TISSUSE
Emulating Human Biology

# Simplify Substance Profiling with “Human-on-a-Chip”

**Funktionsintegration in Kunststoffe**

**21. November 2018**

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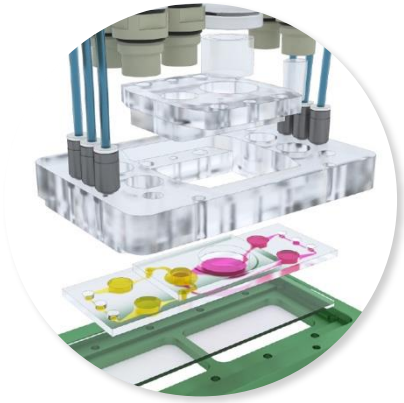
*www.tissuse.com*

# TissUse at a Glance

- Spin-off from Technical University of Berlin, founded in 2010
- Solid 3rd party funding, revenue-based financial independence
- 20 employees + 30 associated researchers
- 8 patent families, 96 patents



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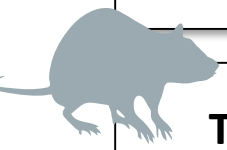
# Traditional Drug Testing Still Leads to Dramatic Failure Rates in Clinical Studies

## *Challenges*

**85 % failure rates of NCE**
from pre-clinic into clinic
*(46 % due to toxicity, 35 % due to lack of efficacy)*

**US$ 223 m*** and **precious time lost**
*(*per failed NCE)*

**25–100 million vertebrate animals**
per year used *(USA)*

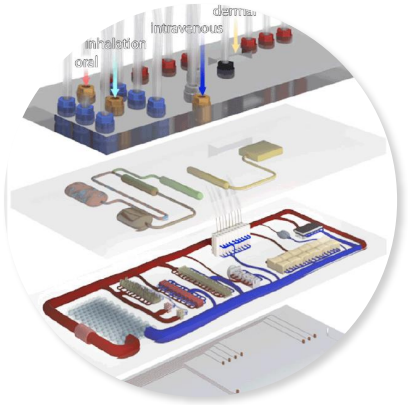


**Translation**
animal model to human **only 8 %**
*(oncology)*

Animal model: **systemic but NOT human;**

2D & 3D cell culture: **human but NOT systemic**

## *Our solution*




**Predict substance performance by targeted Multi-Organ-Chip (MOC) testing**

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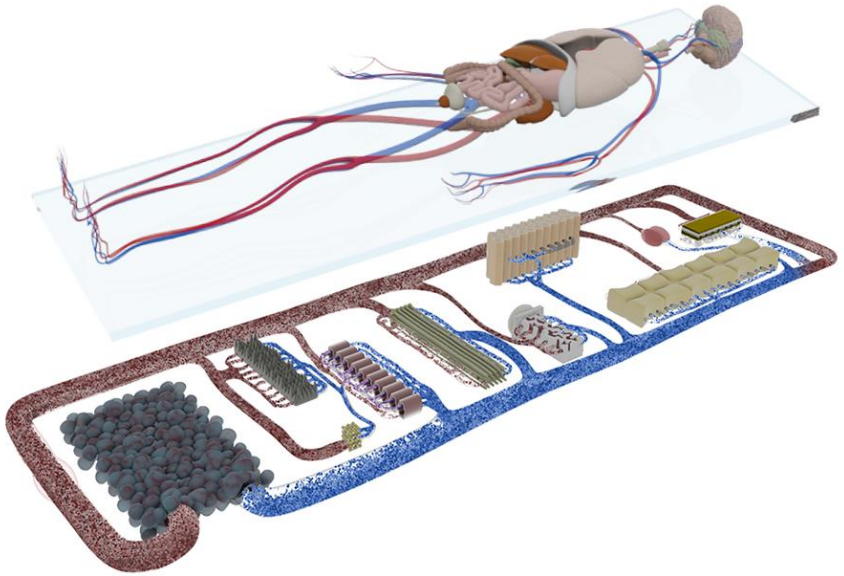
# Our Solution Approach:
## *Testing the Patient Without the Patient*

**We develop automated on-chip testing of human organ models to achieve highly relevant and accurate results:**

- Equip chips with indication-relevant organ models to measure safety/efficacy on whole organism before exposure
- Eventually, equip chip with subunits of patient's own relevant diseased organs to predict personalized treatment outcome

**Multi-Organ-(Human)-on-a-Chip:**
***human AND systemic***



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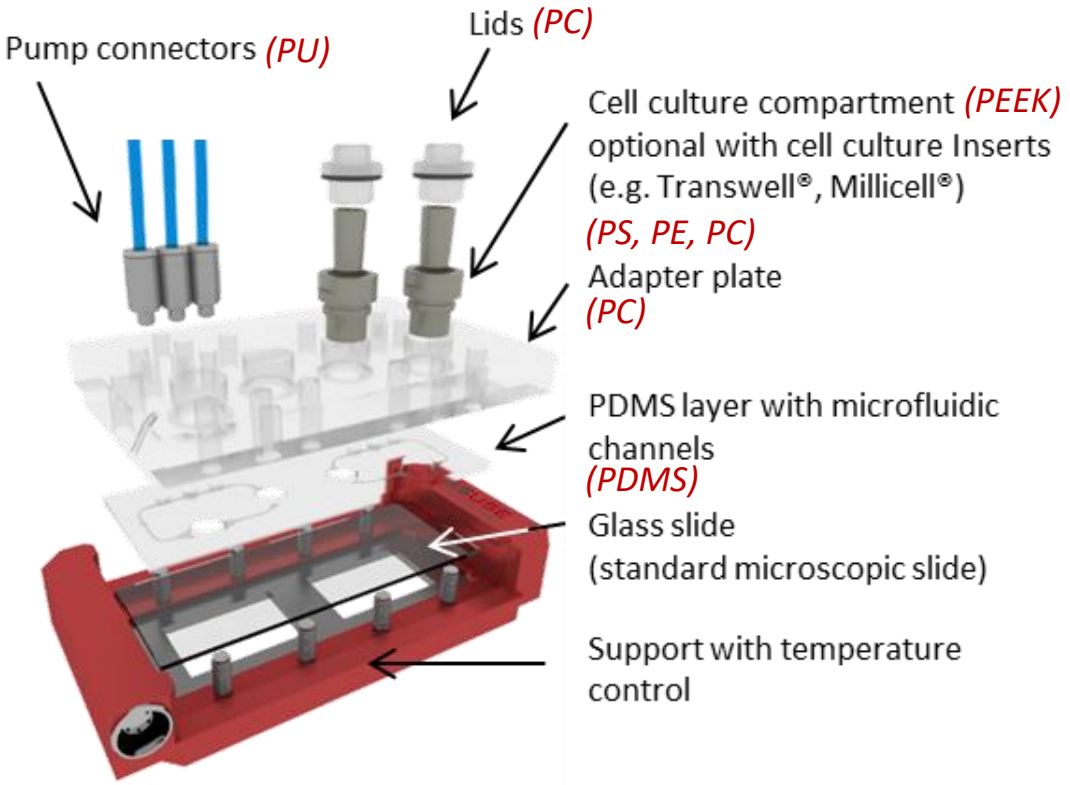
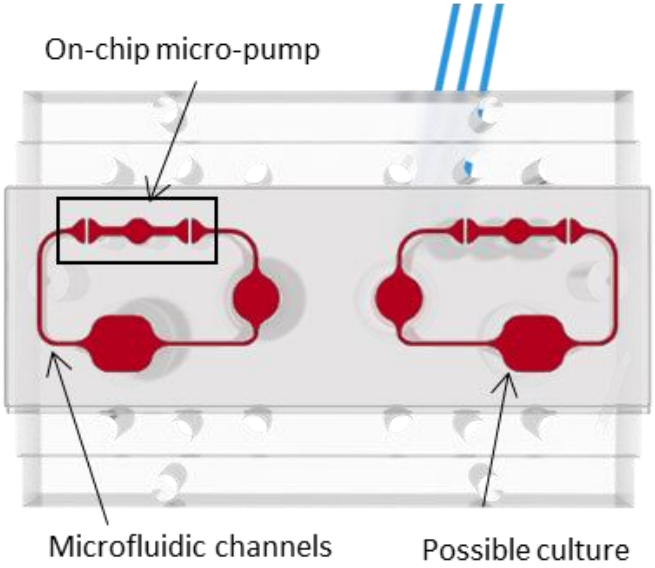
# The Multi-Organ-Chip (MOC)

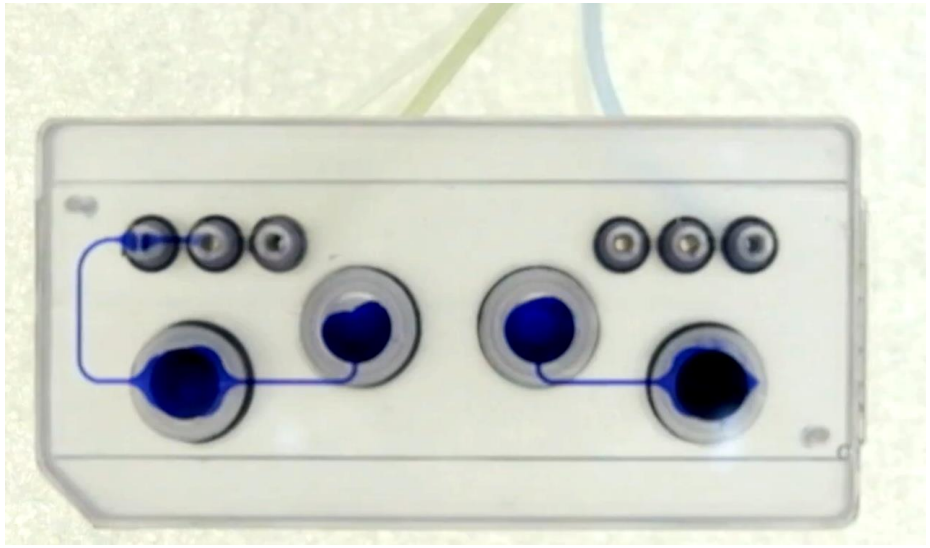
***Features:***

- Size of a standard microscope slide
- Compatible with life tissue imaging
- On-chip micro-pump enabling pulsatile flow
- Long term cultivation of iPSCs, primary cells, 3D tissues and cell lines



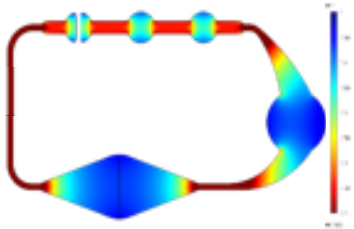
# 2-Organ-Chip



Standard cell culture inserts *(96-/12-/24-well format)*

COMSOL Multiphysics® 5.2.



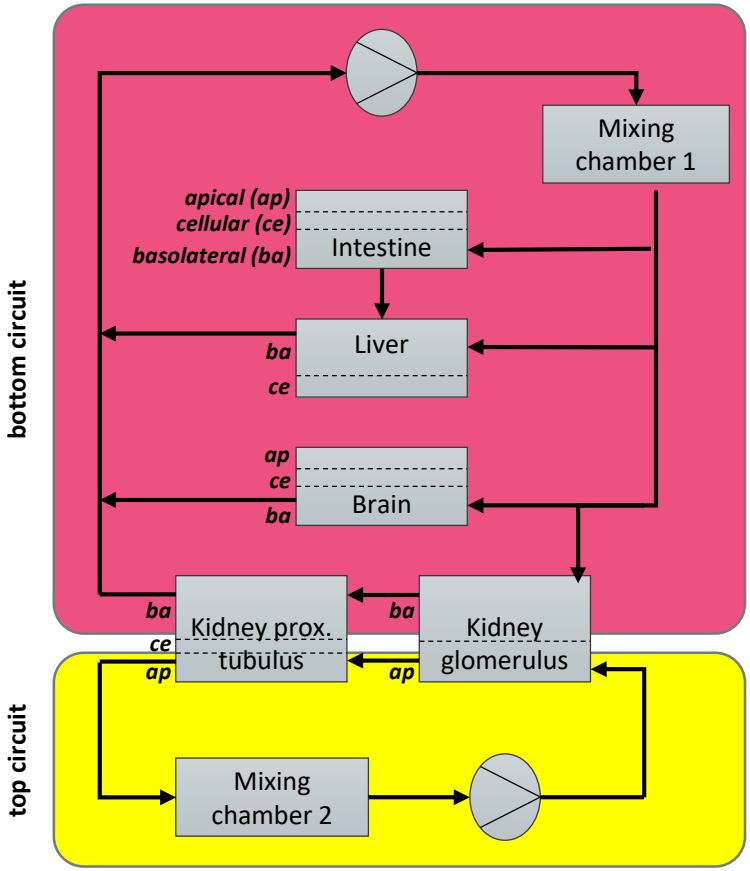
- Plug-in option for insert-based barrier models

# The 4-Organ-ADMET-Chip

*PBPK – compliant ADME profiling*

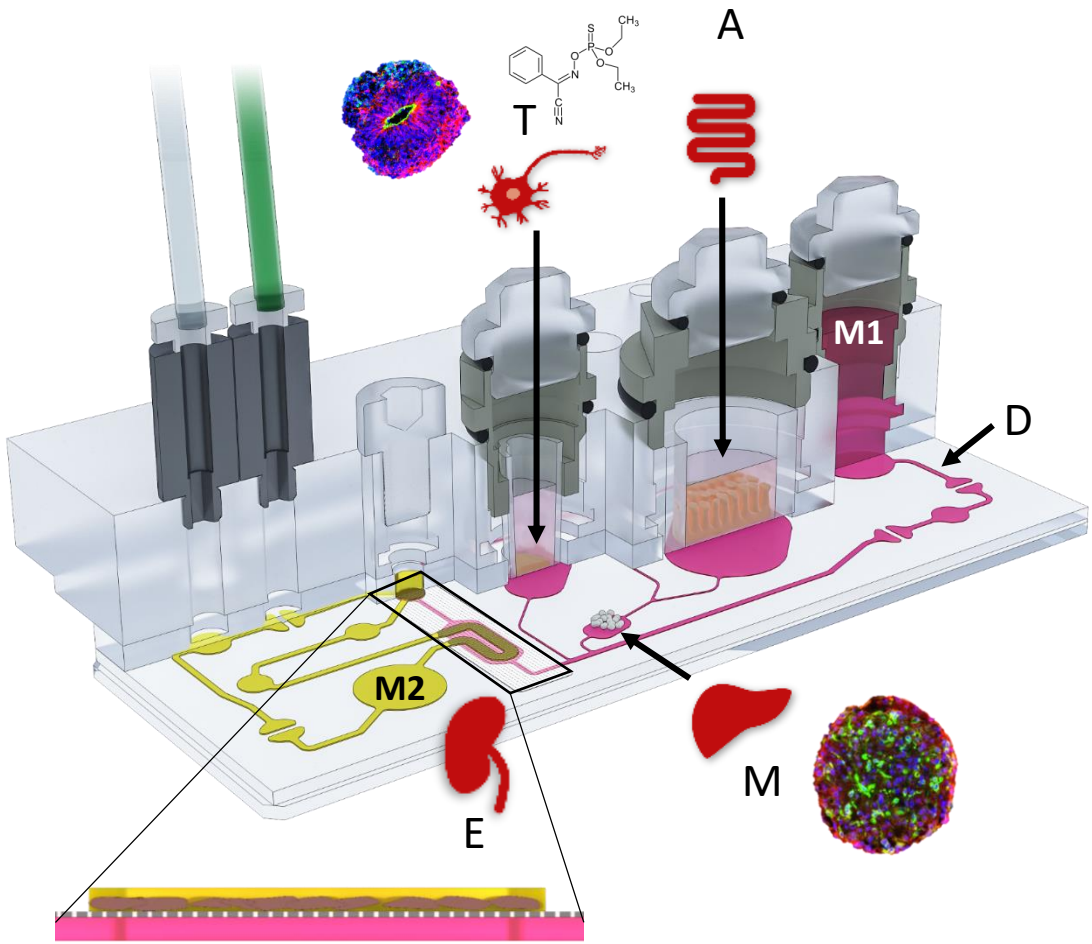
# An autologous 4-Organ-ADMET-Chip

## physiology-based pharmacokinetic model




## PBPK-compliant Chip Design

**ADMET - Absorption – Distribution – Metabolism – Excretion – Toxicity**



# Human-on-a-chip (HOC)

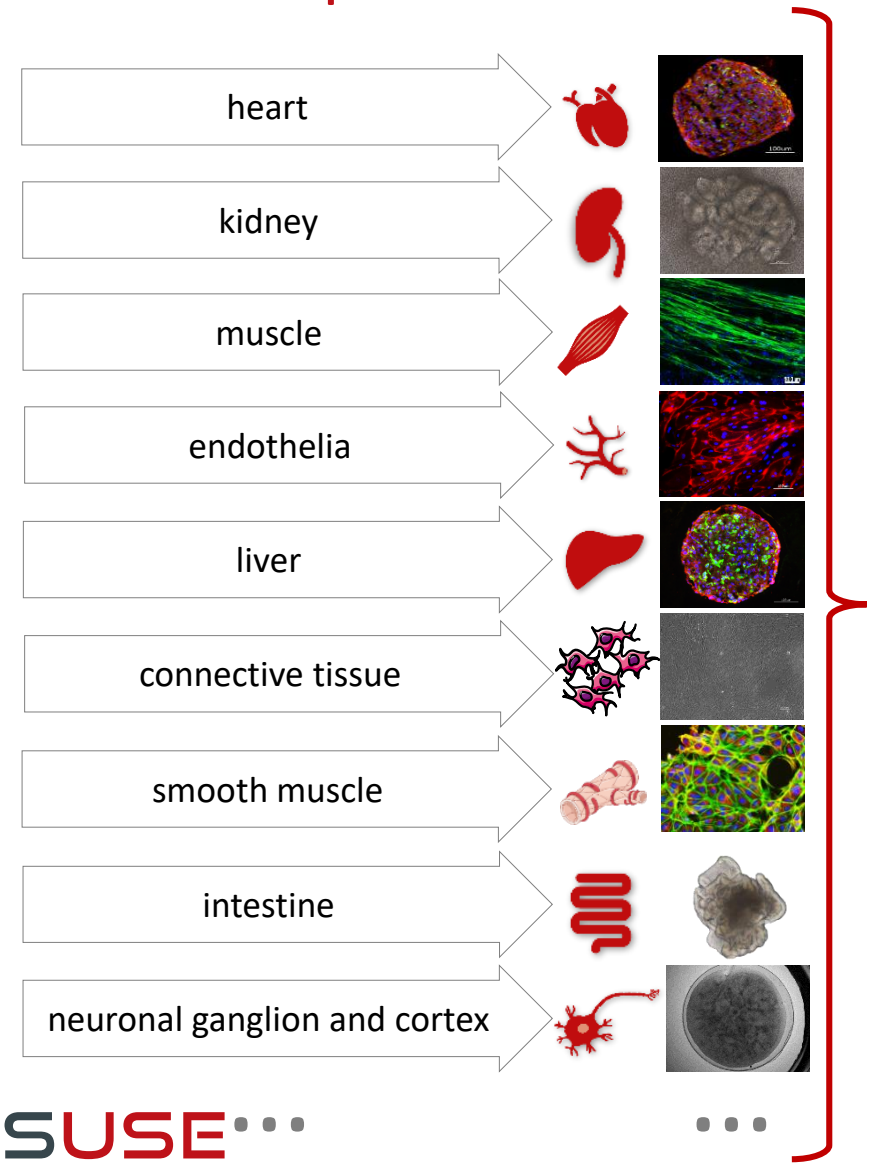
*Musculoskeletal, Circulatory system, Nervous system, Integumentary system, Immune system*

*Respiratory system, Digestive system, Urinary system,*

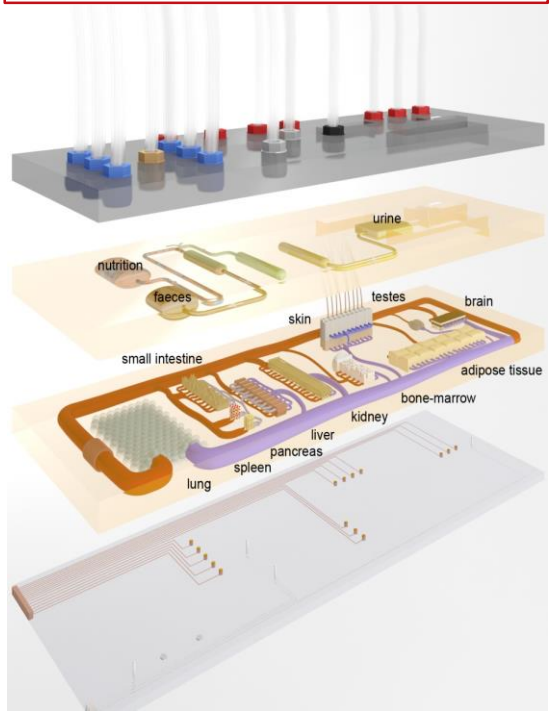
*Reproductive system, Endocrine system*

# Video Human-on-a-chip (HOC)

# The HOC concept




*Human-on-a-Chip*

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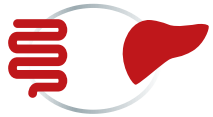
# Examples of Established Multi-Organ-Chip Assays

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)*

Bone marrow
*Sieber et al. (2017)*

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

Intestine – Liver – Neuro – Kidney
*Ramme et al. (2018)*
*(in review)*

Optional: add vasculature
*Schimek et al. (2013)*
*Hasenberg et al. (2015)*

# Examples of Industrial Adoption

| *Industry* | *Partner* | *Organ model* | *Assay format* | *Context of use* |
|---|---|---|---|---|
| Pharma safety | AstraZeneca |  Bone-marrow | 8 weeks<br>repeated exposure | Lineage specific<br>bone marrow toxicity |
| Consumer<br>products industry | *undisclosed* |  Lung – Liver | 5 days<br>single exposure | Hazard potential |
| Biotech | *undisclosed* |  Intestine – Muscle | 12 days<br>repeated exposure | Feed additives |
| Chemicals<br>& cosmetics | Beiersdorf |  Skin – Liver | 5–14 days<br>repeated exposure | i.v. versus topical<br>MoA risk assessment |
| Pharma safety | *undisclosed* |  Intestine – Liver | 14 days<br>repeated exposure | Oral absorption<br>and liver metabolism |
| Pharma efficacy | AstraZeneca |  Liver – Pancreas | 14 days<br>repeated exposure | Diabetes drugs |
| Pharma “safficacy” | BAYER |  Skin – Tumor | 5 days<br>repeated exposure | Anti-tumor drugs |
| Pharma efficacy | transgene |  Pancreas – Vasculature<br>- Tumor | 10 days<br>repeated exposure | Anti-tumor drugs |



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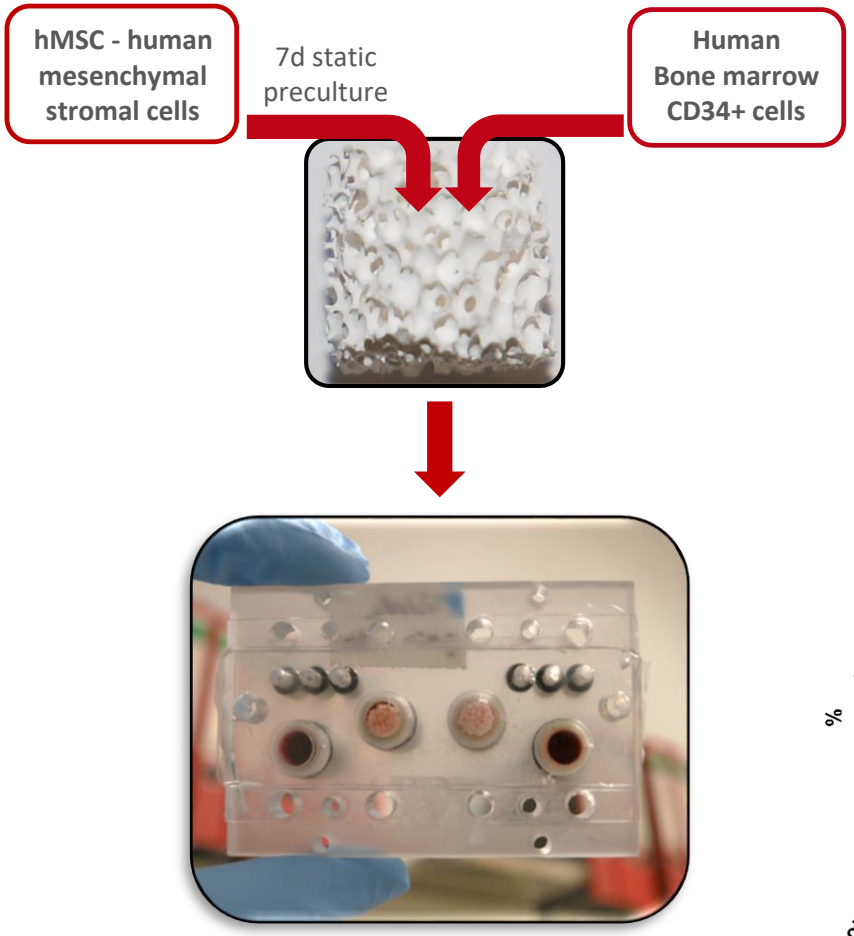
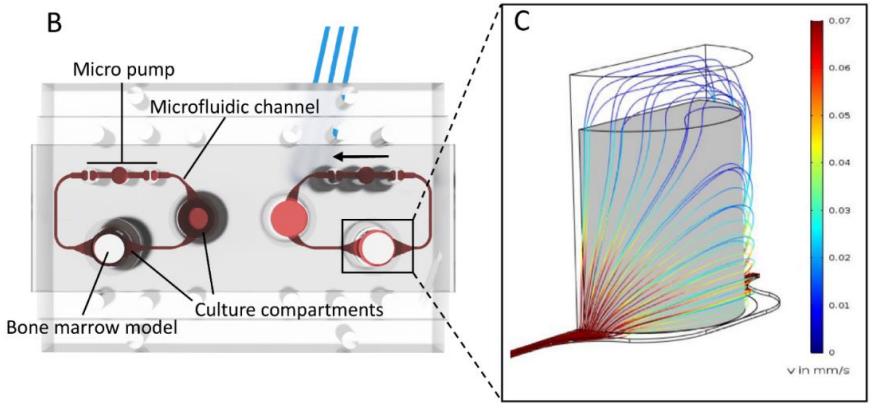
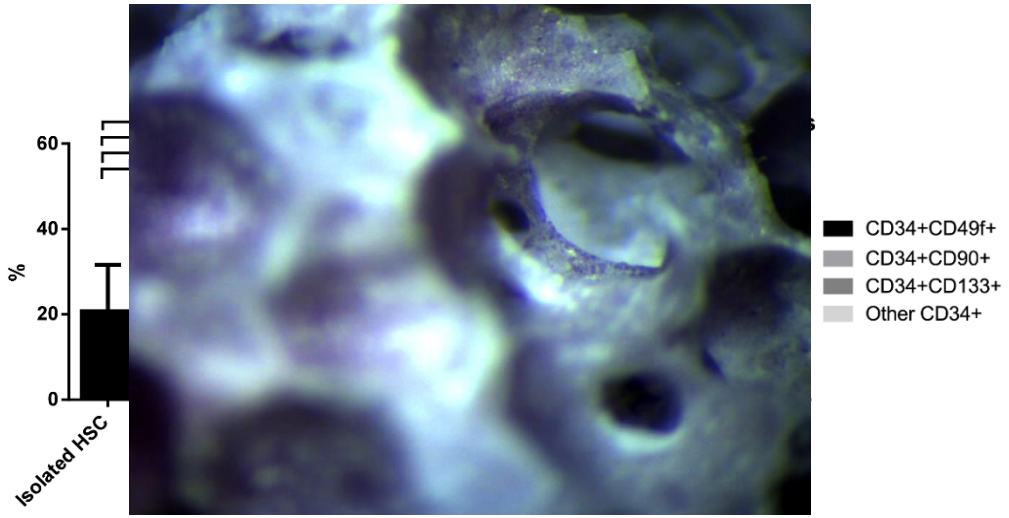
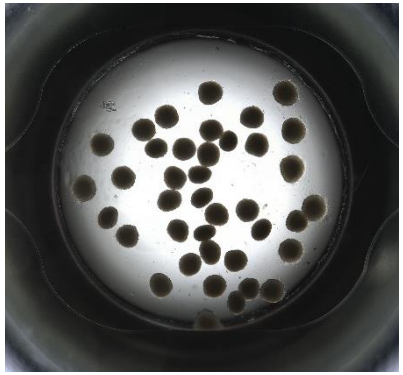
# TissUse *bone marrow* on-a-chip

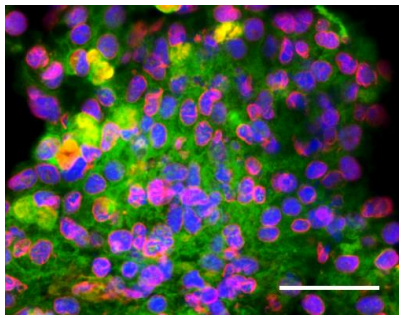


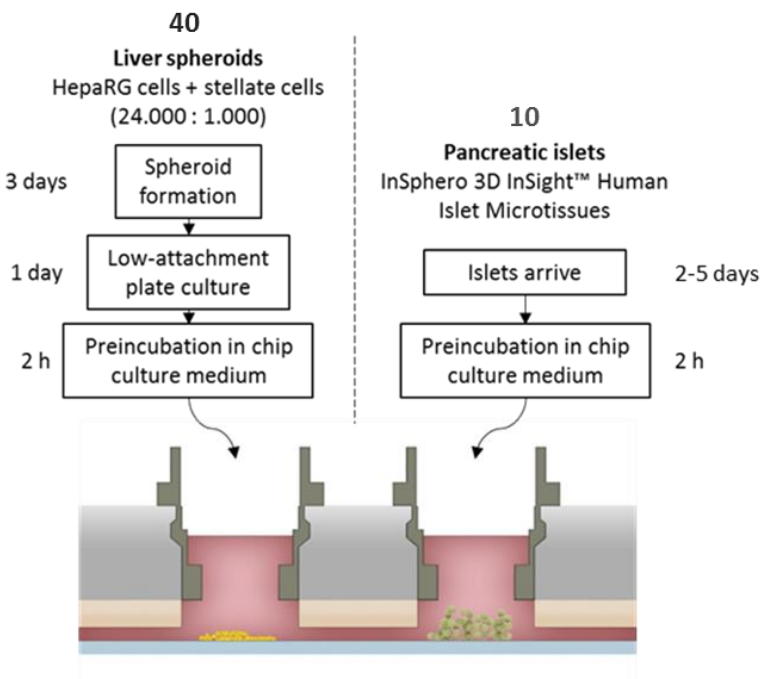



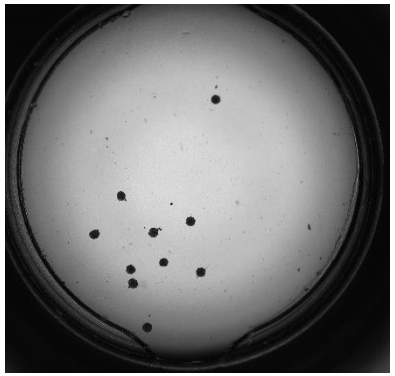
# Experimental setup of the *liver-islet co-culture*

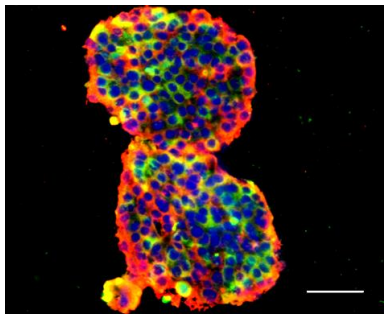




Albumin Cyp3A4 DAPI

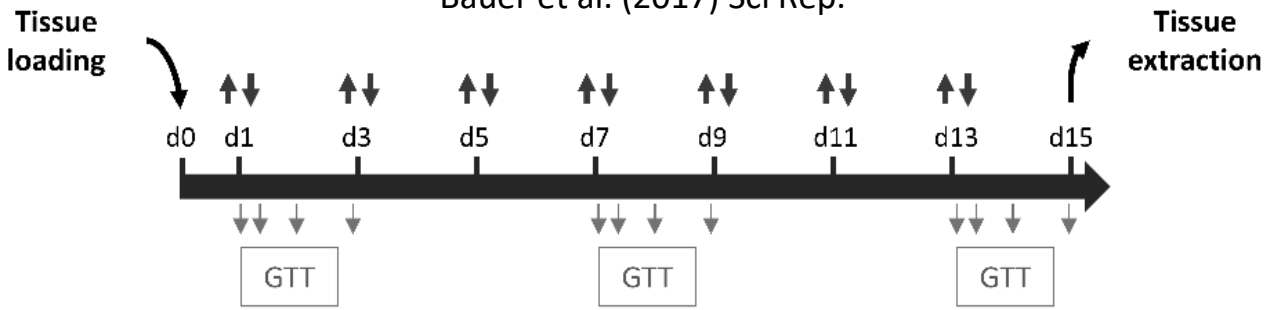




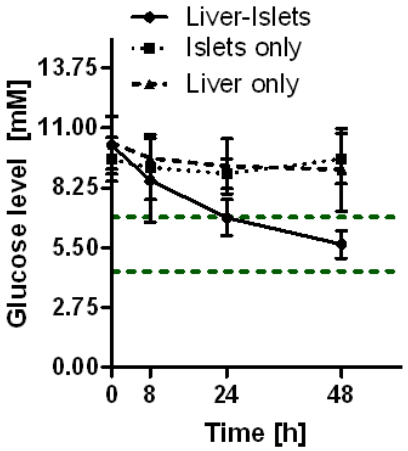
Insulin Glucagon DAPI

Bauer et al. (2017) Sci Rep.

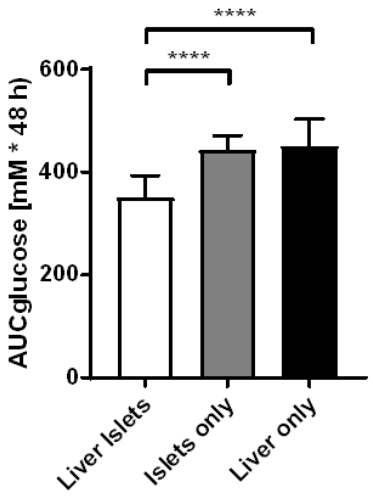


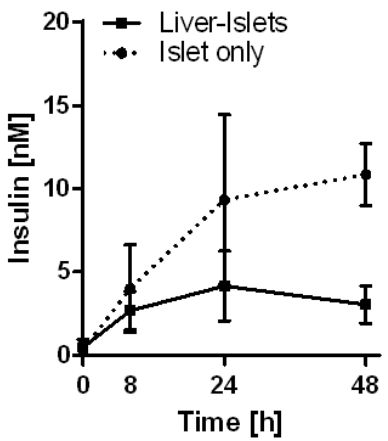

GTT=glucose tolerance test

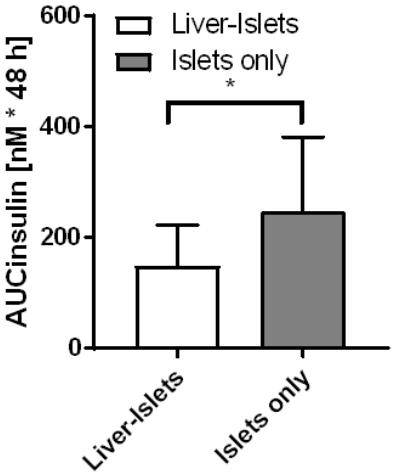
# On-chip cross-talk between pancreatic islet microtissues and liver spheroids




Dotted lines indicate physiological postprandial glucose range (3.9–7.8 mM)



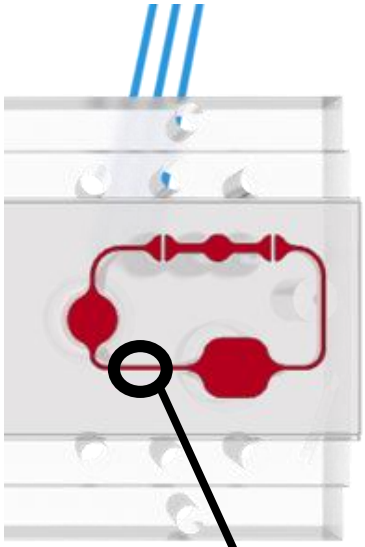



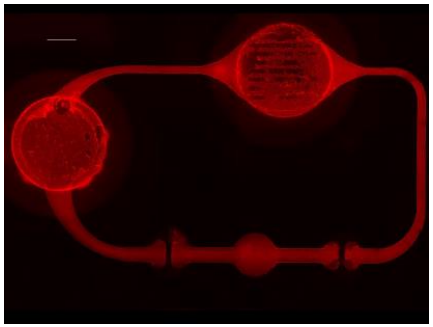




Bauer et al. (2017) Sci Rep.

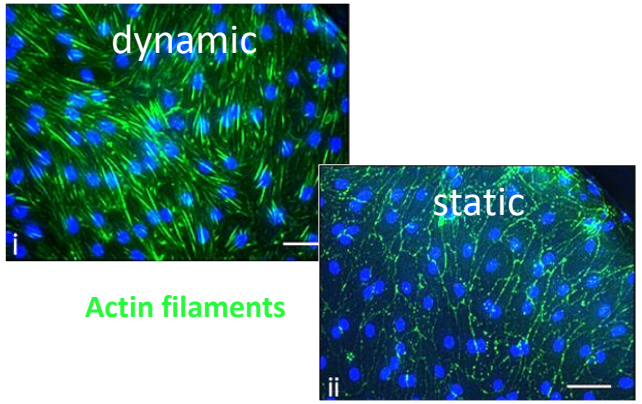
✓ **Liver-Islet crosstalk can be shown by an insulin mediated glucose utilization and a glucose level dependent insulin secretion.**

# Vascularizing Two-Organ-Chips



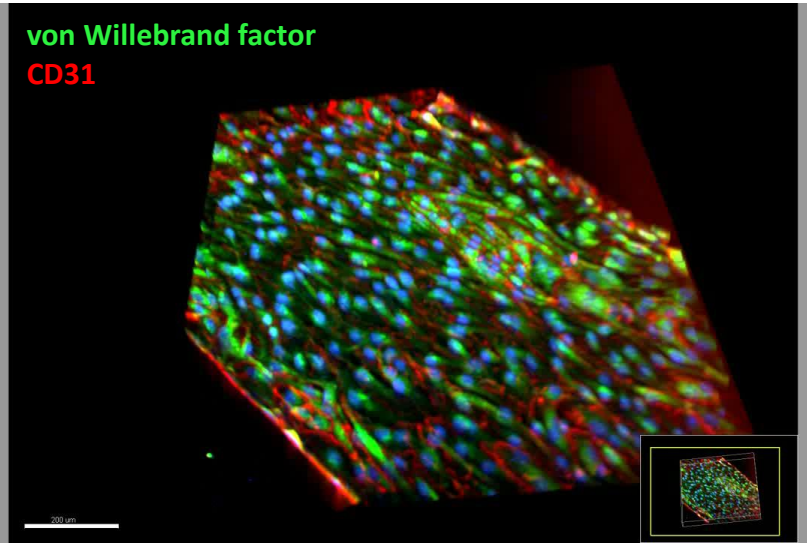


**Calcium AM** live imaging of human dermal microvascular endothelial cells (HDMEC´s) along the entire two-organ circuit




Actin filaments

66h time lapse, HDMEC coverage at pulsatile flow

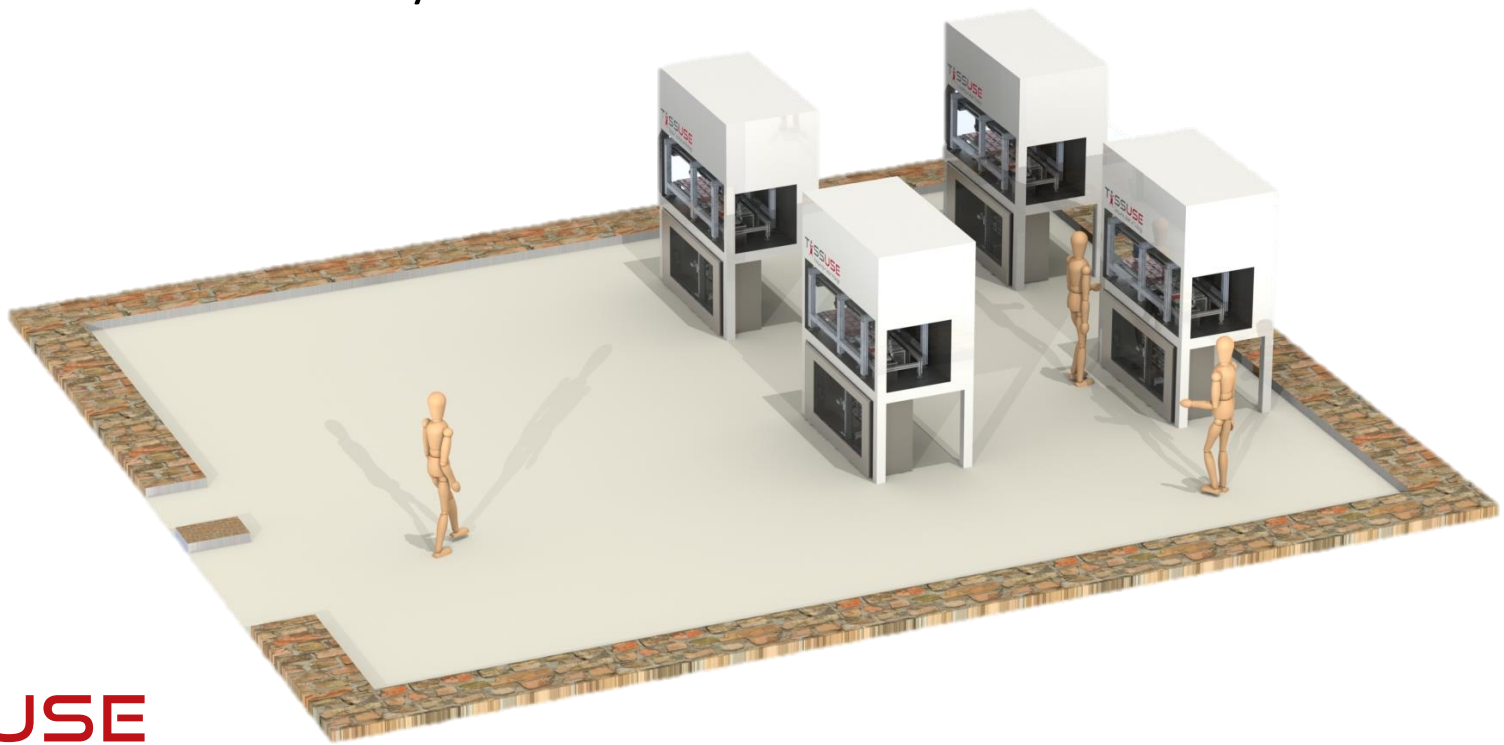






Schimek et al. (2013) LabChip

# 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 costumized number of robots from 2019



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