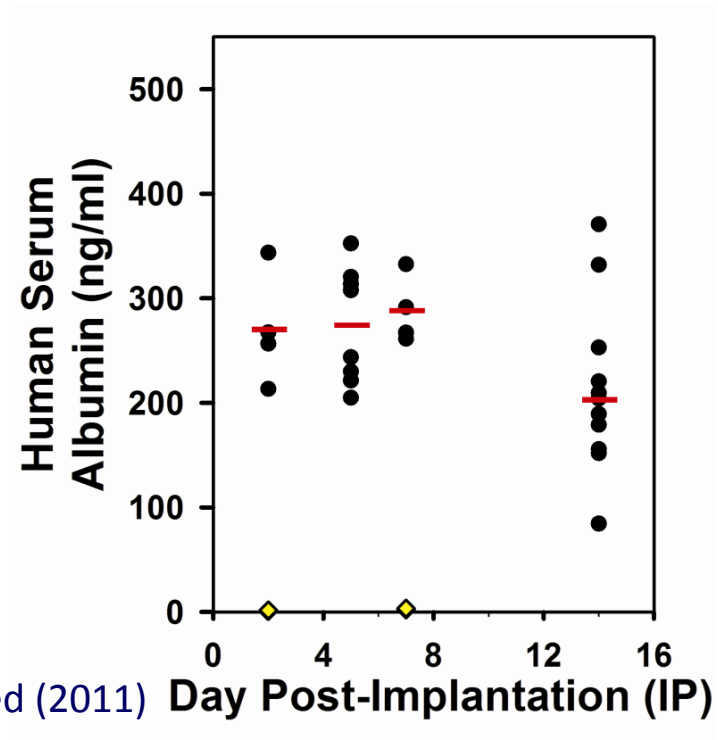
PEG Based Tissues



Albrecht+ *Nature Methods* (2006) Underhill/Chen+ *Biomaterials* (2007)
Albrecht+ *Lab-on-a-Chip* (2007) Liu+ *FASEB J (*2007)
Chen/Underhill+ *Integr Biology (*2010) Li+, submitted (2011)

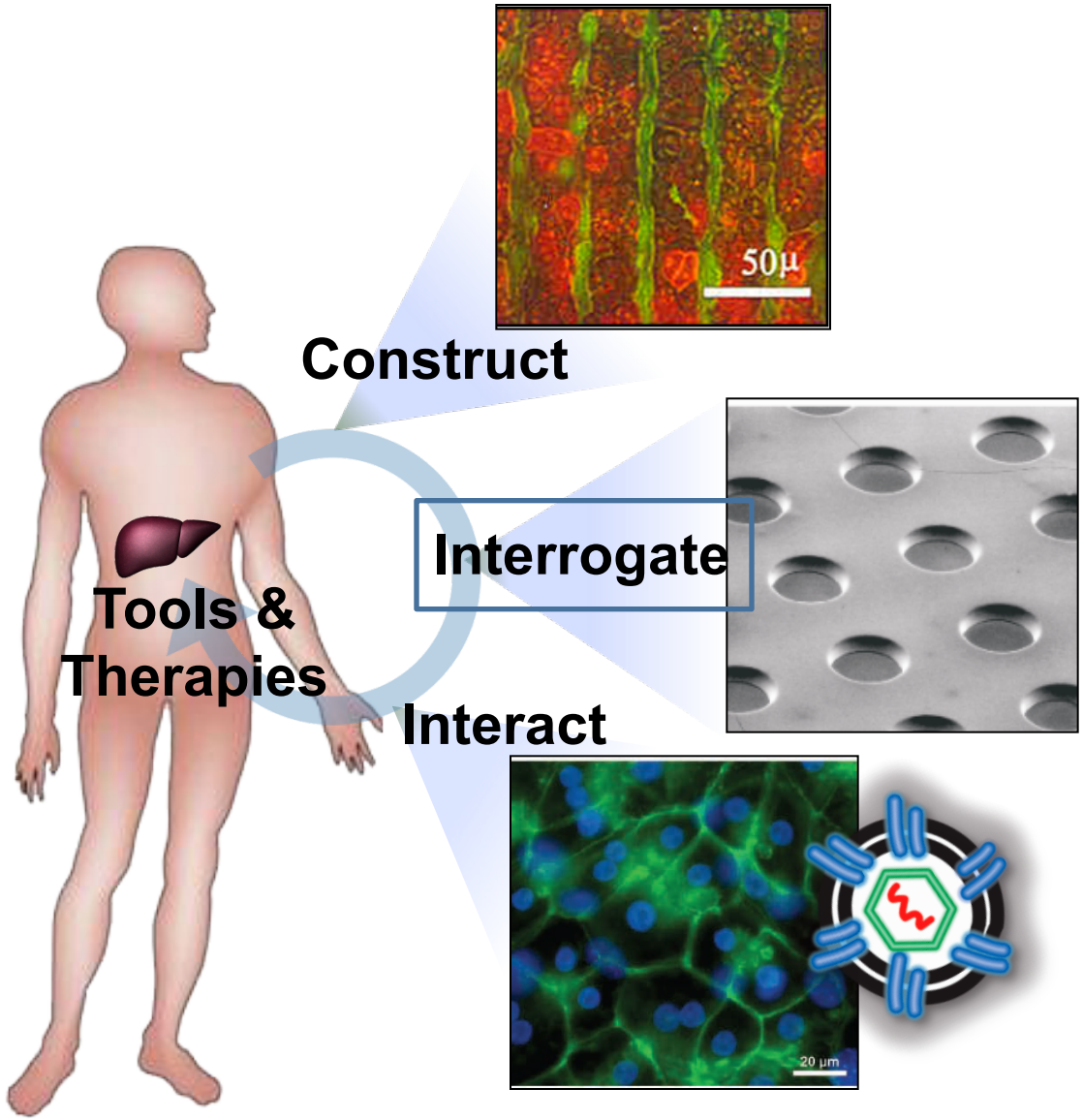
Functional Assessment



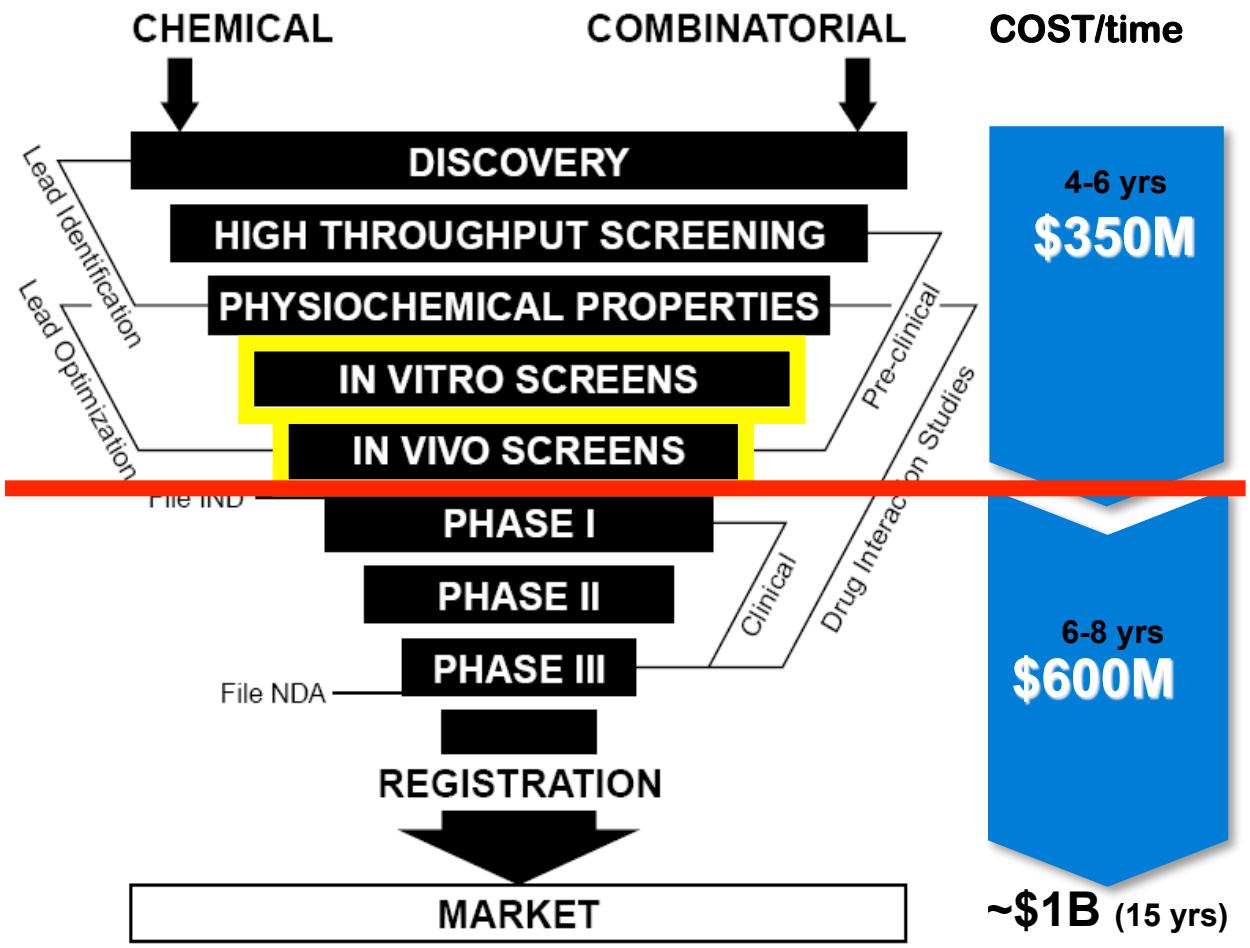


Chen+ , submitted (2011)

Engineering Human Hepatic Tissues

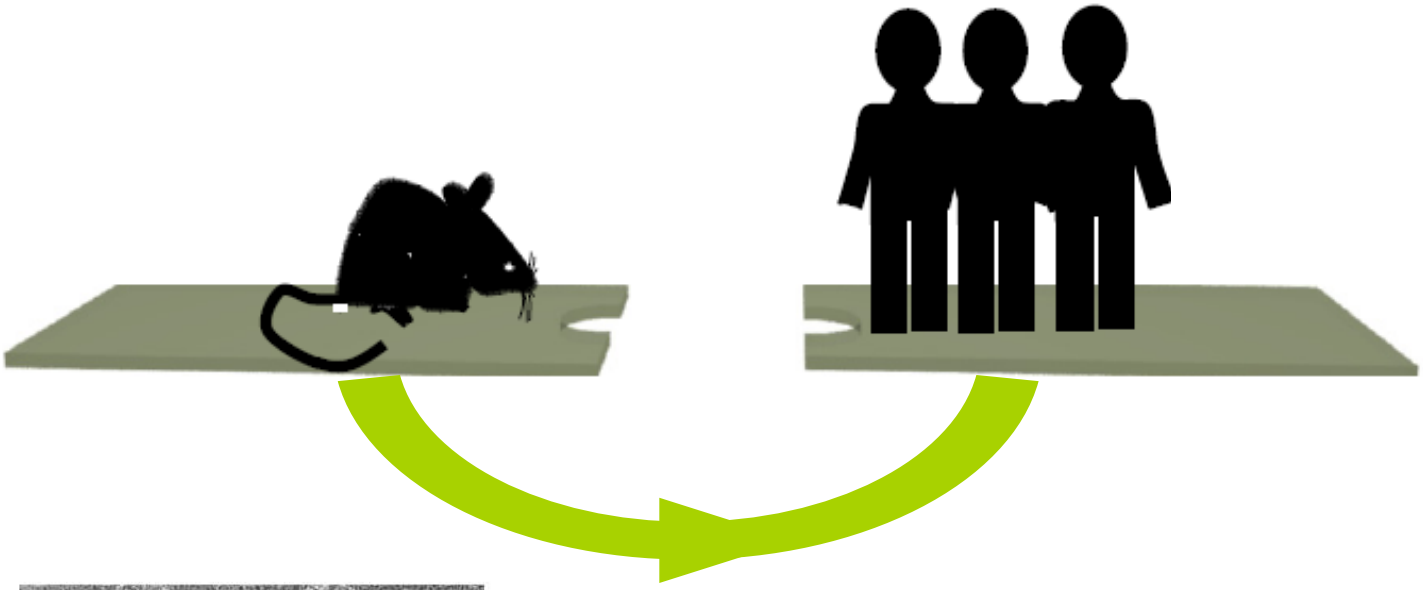


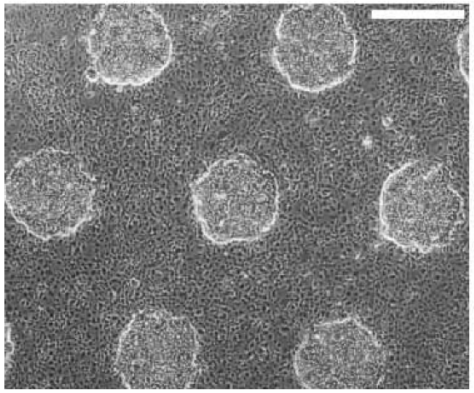
Drug Development Failures Are Expensive and Dangerous



Olson H+ *Regul Toxicol Pharmacol* (2000), Xu JJ+ *Chem Biol Interact* (2004)
Kola and Landis, *Nat Rev Drug Disc* (2004)

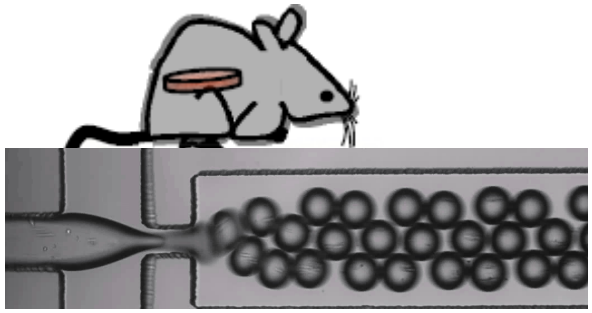
Bridging the Gap with Human Tissue Models



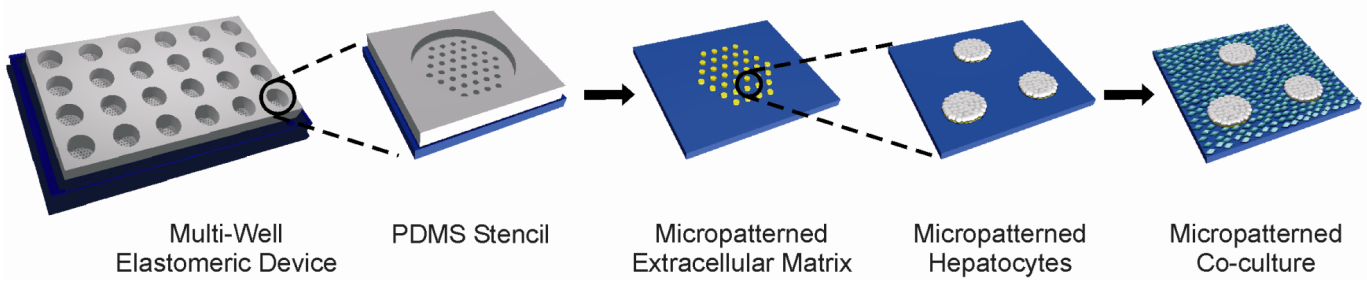


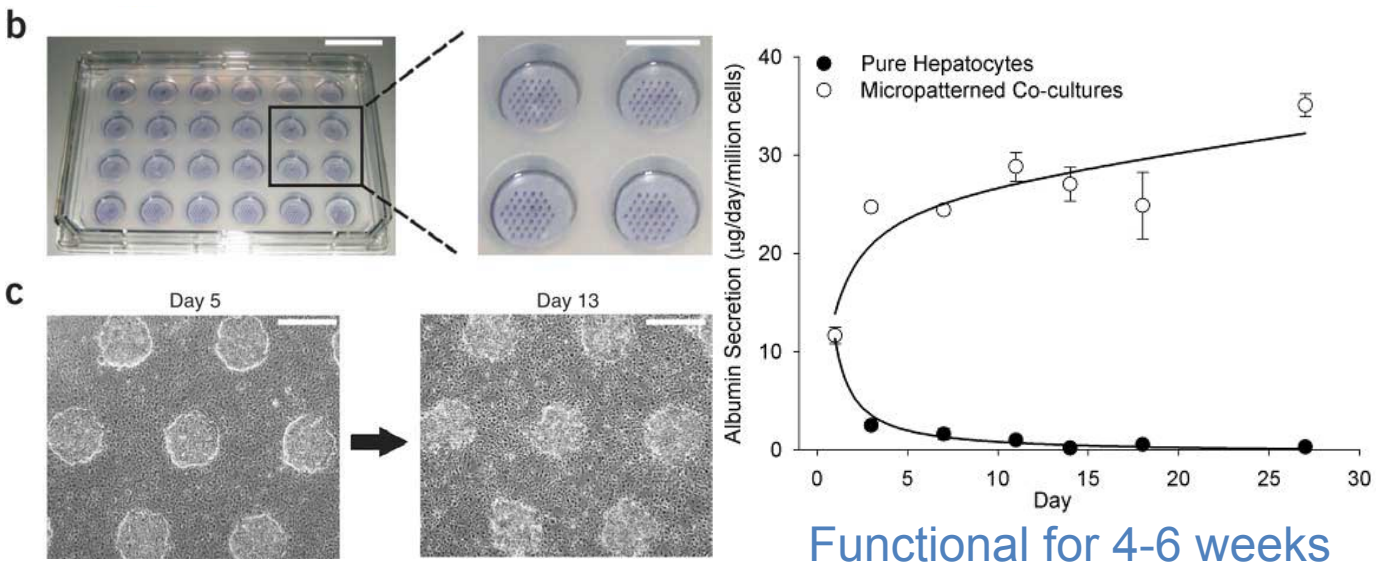
←2D in vitro

3D in vivo→



Multiwell Human Micropatterned Co-Cultures

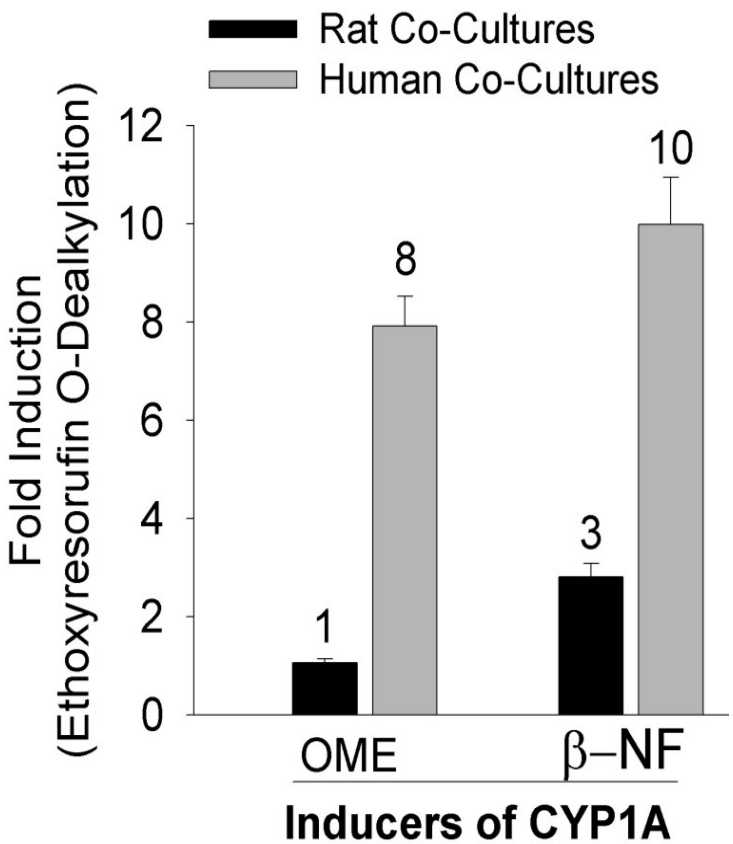




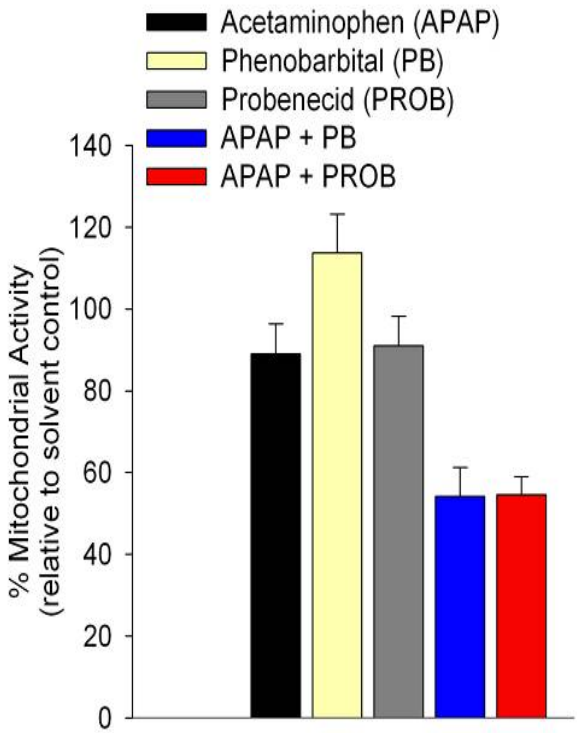
Functional for 4-6 weeks

Khetani+, Nature Biotechnology, 2008; Hui+, PNAS, 2007;
Khetani+, Hepatology, 2004; Khetani+, FASEB J, 2009

Multiwell Human Micropatterned Co-Cultures



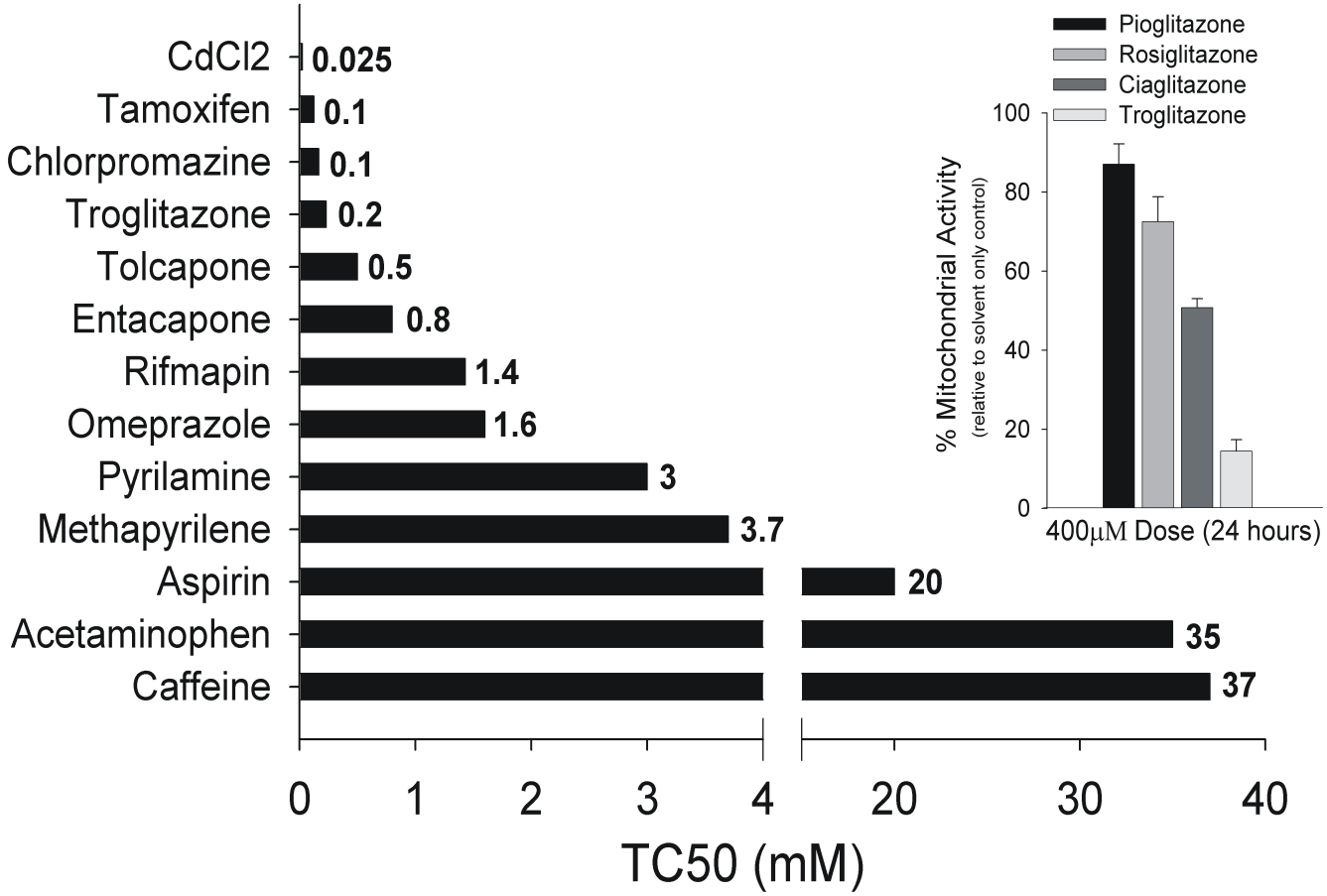
Species Differences



Drug-Drug Interactions

Khetani and Bhatia, *Nature Biotechnology 2008*

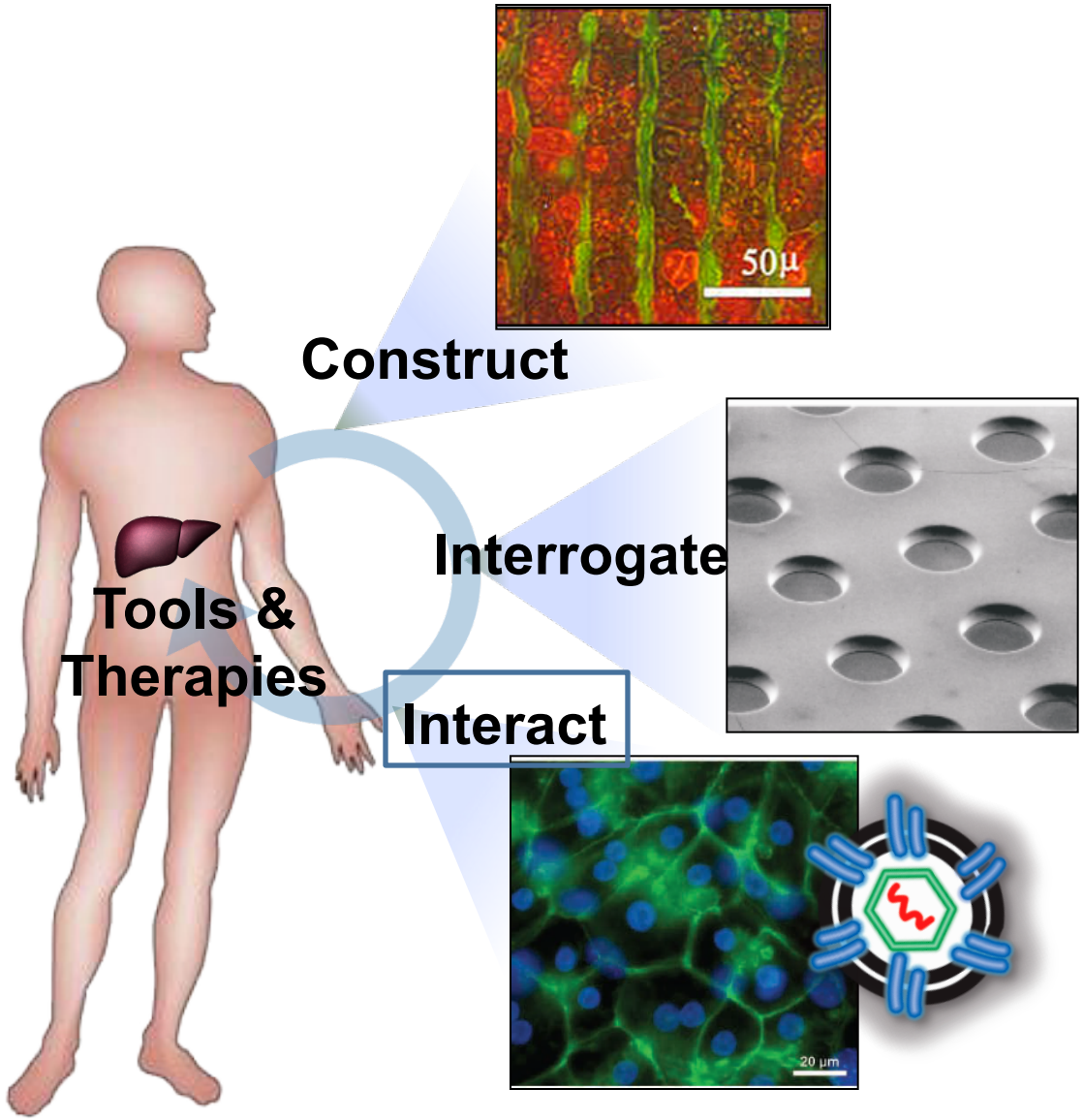
Multiwell Human Micropatterned Co-Cultures



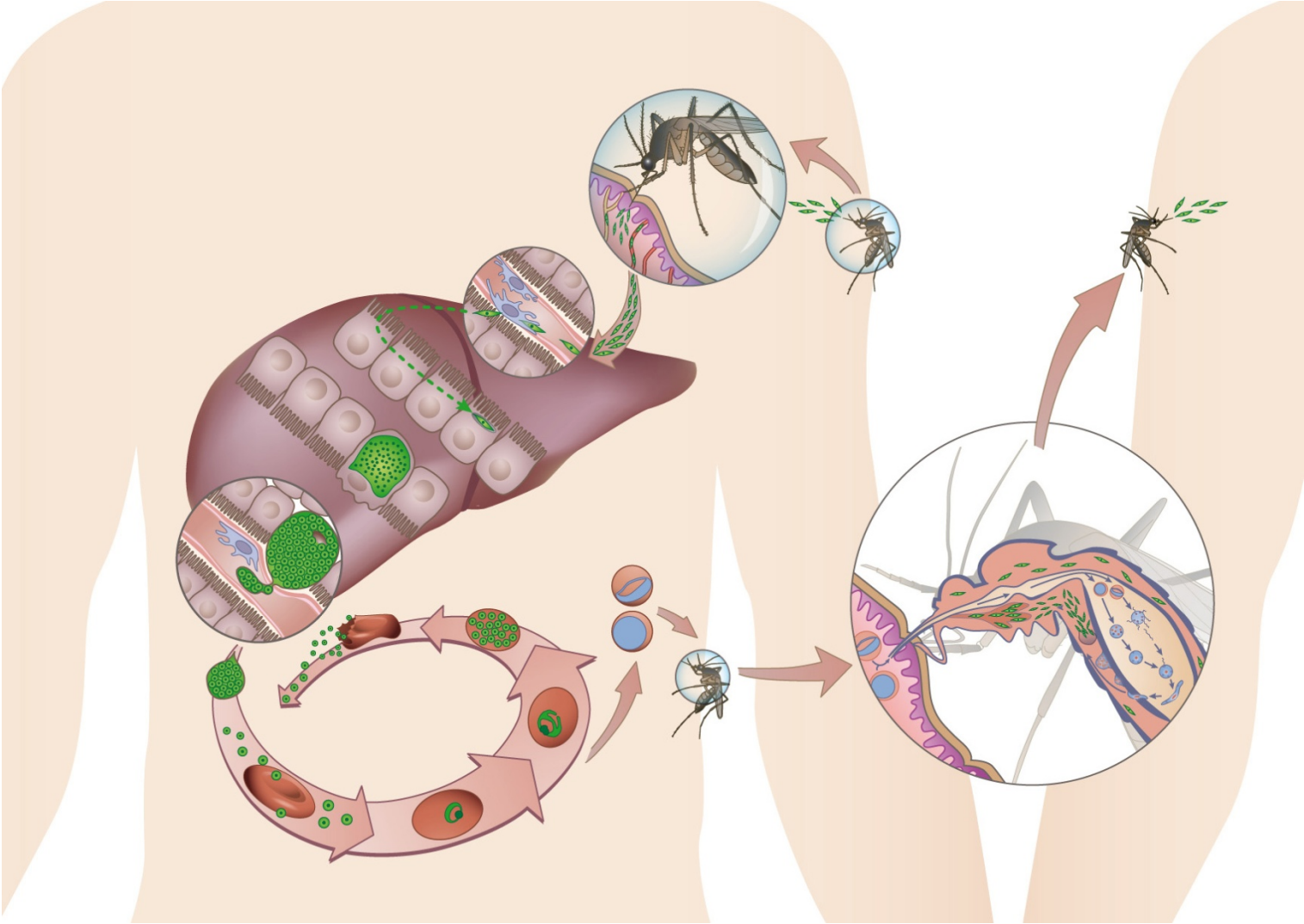
Acute/Chronic Toxicity

Khetani and Bhatia, *Nature Biotechnology 2008*

Engineering Human Hepatic Tissues

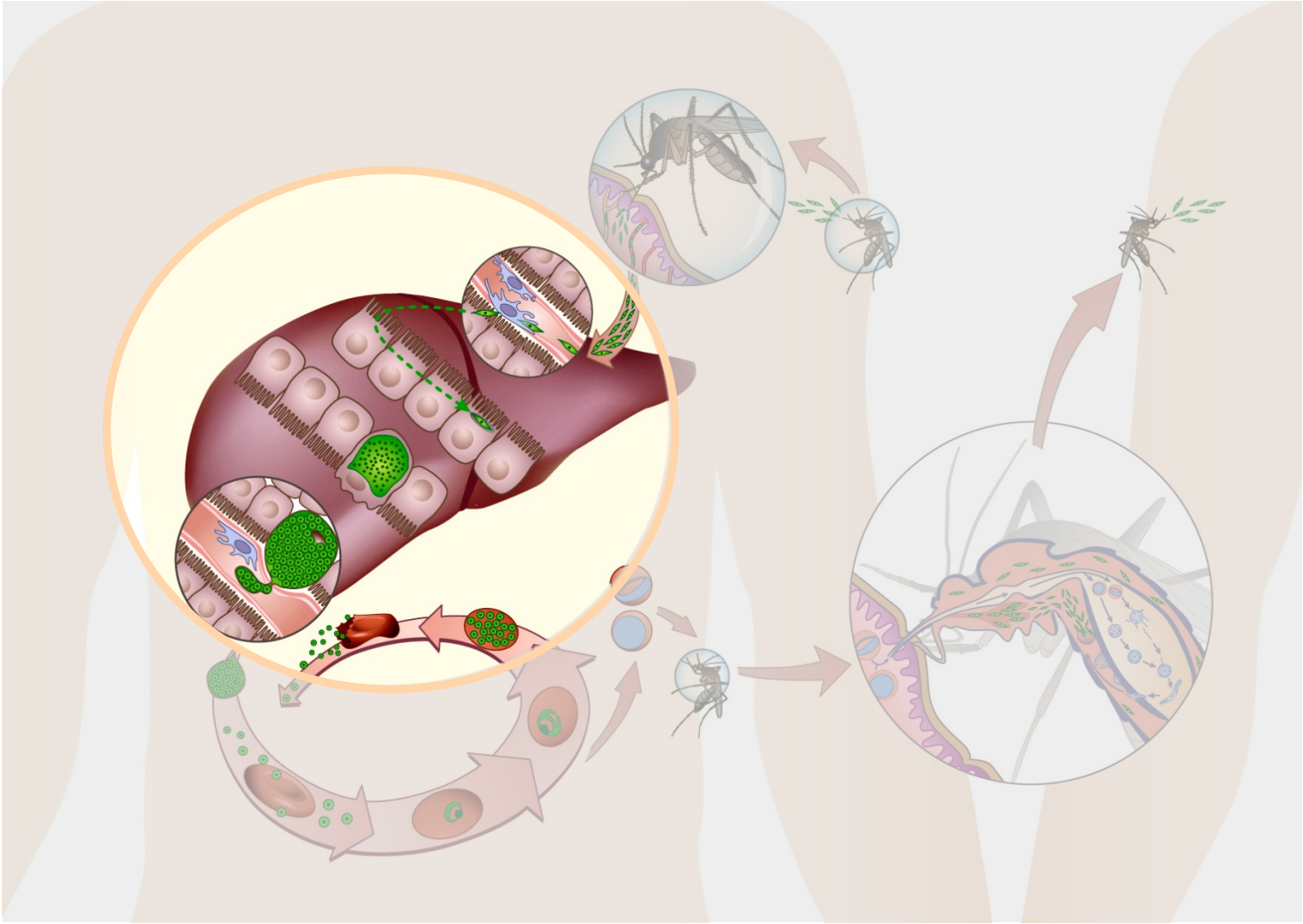


Plasmodium Life Cycle



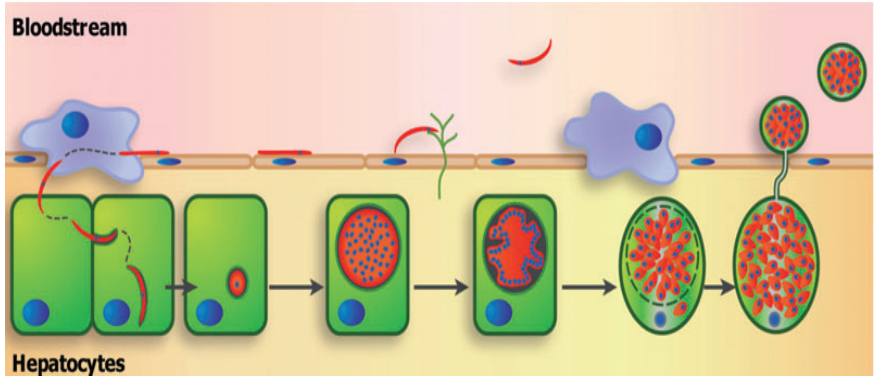
Maria Mota

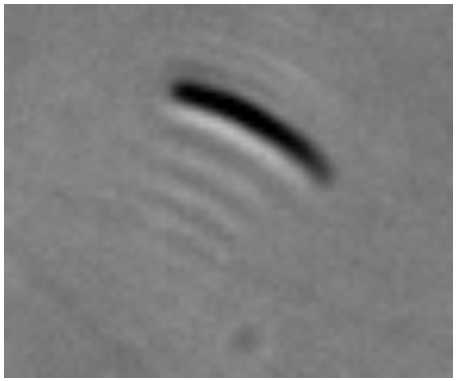
Plasmodium Life Cycle



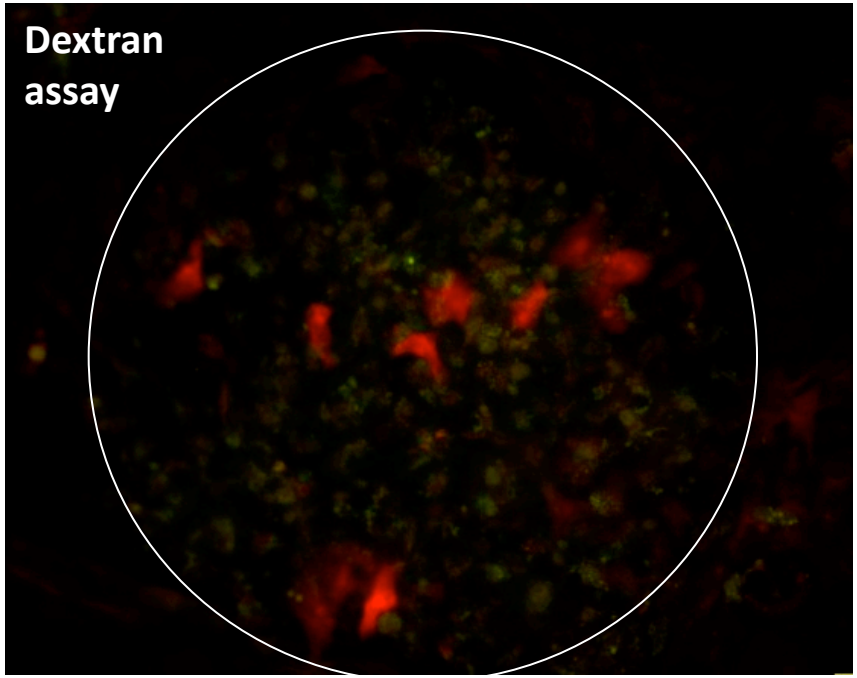
Maria Mota

Sporozoites in Microscale Human Livers





Migration

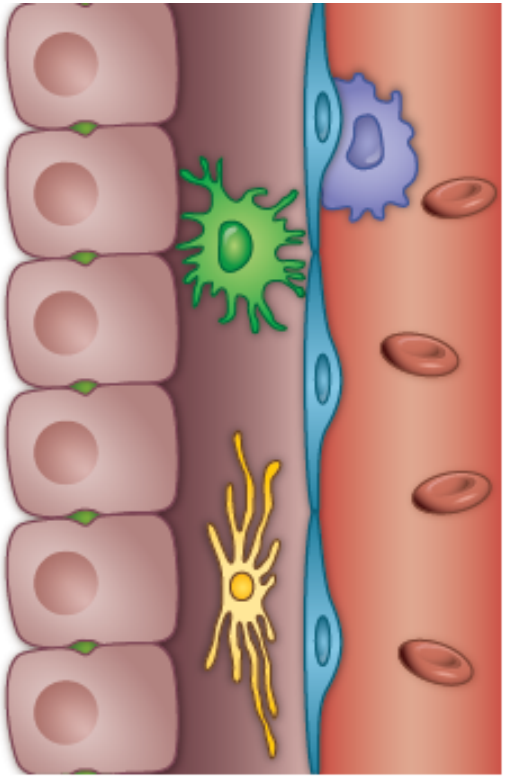


March-Riera+, unpublished

Tiny Technologies for Tissue Microenvironments

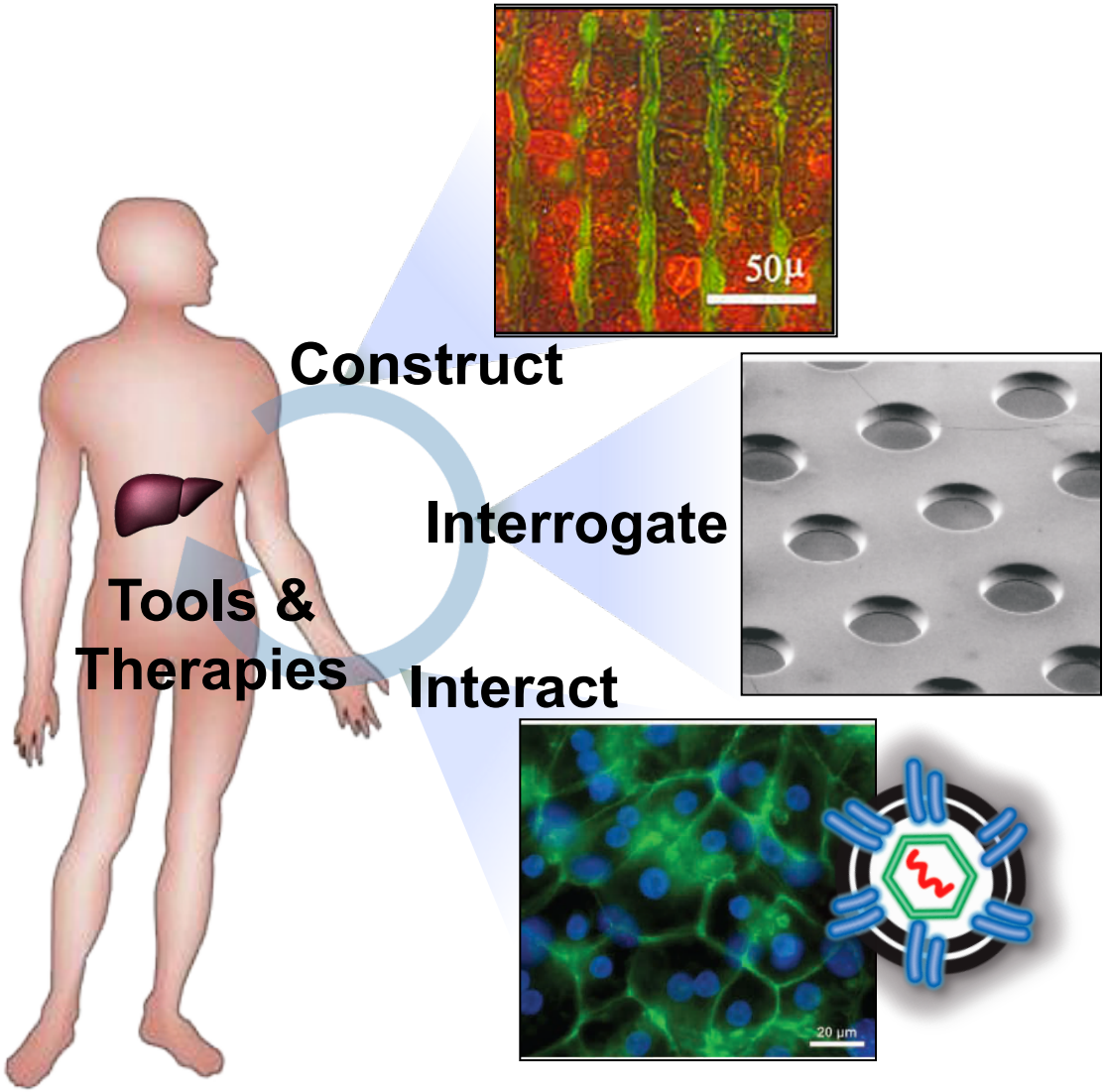
100 μm — 100 nm

3D Printing
Photolithography
Droplet assembly
Biomaterials
Soft-lithography
Microfluidics
Micropatterning
Self-assembly
Bio-responsive
Nanomaterials



Healthy or Diseased Microenvironment

Hepatic Tissue Engineering



Acknowledgements

- **Collaborators**
  - D. Wirth/ M.Duraisingh (HSPH), Harvard
  - C. Chen (BME), UPenn
  - S. Duncan, M.C. Wisconsin
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  - T. Golub, (Broad Institute), MIT
  - D. Haber/M. Toner (MGH)
  - W. Hahn, (Broad Institute), MIT
  - S. Hoffman (Sanaria)
  - R. Langer/D. Anderson, MIT
  - D. Livingston (DFCI)
  - L. Mahadevan (SEAS), Harvard
  - D. Melton (SCRB), Harvard
  - C. Rice, Rockefeller
  - E. Ruoslahti (Burnham Institute)
  - M. Sailor (Chemistry), UCSD
  - D. Schuppan (BIDMC)
  - P. Sharp (Biology), MIT
  - J. Shah (Systems Bio), Harvard

- **Laboratory for Multiscale Regenerative Technologies**
  - Post-doctoral Fellows: N. Singh, D. Wood, G. Kwong, K. Stevens, R. Schwartz, K. Christine, S. Desai
  - Graduate: A. Chen, Y. Ren, J. Shan, N. Reticker-Flynn, C. Li, K. Lin, K. Trehan, J. Lo, D. Braga-Malta, S. Ng, A. Bagley
  - Staff: S. Katz, L. Ingaharro, S. Kangiser, E. Lehtola; Research Scientists: G. Underhill, S. March-Riera
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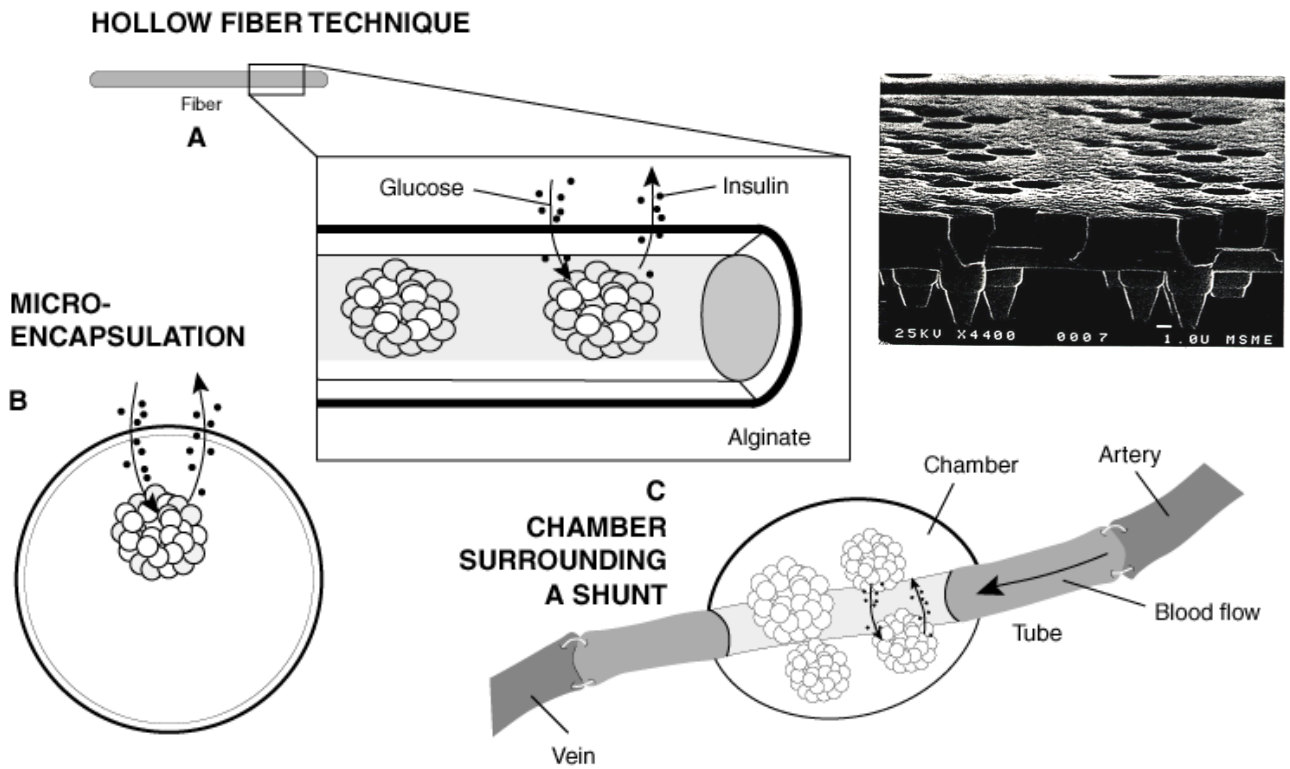
  - Bill & Melinda Gates Foundation, Harvard Stem Cell Institute, Broad Institute
  - Stand Up to Cancer, Koch Institute for Integrative Cancer Research

Pancreas (Hybrid)

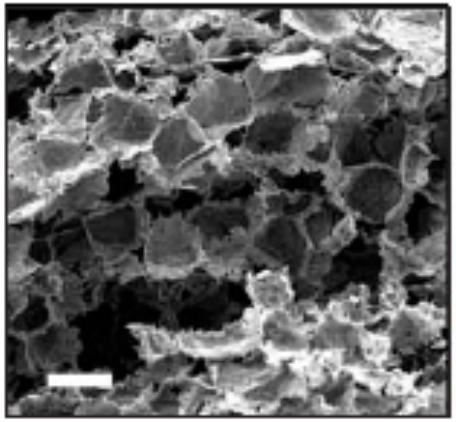


Modified from SCIENTIFIC AMERICAN, July 1995; Desai et al., 1999

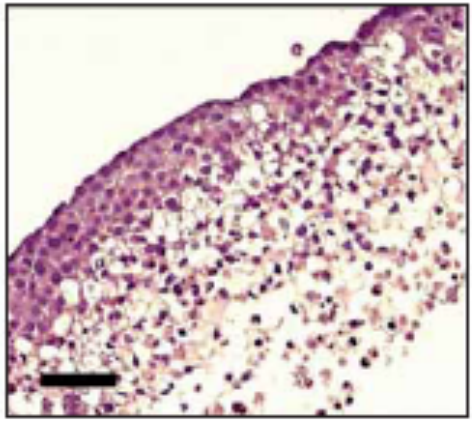
Utility as Model Systems

Tumor Models

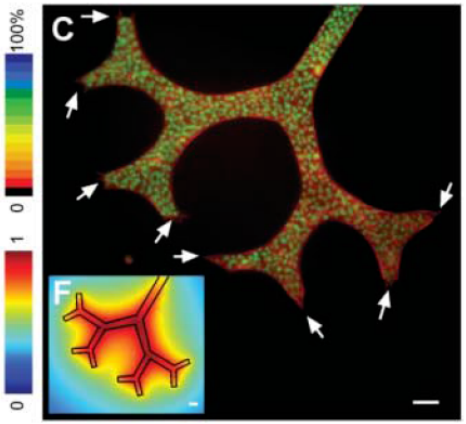
PLG scaffold



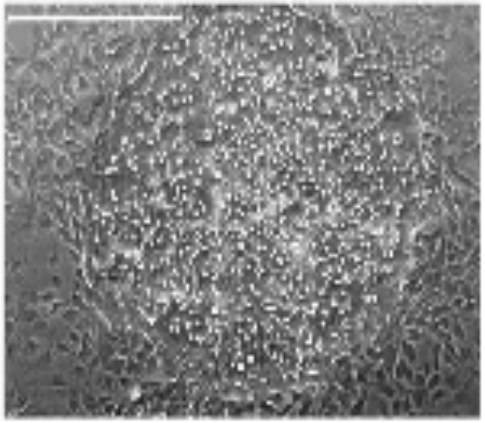
In vitro



Morphogenesis

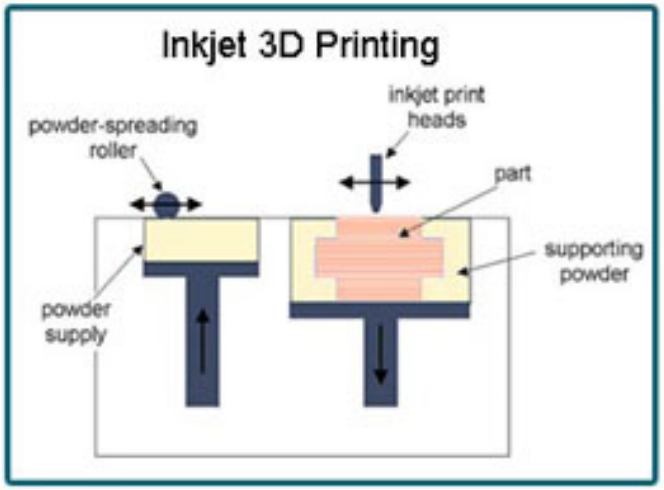


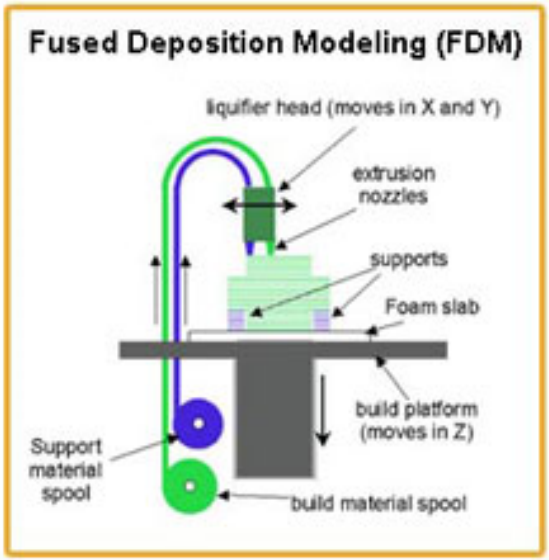
Liver Models

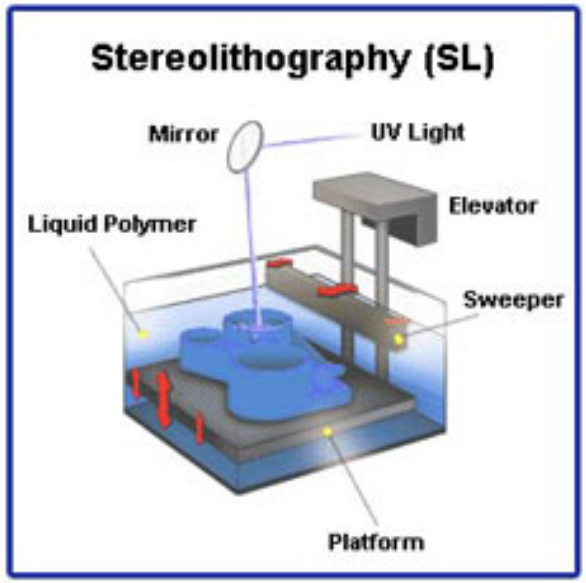


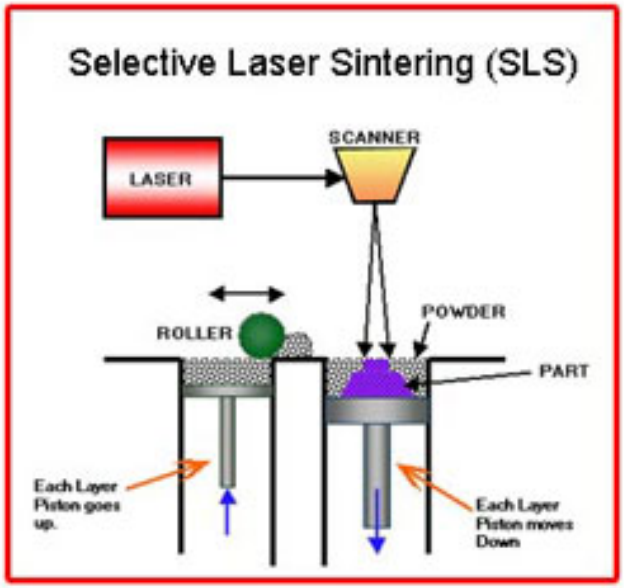
Fischbach C+/Mooney DJ, Nat Methods (2007); Nelson CM+/Bissell, Science (2006); Khetani & Bhatia, Nat Biotech (2008)

3-D Fabrication & Assembly



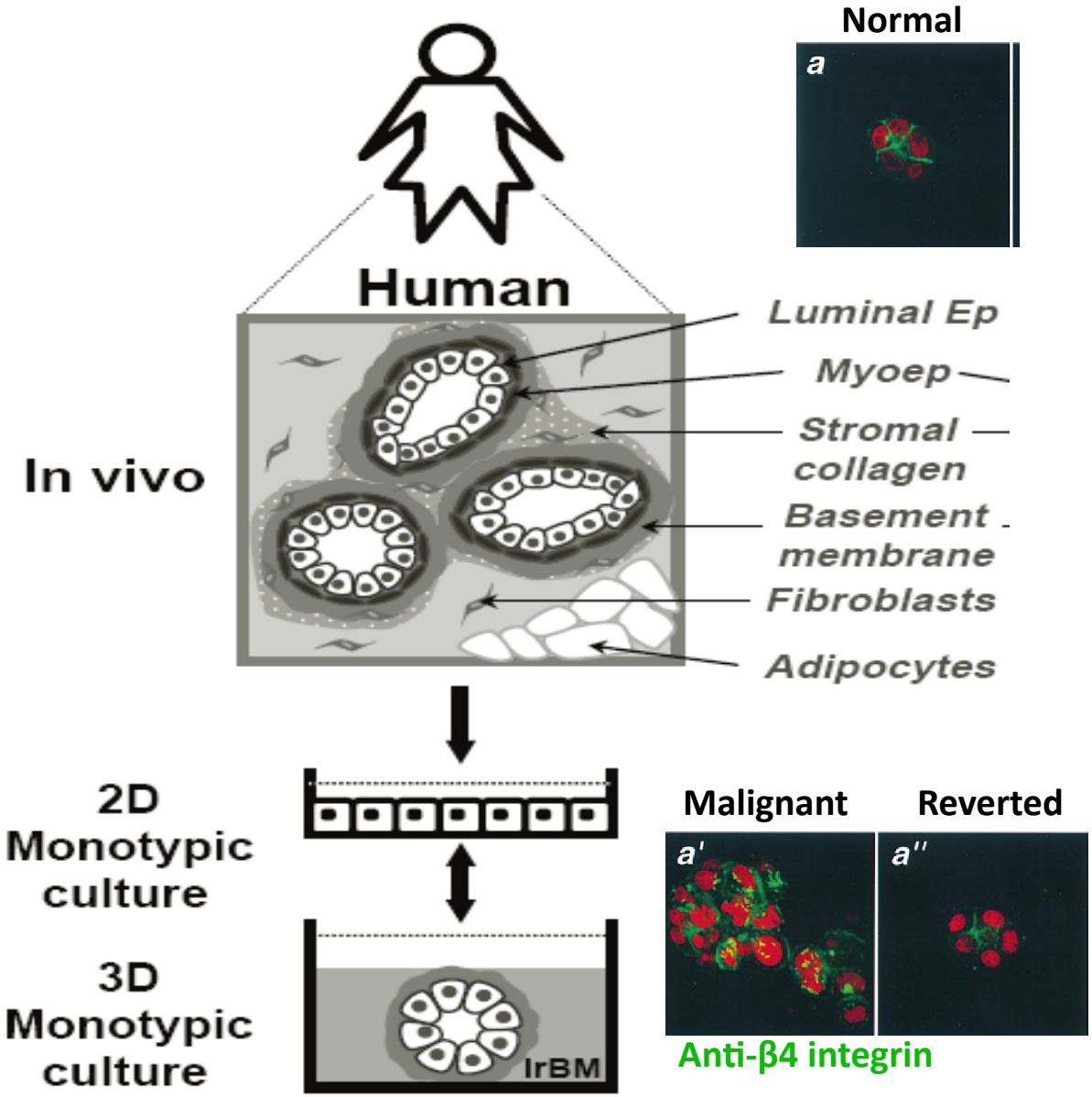






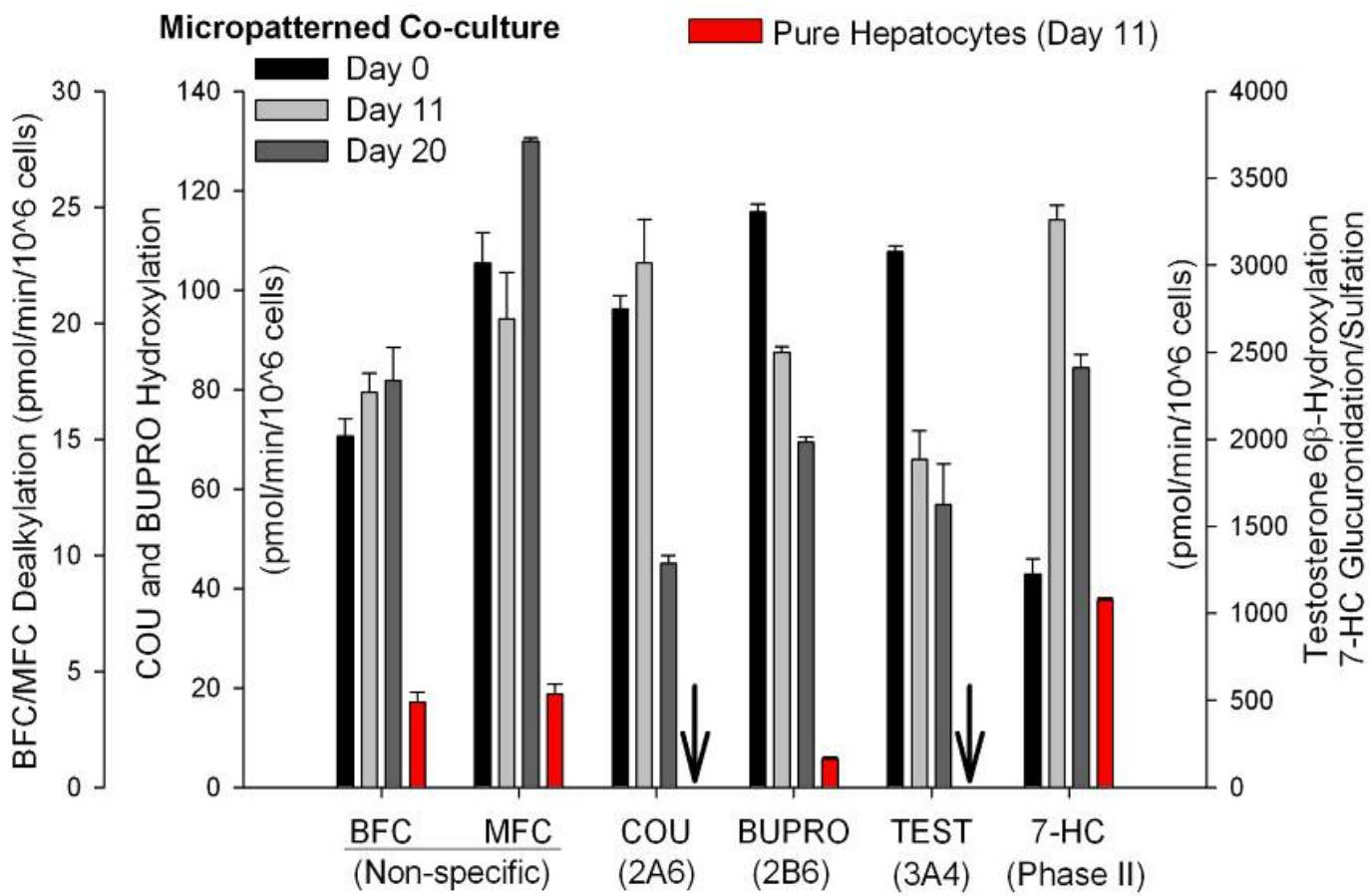
www.3dprinting.org

3-D Cell Organization



Schmeichel / Bissell, *J Cell Sci* (2003)

Multiwell Human Micropatterned Co-Cultures



CYP450 and Phase II Activity

Khetani and Bhatia, *Nature Biotechnology 2008*