Beyond 3D-Models – Building Confidence in Microphysiological Models

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Drug Development Costs Vs. Approval

Figure 1 Costs of drug development have risen while overall probability of regulatory approval has reduced. Image taken from DiMasi JA et al. J Health Econ. 2016;47:20-33.
3 Rs
Complex *In Vitro* Models

- Centralized hub for In Vitro Alternatives (IVA)
- IVA Industry Group
Cellular growth and Chemical Test

Microfluid design
Inoculation
Cellular growth and Function establishment
Physical test

<table>
<thead>
<tr>
<th>Material</th>
<th>Relevant Property</th>
<th>Proposed Application</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Collagen (Chitosan)</td>
<td>Biocompatibility, versatile control of structure and chemistry</td>
<td>Biosensing, film assembly</td>
<td>[21,22]</td>
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<tr>
<td>Silkworm (Bombyx mori)</td>
<td>Biocompatibility, mechanically robust, flexibility, high mechanical modulus, and toughness</td>
<td>Fabrication of microfluidic channel</td>
<td>[23,24]</td>
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<tr>
<td>Agarose hydrogel</td>
<td>Low cytotoxicity, biodegradability, mechanical stability at low solid fractions</td>
<td>Cell culture, sensors, and actuators</td>
<td>[25-27]</td>
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<tr>
<td>Teflon</td>
<td>Ease of fabrication with maximum chemical resistance</td>
<td>High precision assay, super clean tools, valves, and pumps fabrication</td>
<td>[28]</td>
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<tr>
<td>Acrylonitrile Butadiene Styrene (ABS)</td>
<td>High resolution, excellent surface finish</td>
<td>Making of the master model, microfluidics interface (MI), pathogen detection, biological assay</td>
<td>[20-34]</td>
</tr>
<tr>
<td>Photocurable resin/polymer</td>
<td>Very high resolution with small features</td>
<td>Biology observation of cell growth</td>
<td>[35,36]</td>
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<tr>
<td>ABS, polycarbonate, polyphosphazene, elastomers</td>
<td>Cheap material, ease of support removal</td>
<td>Pathogen detection of bacteria and viruses</td>
<td>[37,38]</td>
</tr>
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<td>Polyamide</td>
<td>Fast build speed, multi-material printing, very durable and high-temperature stable material</td>
<td>Making of the master mold</td>
<td>[39,40]</td>
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<tr>
<td>Hydrogels</td>
<td>Swelling and contraction, act as sensors and actuators</td>
<td>Self-regulating valves, microarray, drug release systems, binding of antigens and proteins and glucose. Flow sensors pH regulation, flooding cooling devices.</td>
<td>[29,41,42]</td>
</tr>
<tr>
<td>Polymers methacrylate (PUMA)</td>
<td>Economical to manufacture, biocompatible, nontoxic, strong electrosome mobility</td>
<td>High-aspect-ratio microstructures</td>
<td>[43]</td>
</tr>
<tr>
<td>Polyethylene-glycols (PEGs)</td>
<td>Relatively inexpensive, available in a wide variety of molecular weights, biocompatible, negligible cytotoxicity</td>
<td>Microfluidic valves, Channel cover to improve the microfluidic lifetime</td>
<td>[44,45]</td>
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<tr>
<td>Polyanhydrides (PHAs)</td>
<td>Biocompatibility, tunable biodegradability</td>
<td>Microfilm barrier for vapor and oxygen</td>
<td>[46]</td>
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<tr>
<td>Gelatin methacrylate (gel-MA)</td>
<td>Photopolymerizable, porous membrane</td>
<td>Mechanistic vascular and valvular biology cell support matrix</td>
<td>[47,48]</td>
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<tr>
<td>Polylactic acid (PLA) and Polylactic acid (PGA)</td>
<td>Tunable biodegradation</td>
<td>Porous scaffold for cell culture with better adhesion</td>
<td>[49]</td>
</tr>
<tr>
<td>Poly(propylene carbonate) (PPC)</td>
<td>Biocompatibility, design adaptability, mechanical compliance, low cytotoxicity, degradability</td>
<td>3-D microfluidic system, Microbioreactor</td>
<td>[50]</td>
</tr>
<tr>
<td>Poly(ethylene glycol) diacylate (PEGDA) and gelatin methacrylate</td>
<td>Biocompatibility, neo-vascularization potential, multi-material fabrication capability at a high spatial resolution</td>
<td>Tissue engineering, regenerative medicine, and bio-sensing</td>
<td>[51]</td>
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<tr>
<td>Poly(methyl methacrylate)</td>
<td>Favorable mechanical and thermal resistance, chemical compatibility</td>
<td>Genomic analysis</td>
<td>[52]</td>
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<tr>
<td>Styrene Ethylene Butylene Styrene (SEBS)</td>
<td>Biocompatibility, Rheological characteristics</td>
<td>Fabrication of complex and more sophisticated microfluidic networks (µFNs)</td>
<td>[53]</td>
</tr>
<tr>
<td>Styrene Ethylene Butylene Styrene (SEBS)</td>
<td>Electrical surface properties, stable and relatively high zeta potential magnitude</td>
<td>Microcapsules for Electroskinetic Applications</td>
<td>[54]</td>
</tr>
<tr>
<td>Styrene Ethylene Butylene Styrene (SEBS)</td>
<td>Reduced drug absorption, Optical transmittance, Mechanical performance</td>
<td>Cell culture</td>
<td>[55]</td>
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</table>
Tissue Chip Testing Centers

Texas A&M University, College Station

TEX-VAL: Texas A&M Tissue Chip Validation Center

Massachusetts Institute of Technology

“Translational Center of Tissue Chip Technologies” for Quantitative Characterization of Microphysiological Systems

University of Pittsburgh

University of Pittsburgh Microphysiological Systems Testing Database Center
Technology Transfer of the Microphysiological Systems: A Case Study of the Human Proximal Tubule Tissue Chip

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2D and 3D platforms

University of Pittsburgh Drug Discovery Institute Microphysiology Systems Database (https://mps.csb.pitt.edu/).
### Duration
- Set up time including cells
- Viability
- Activity / metabolic functionality

### System
- Cell composition
- Physiological function
- Capacity
- Maintenance level
- Throughput
- Space requirements
- Equipment requirements
- Microfluidics
- Controls

### Abilities
- Sampling
  - Frequency (some systems do not allow for daily sampling)
  - Type (liquid, histology)
- Imaging
  - In situ
Testing Parameters

- Cell sourcing including commercial versus non-commercial
- Media sourcing including commercial versus non-commercial

Testing

- Protein and gene expression
- Reproducibility level
- Comparisons
  - 2D systems
  - In vivo models
- Baseline function assays
- Toxicity assays
- In vitro to in vivo extrapolations

Restrictions

- In house only
- Limited cell types
Target ID and Validation

- Hazard Identification: Confirm presence of relevant targets
- Risk Assessment: Baseline effect on physiology
- Mechanism of Action: Assess impact on disease phenotype
- Risk Mitigation: Identify and assess potential side effects

Lead Identification

- Hazard Identification: Thousands of compounds
- Risk Assessment: Tens to hundreds of compounds
- Mechanism of Action: Two to three compounds
- Risk Mitigation: One to two compounds

Lead Optimisation

- Hazard Identification: High Throughput systems
- Risk Assessment: Medium to high throughput systems
- Mechanism of Action: Low throughput systems
- Risk Mitigation: Low throughput systems

Preclinical Safety

- Hazard Identification: Mechanistic understanding or safety profiling
- Risk Assessment: Linked organs e.g. for drug distribution
- Mechanism of Action: Boutique individual organs for mechanism or safety

Precision medicine

Orphan diseases

Nanomedicine
Organ

- Multicellular architecture
- Native tissue characteristics
- Whole organ physiology & phenotype
- Long term stability & reproducibility

Disease

- Pathophysiology
- Recapitulation of clinical responses
- High-throughput & -content
- Personalized medicine

model requirements

Materials
Large-scale manufacturing
Cells and media
Samples for analysis
Readouts
Species?

HUMAN

ANIMAL
IQ MPS Affiliate
Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective

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Developing Organs On-a-Chip: Chemical Safety Research Collaborators Provide Research Review

University of Washington

Vanderbilt University

Texas A & M University

University of Wisconsin - Madison