Multi-Organ-Chip technology

Lush Prize Conference 2018

Ilka Maschmeyer
TissUse – Location

Oudenarder Strasse 16
13347 Berlin

pharma contracts
Manufacturing
iPS cell banking

Consumer product industry contracts
organogenesis research
“Human-on-a-chip” development

Gustav-Meyer-Allee 25
13355 Berlin
Drug development today

- Pre-clinics: up to $2.5 B, 13.5 years
- Discovery, Lead optimization, Pre-clinics, Phase I, Phase II, Phase III, Submission, Patients' Market

- Pre-clinical: laboratory animals, human 2D & 3D-cell culture

- Safety: ~60 volunteers/substance
- Efficacy: ~3000 patients/substance

- Time (years):
  - -13.5
  - -11
  - -9
  - -8
  - -6.5
  - -4
  - -1.5
  - 0

- Today:
  - laboratory animal studies
  - in vitro testing
  - clinical trials

- Market

- TISSUSE
  - Emulating Human Biology
The drug development dilemma

animal models
systemic but not human

static 2D & 3D
human cell culture
human but not systemic

"Human-on-a-Chip"
human and systemic
Multi-Organ-Chip platform development


2-Organ-Chip
- prime metabolic organ
- blood protein supplier
- target for cosmetics
- dermal administration

4-Organ-Chip
- target for food additives
- oral administration
- urine removal
- toxicity target

Skin
Liver
Intestine
Kidney

Human-on-a-Chip

→ 2018
Industrial adoption of the skin-liver model

Substance administration route matters

Beiersdorf

Tech transfer

CRABP2 (Day 7)
(cellular retinoic acid–binding protein 2)

CRABP2/GAPDH fold change

li = liver; sk = skin

EpiSkin®

Air
Time course of retinoic acid penetration through the EpiDerm model in transwells

LC/MS Q-Exactive analyses of pooled samples obtained from 2 skin models/time point

Applied: 3 µl of 83.4 µM RA in 0.1% DMSO/H₂O. Endvolume 250 µl
Retinoic acid metabolite analyses
Retinoic acid metabolite analyses

induced direct glucuronidation

Repeated systemic exposure

Repeated topical exposure

Cumulative long-term effects assessable
Systemic vs topical application: permethrin metabolite kinetics

- Metabolite kinetics of single topical application were different from a single *systemic* application
- Repeat topical application resulted in similar metabolic profile to repeated systemic application – only M2 and M16 were present at lower concentrations
MOC model lab comparison: permethrin metabolite kinetics

**TissUse**
Systemic: single application

![Graph showing metabolite peak area over time for TissUse system with single application.](image)

**TissUse**
Systemic: repeat application

![Graph showing metabolite peak area over time for TissUse system with repeat applications.](image)

**BDF**
Systemic: single application

![Graph showing metabolite amount over time for BDF system with single application.](image)

**BDF**
Systemic: repeated application

![Graph showing metabolite amount over time for BDF system with repeated applications.](image)
# Our 3D organoid engineering pipeline

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Tissue Explants</th>
<th>Primary Cells/iPS-Derived</th>
<th>Cell Lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver 1.</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Intestine 2.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Kidney 3.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Brain 4.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Pancreas 5.</td>
<td>islets</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscles 6.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Adipose tissue 7.</td>
<td>subcutaneous explants</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Skin 8.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hair 9.</td>
<td>follicular unit extraction</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lung 10.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Bone-marrow 11.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lymph node* 12.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Vasculature 13.</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>3D Lung tumor</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

*in collaboration with ProBioGen, Germany

- **13 single organ models established**
- **12 multi-organ combinations established**

(as of July 2017)

- validated commercially available 3D models
Examples of Established Multi-Organ-Chip Assays

Skin – Liver
Wagner et al. (2013)
Maschmeyer et al. (2015)

Intestine – Liver
Maschmeyer et al. (2015)

Liver – Neuro
Materne et al. (2015)

Liver – Pancreas
Bauer et al. (2017)

Immunocompetent Skin (biopsies) and hair follicles
Atac et al. (2013)

Liver – Lung

Skin – 3D Tumor
Hübner et al. (2018)
(accepted)

Bone marrow
Sieber et al. (2017)

Intestine – Liver – Skin – Kidney
Maschmeyer et al. (2015)

Intestine – Liver – Neuro – Kidney
Ramme et al. (2018)
(submitted)

Optional: add vasculature
Schimek et al. (2013)
Hasenberg et al. (2015)
Outlook: Our Upcoming MOC-Robot Will Further Increase Efficiency and Cost-Effectiveness of Our End-to-End-Solution

- Automated chip operation (24 chips per robot)
- Integrated cold storage for different liquids
- Automatic media exchange, liquid sampling, microscopy, etc.
- Robot facility with customized number of robots from 2019
Acknowledgements

Our “Humans” on a ship

Ilka.maschmeyer@tissuse.com
www.tissuse.com