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

"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”

In flow
Liver cells
Cancer cells
Out flow
Cell retaining membrane
Porous scaffolds
Cell retaining membrane

US Patent No. 7763456, 2010
Drug Discovery and Development

Lengthy and costly!
## Effectiveness of drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension Drugs</td>
<td>10-30%</td>
</tr>
<tr>
<td>Heart Failure Drugs</td>
<td>15-25%</td>
</tr>
<tr>
<td>Anti Depressants Drugs</td>
<td>20-50%</td>
</tr>
<tr>
<td>Cholesterol Drugs</td>
<td>30-70%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40-70%</td>
</tr>
</tbody>
</table>

*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.

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

How it relates to DNA sequence variation

Drug X

Ethical issues

Cost, inaccuracy

In vitro 3D tissue model system

Computer control

Peristaltic pump

3D tissue model system with real-time monitoring

WHAT STARTS HERE CHANGES THE WORLD

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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

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

- 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

- Personalized
- Predictive
- Preemptive
- Participatory

Era of Precision Medicine

Collins, 2007
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.
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How would you like to have a pill with your name printed on it?
Thank you!

Questions?