WHAT STARTS HERE CHANGES THE WORLD
THE UNIVERSITY OF TEXAS AT AUSTIN

Mechanical engineering department

Advances in Biomedical Manufacturing: 3D Tissue Model Systems for Personalized Medicine

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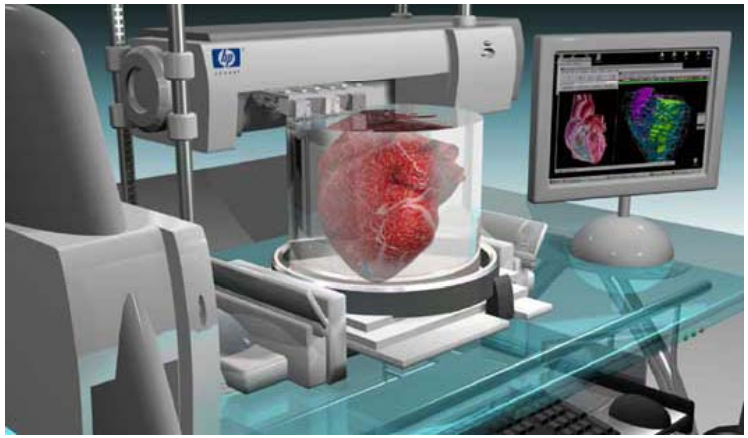
Overview

- Biomedical Manufacturing and Personalized Medicine
- Two-chamber 3D Tissue Model Systems
- Challenges and Opportunities for Manufacturing
- Concluding Remarks

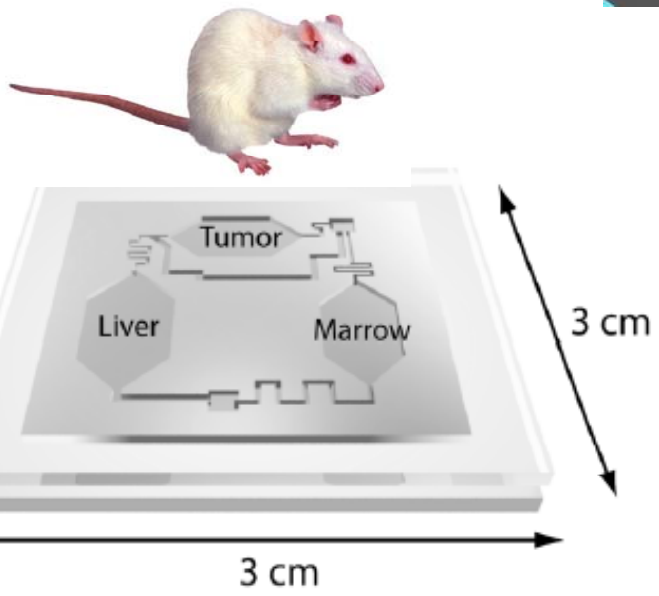
What is Biomedical Manufacturing?

- Cells, proteins, and other bioactive compounds are being used as building blocks to produce therapeutics and tissue engineered substitutes. Cell-integrated biochip devices and engineered tissue model systems are being fabricated for disease and pharmacokinetic studies.
- Meanwhile, proven technology from the traditional manufacturing industry is contributing to the improvement of surgical procedures and implant quality.

Bio-printing



nextnature.net

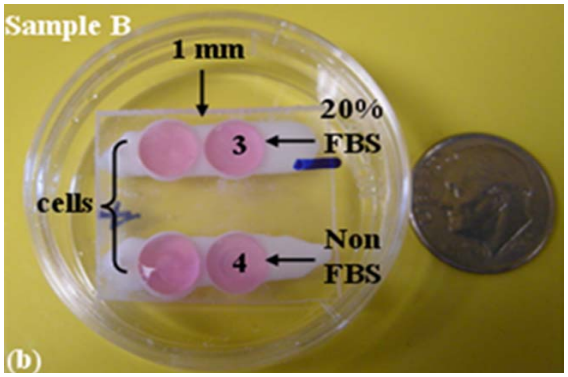


microCCA

"Silicon Guinea Pig"

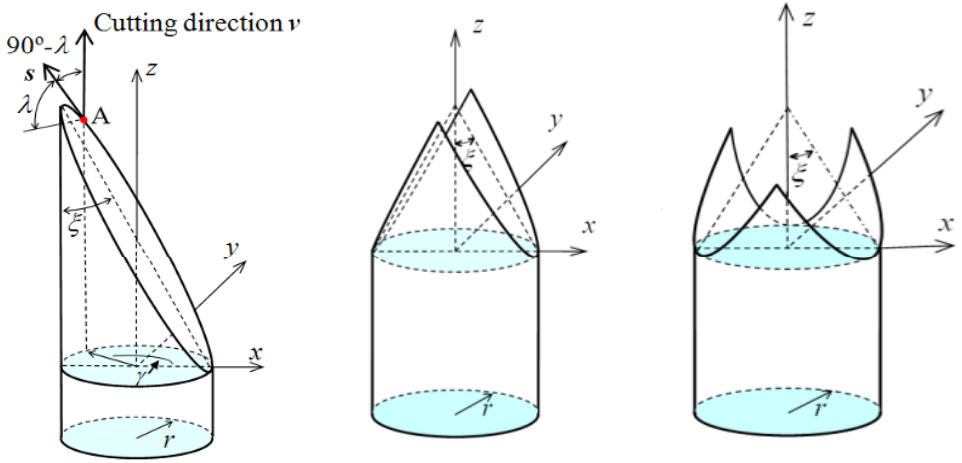
Shuler group, Cornell U.

3D Cancer Migration

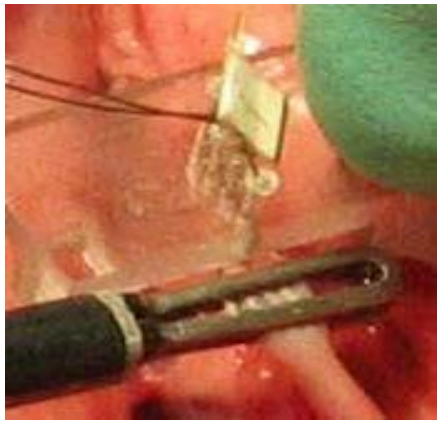


Li group, UT, Ma, et al, 2010

Cutting tool design for biopsy (tissue machining)



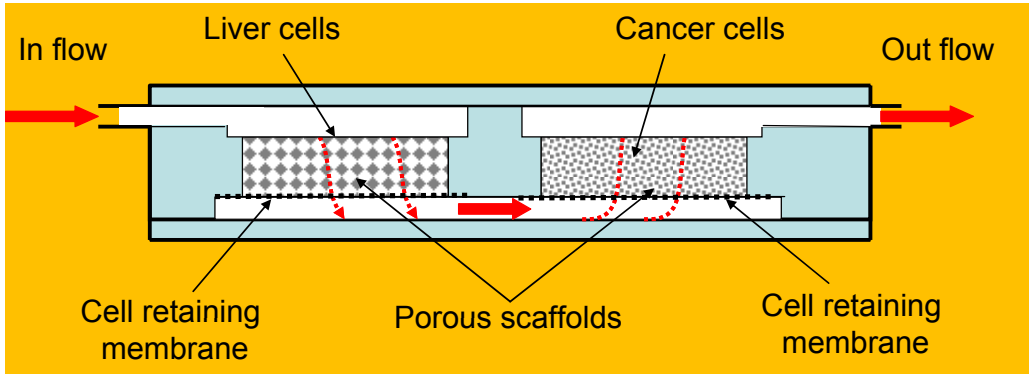
Thermal control of tissue welding



Shih, U of M

3D Tissue Model Systems for Personalized Medicine

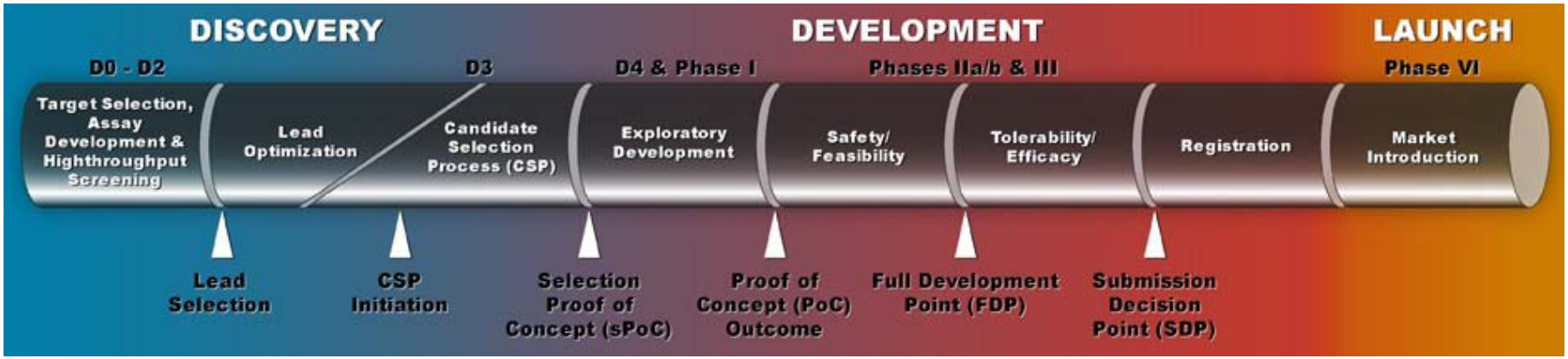
3D polymer “Guinea Pig”

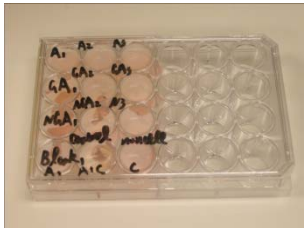


US Patent No. 7763456, 2010

Drug Discovery and Development

Novartis.com





Lengthy and costly !

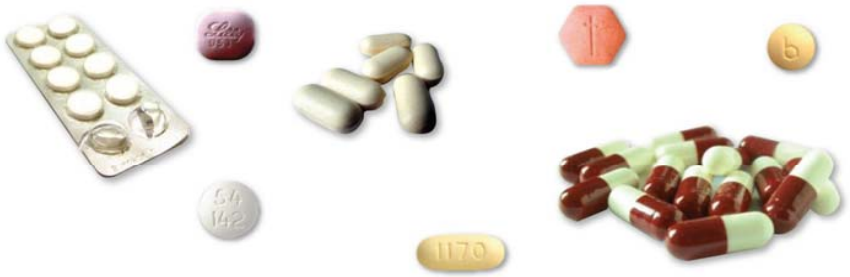
Effectiveness of drugs

Drug	Efficacy
Hypertension Drugs	10-30%
Heart Failure Drugs	15-25%
Anti Depressants Drugs	20-50%
Cholesterol Drugs	30-70%
Asthma Drugs	40-70%

Source: Spear et al. Trends in Molecular Medicine (2001) 7(5):201-204

Danger of Drugs

- 6.7% of patients in hospitals experience serious drug side effects; many die from adverse reactions.

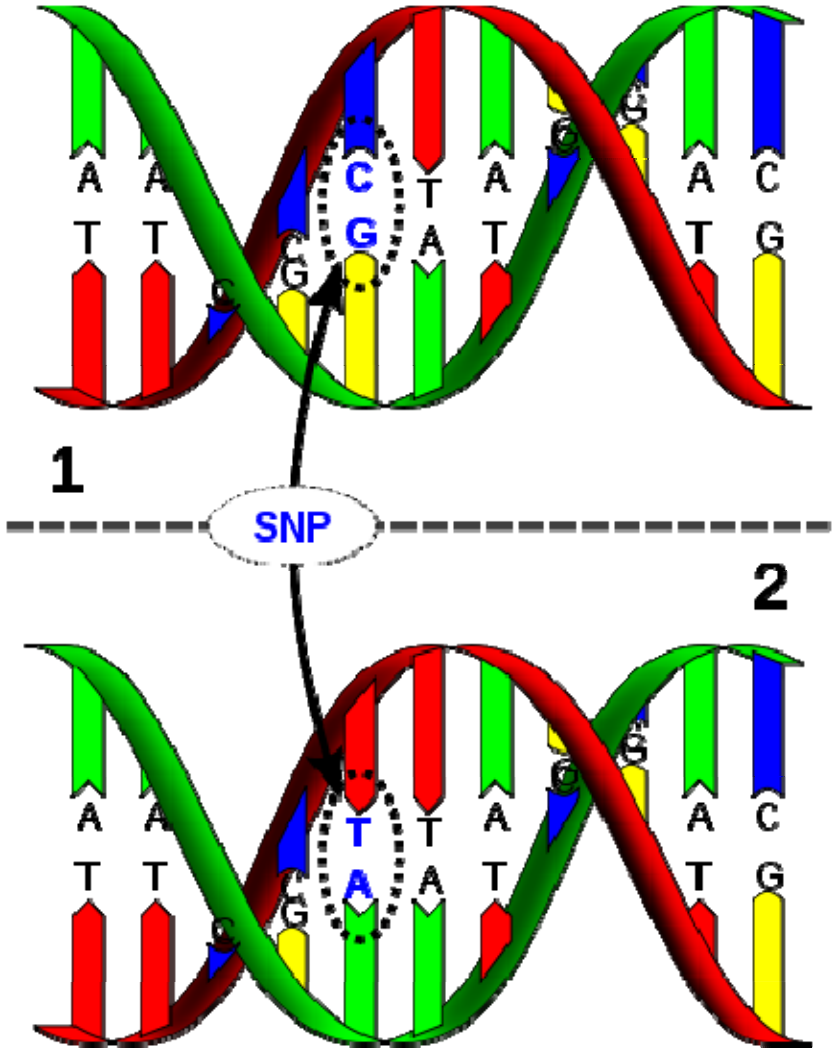


Not only the drug itself, but also the interaction of drugs

*Source: Lazarou et al. JAMA (1998) **279**(15):1200-1205*

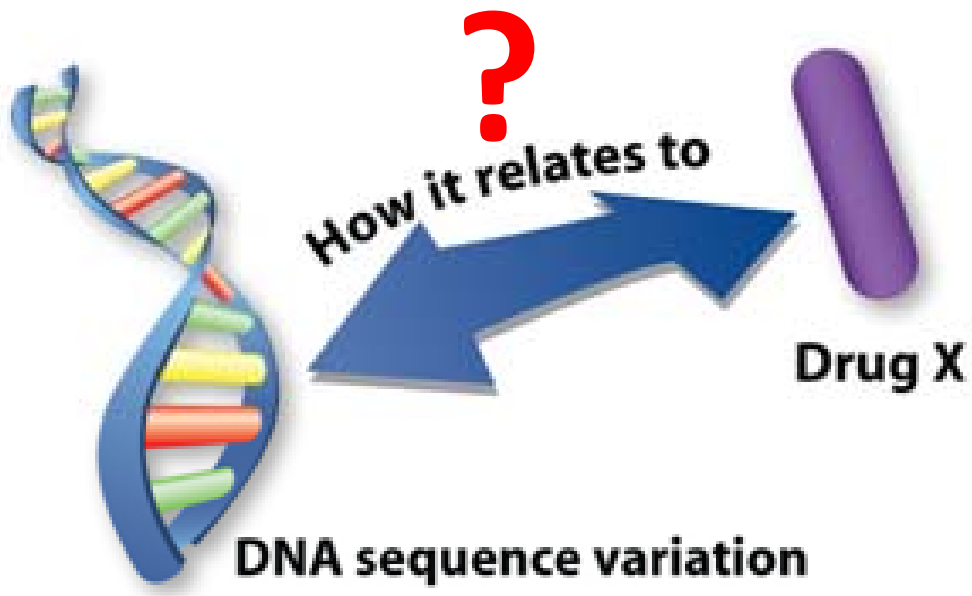
Genetic Variability

- Genetic variability is a measure of the tendency of individual genotypes in a population varies from one to another.



The Goal of Personalized Medicine

- Identify genetic differences between people that affect drug response
- Tailor medical treatments to the individual



Drug Tests

Ethical issues

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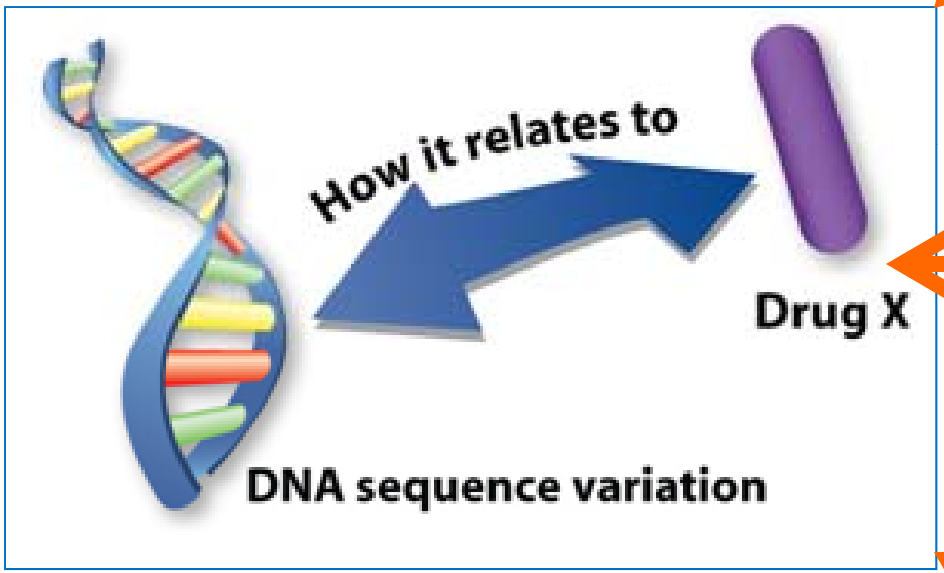

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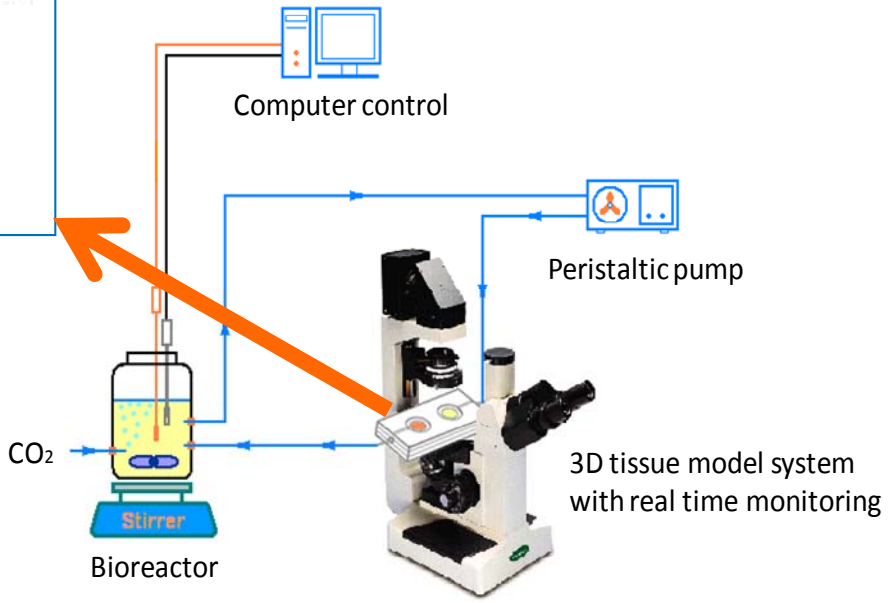
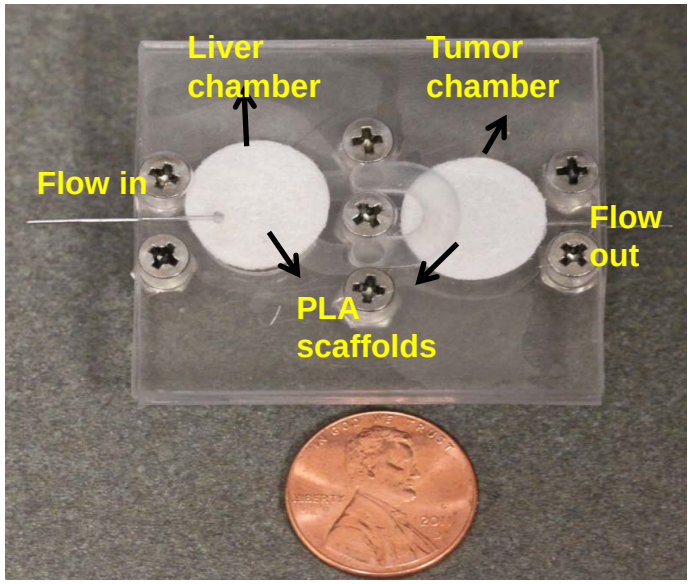
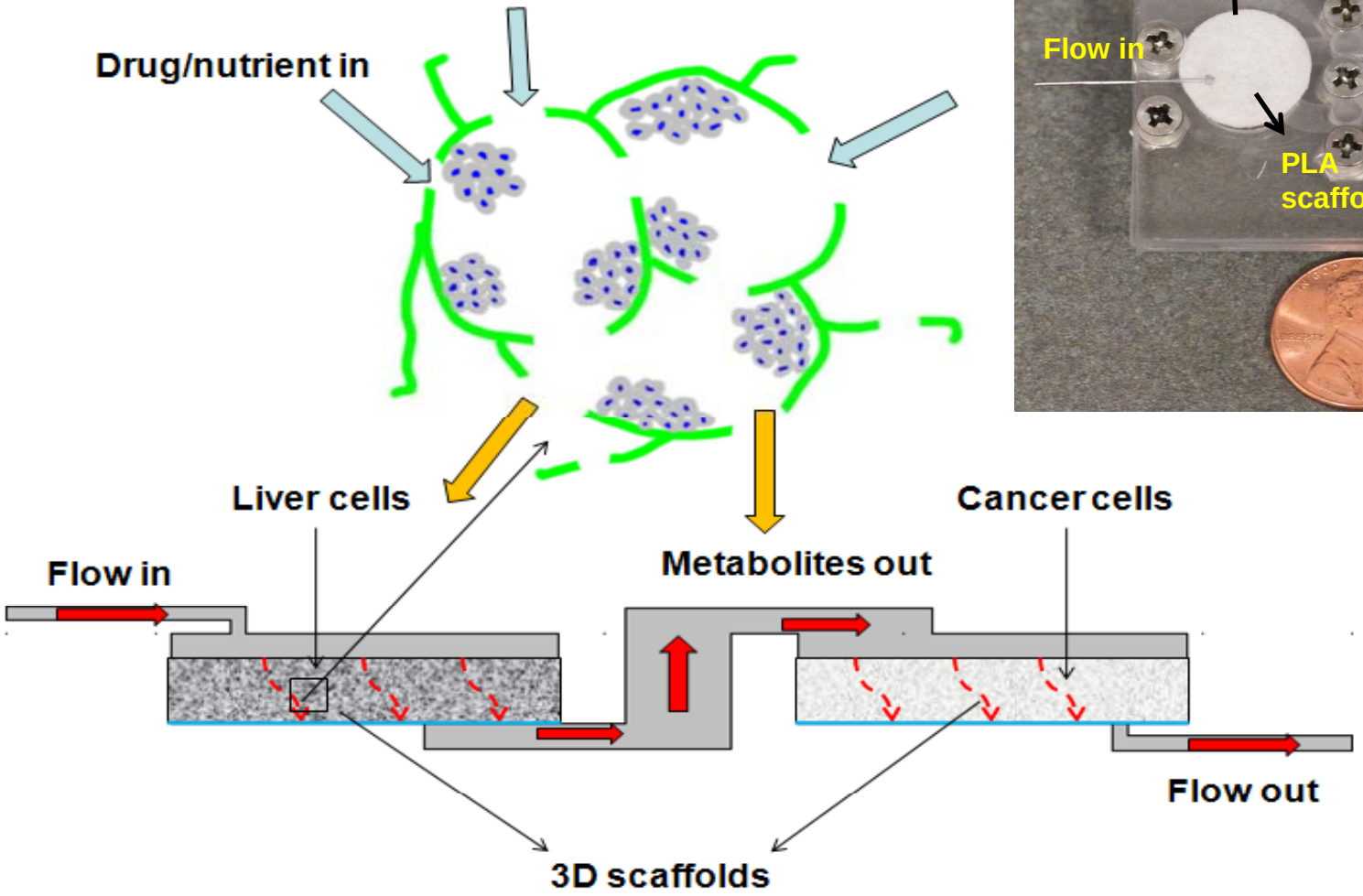
Cost, inaccuracy



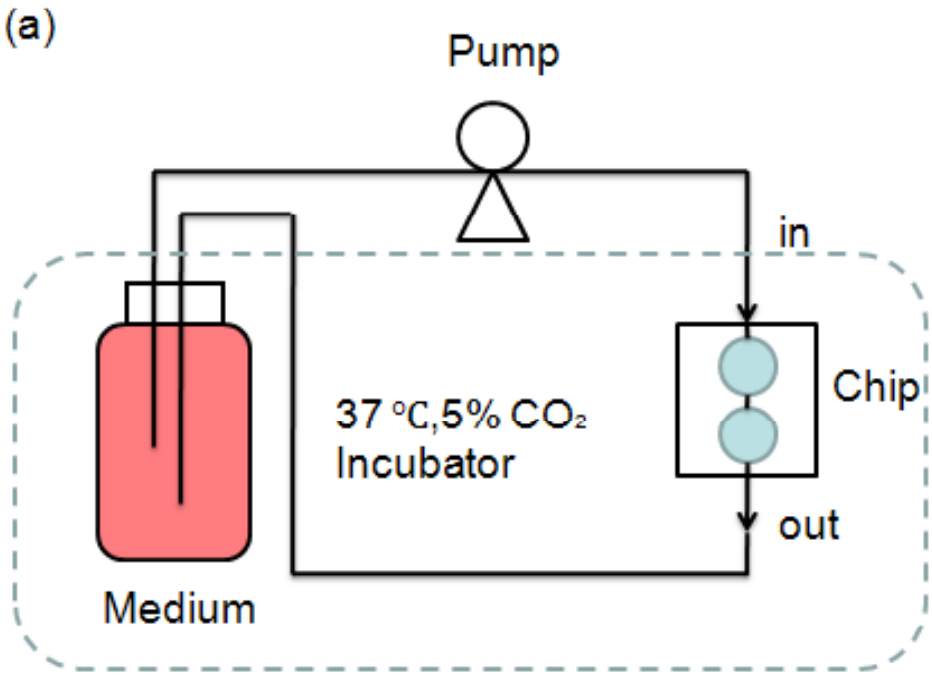
In vitro 3D tissue model system

A Perfused Two-Chamber 3D Tissue Model System



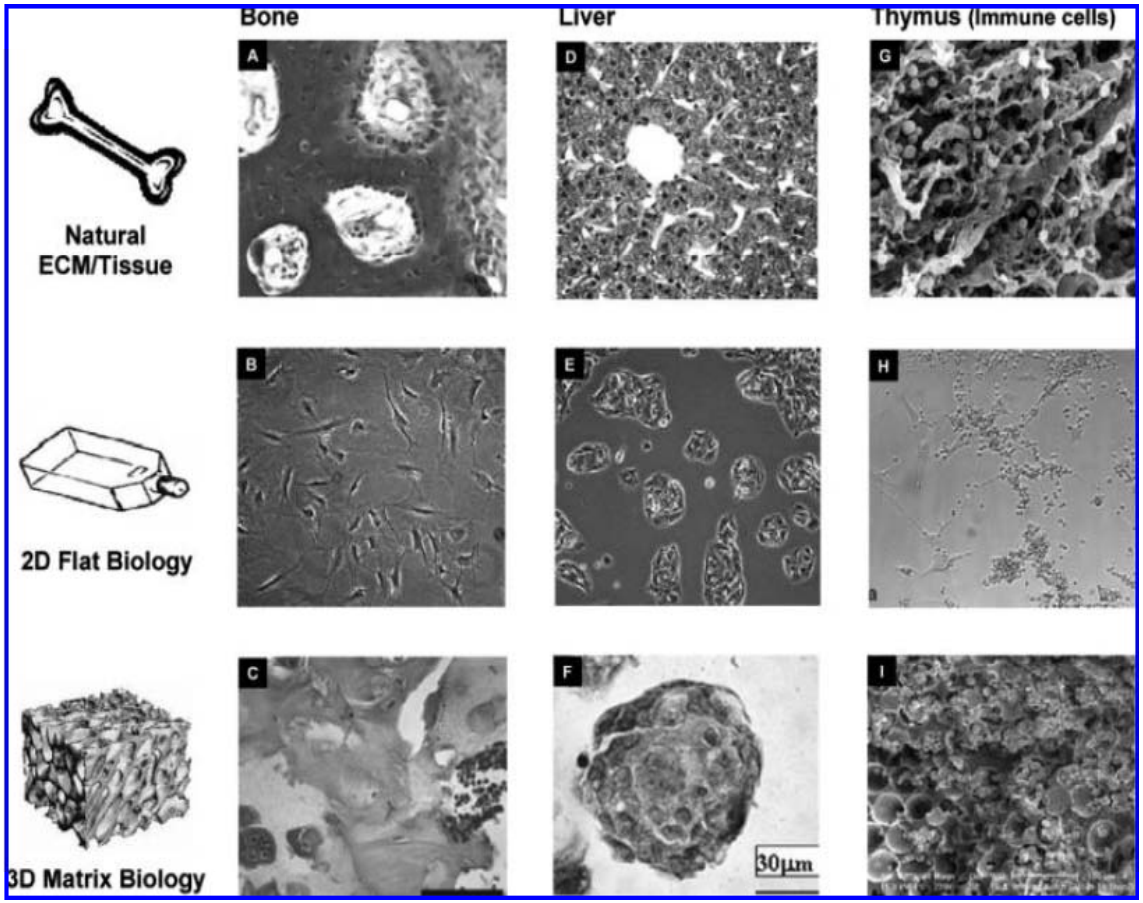


The Circulation System



(a) Schematic diagram of the two chamber system with medium circulation.
(b) A working two chamber system.

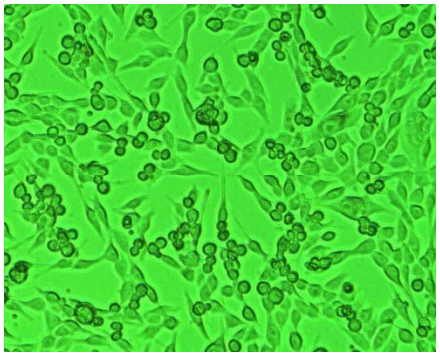
Why 3D Cell Culture?



Comparison of the cell and tissue morphology among nature and 2D/3D culture conditions

Lee *et al. Tissue Eng Part B Rev*, 2008. **14**(1): 61-86

2D cell culture of breast cancer cells



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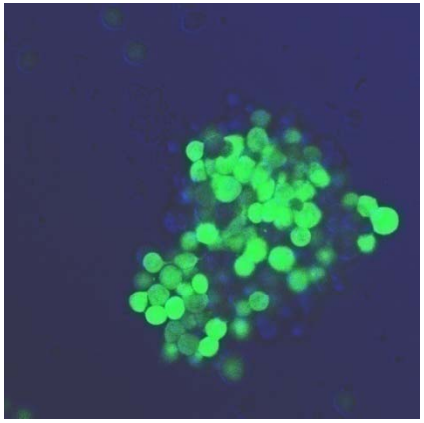
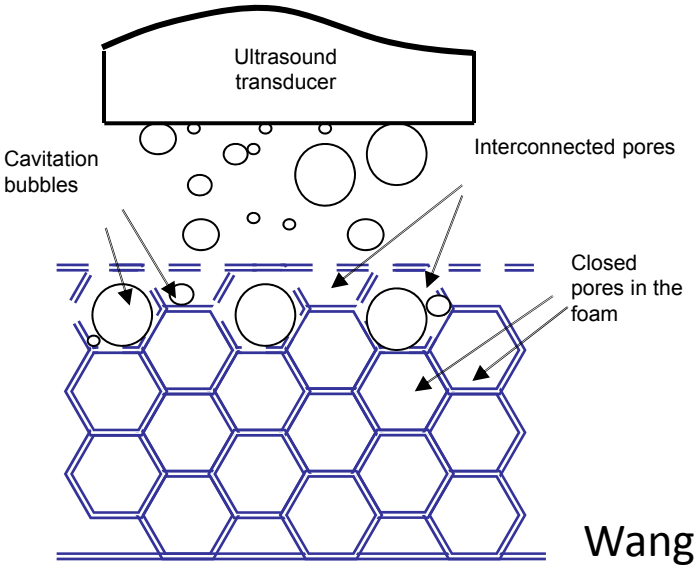
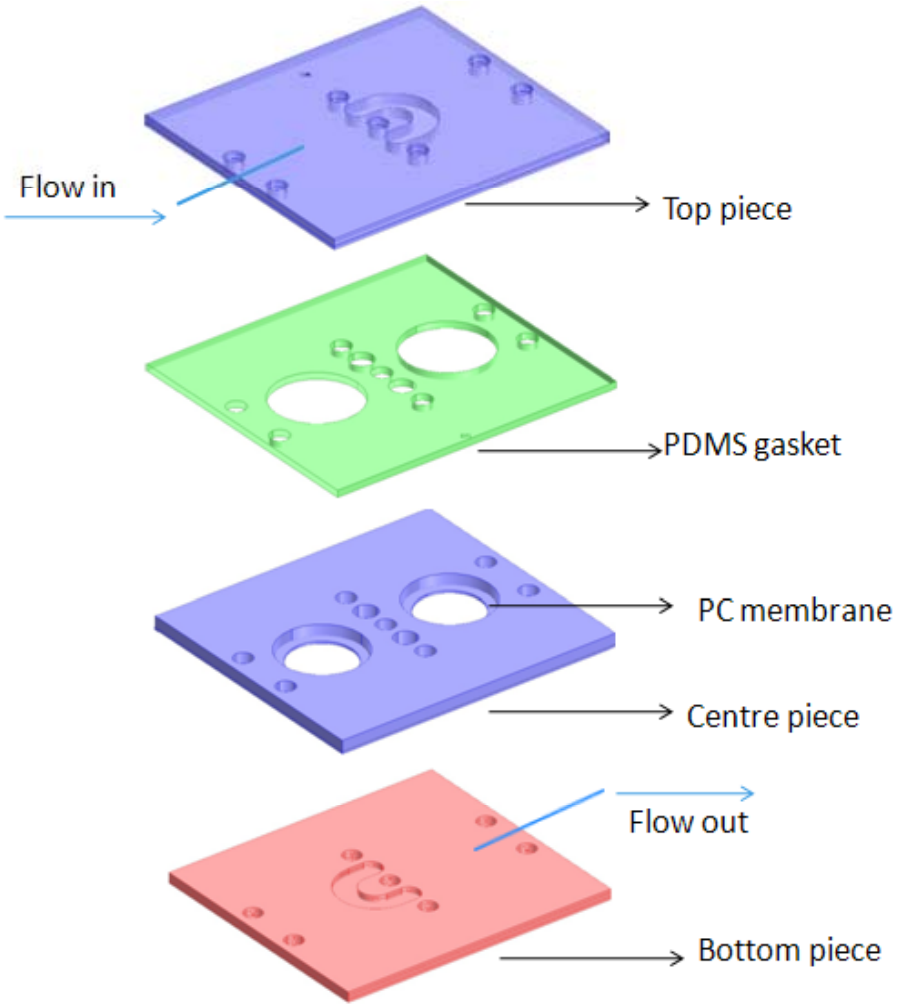


Spheroid cancel cell culture in 3D scaffold, Pore size 300 um, cultured for 21 days.

The Fabrication of the Tissue Model System



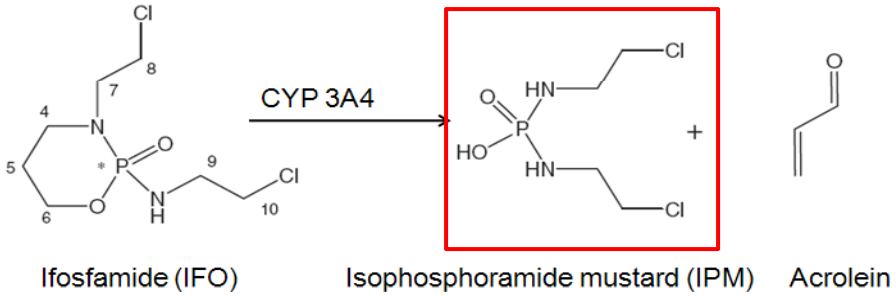


Wang et al., 2010

Drug Assays

- Two types of drugs were tested for treating brain cancer cells (GBM)
  - **Temozolomide (TMZ)**
  - **Ifosfamide (IFO)**
    - **Prodrug**

Active component



Ifosfamide (IFO) metabolism pathway

- **Two genotypes of liver cells**
  - C3A, with regular expression of CYP 3A4 enzyme
  - C3A-sub 28, over expression of CYP 3A4 enzyme

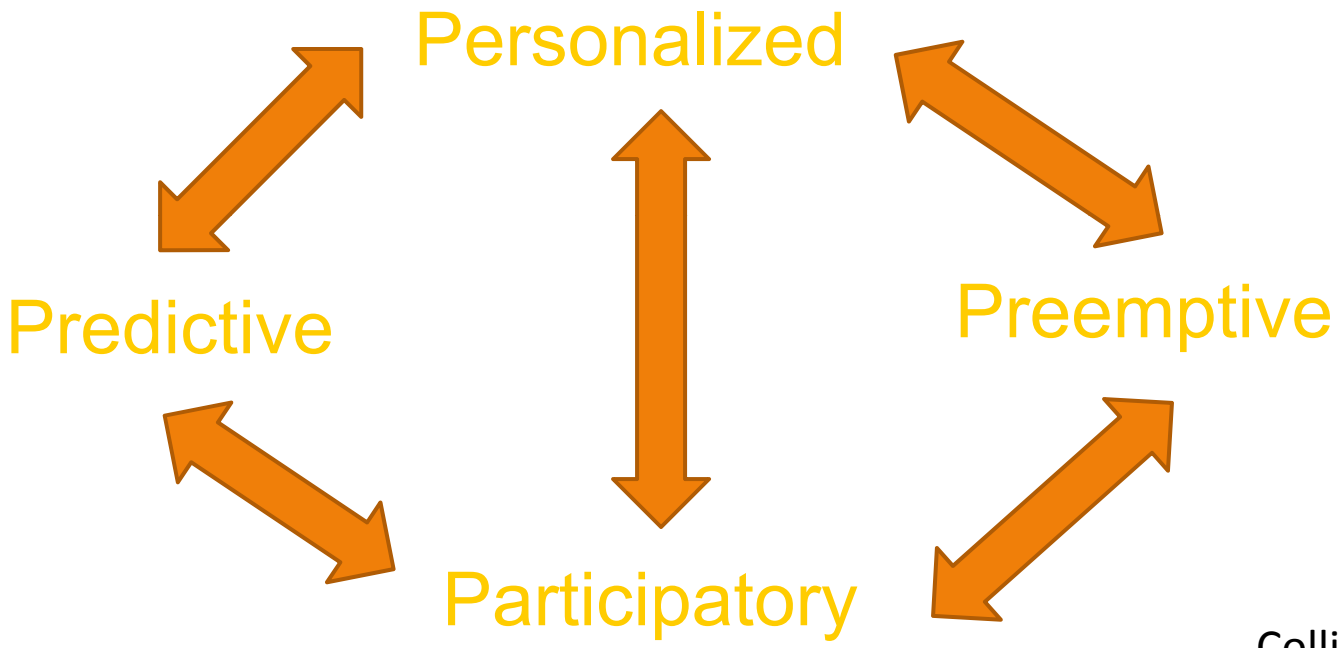
Summary of Drug Testing Results

- We have developed a perfusion-based, two-chamber 3D tissue model system.
- We have demonstrated that the system can be used to study the liver metabolism effects on cancer drugs.
- More importantly, we have shown that the metabolism effects of different genotypes of liver cell can be differentiated with this tissue model system.

Challenges and Opportunities of 3D Tissue Model Systems

- 3D tissue models are complex engineering systems that require interdisciplinary knowledge on materials, design, manufacturing, biology, and clinical applications.
- It is challenging to fabricate a large array of such 3D tissue model systems for high throughput studies.
  - Miniaturization
  - Automatic cell and liquid handling
  - Monitoring and diagnosis of cell conditions in 3D scaffolds
- The return will be significant
  - Application in initial compound screening for drug discovery
  - Application in personalized medicine

The Vision of Future Medicine: 4 P's



Collins, 2007

Era of Precision Medicine

Concluding Remarks

- Manufacturing is an activity of making goods to satisfy human needs, e.g., food, clothes, housing, and transportation.
- With the decline of traditional manufacturing in the US, biomedical manufacturing is a new frontier that will see tremendous growth, since it contributes to the satisfaction of a fundamental human need, i.e., health.
- In-vitro 3D tissue model systems will play an important role in the future paradigm of precision medicine.

Acknowledgements

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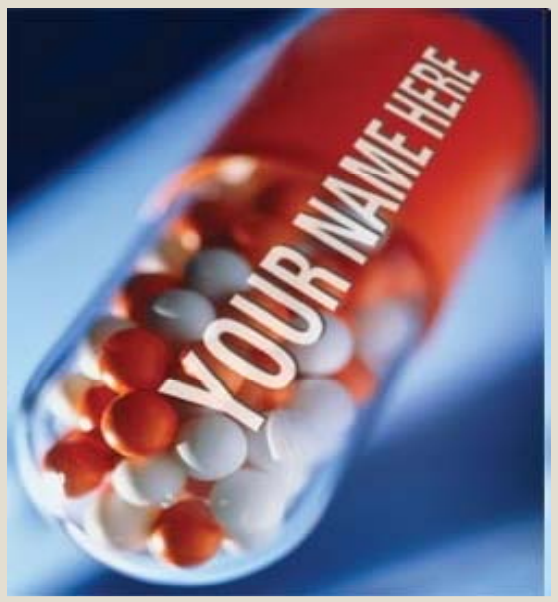
- **Collaborators at Swedish Medical Center and University of Eastern Finland Pharmacy School:** Drs. Biaoyan Lin, Gregory Foltz, Jenni Küblbeck, and Paavo Honkakoski

How would you like to have a pill with your name printed on it?



Thank you !

Questions?