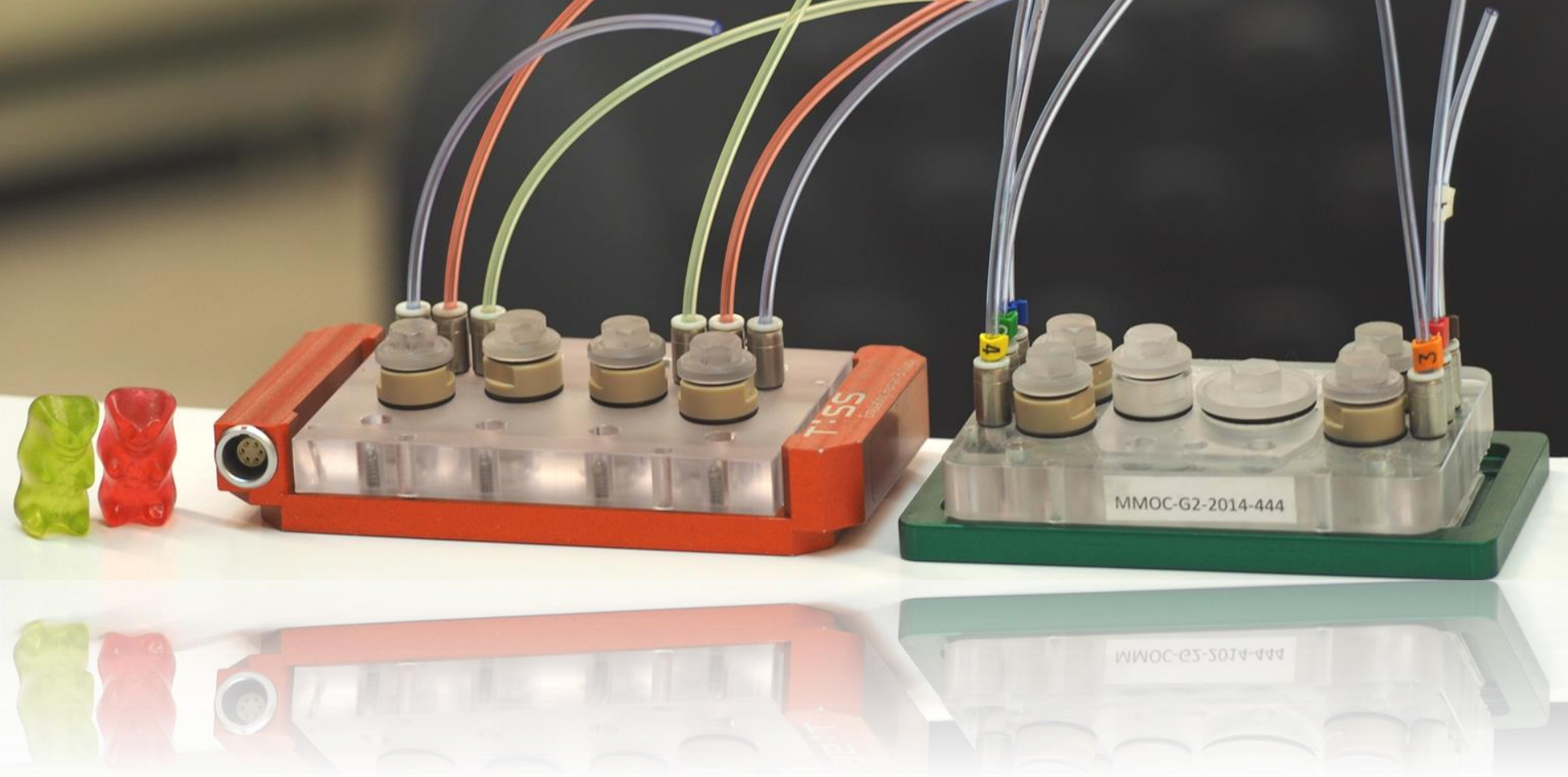


MPS – development status, first industrial adoption and current challenges

Institut für Biotechnologie
Technische Universität Berlin
Medizinische Biotechnologie

Uwe Marx
EMA 05.10.17

TISSUSE
Emulating Human Biology

t4 - Report on biology-inspired MPS

Marx et al. 2016 ***ALTEX*** 33 (3) 272-321
(CC 4.0 open access)

Microphysiological systems

are microfluidic cell culture devices capable of emulating human biology *in vitro* at the smallest biologically acceptable scale.

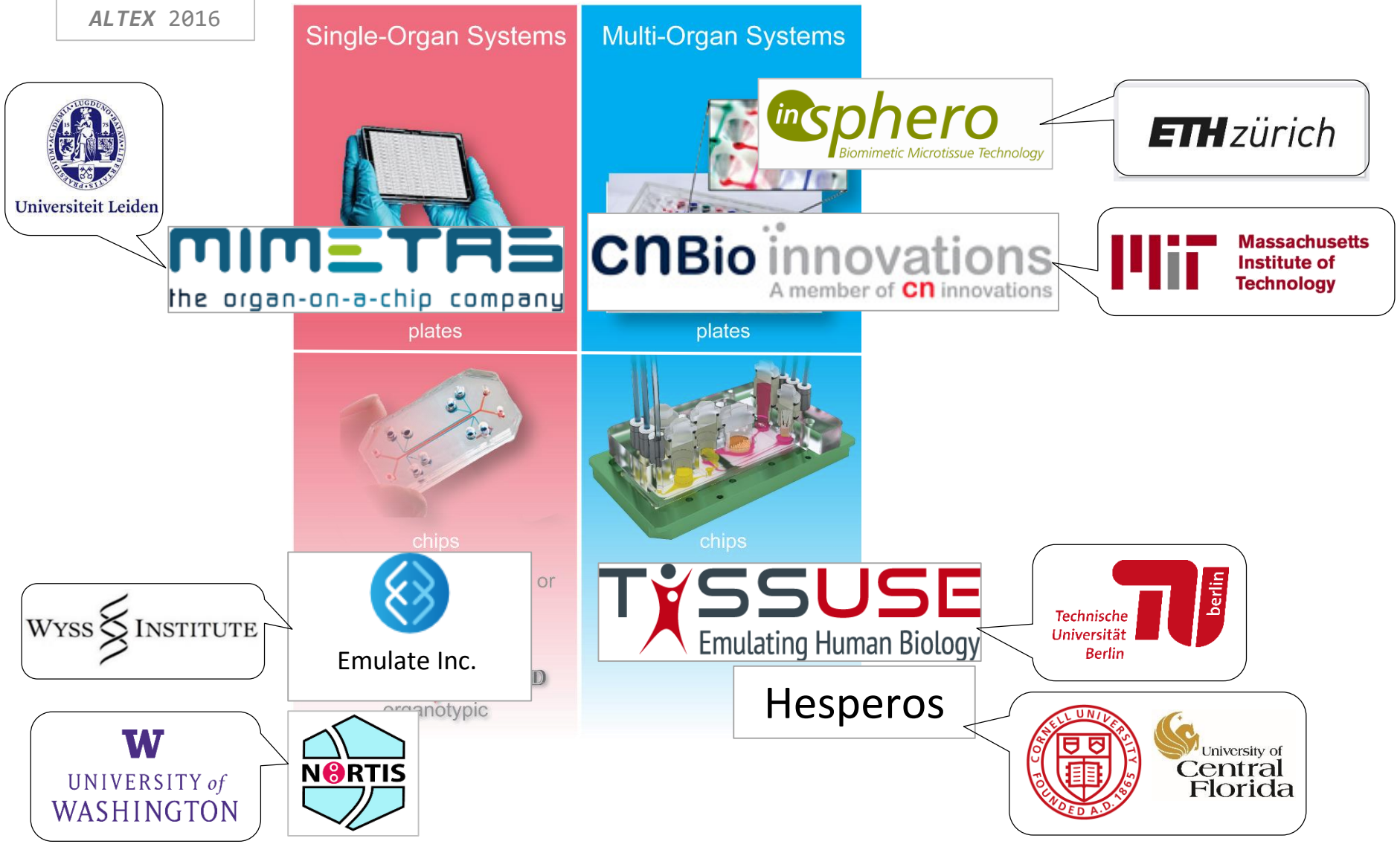
micro: at smallest biologically acceptable scale
- ➢ testing at relevant throughput
- ➢ minimum use of human tissue
- ➢ affordable assay economy

physiological: truly emulating human biology
- ➢ human organ architecture
- ➢ healthy long term homeostasis
- ➢ damage, repair, regeneration, disease

systems: Devices, supporting human-like organ maintenance
- ➢ temperature, humidity, pH, O_2-supply
- ➢ mechanical and electrical coupling
- ➢ optical imaging

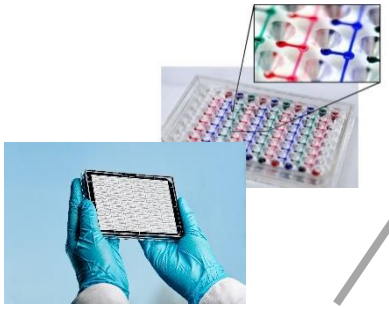
Types of MPS and key commercial providers

Marx et al.
ALTEX 2016



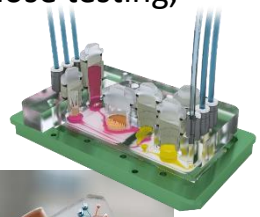
Impact of MPS-tools on drug development

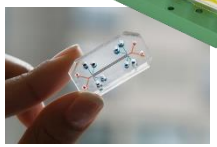
Marx et al.
ALTEX 2016



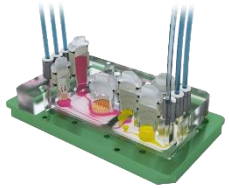
high throughput,
single tissue,
single dose testing,

high content,
systemic repeated
dose testing,





retrospective assessment of
AoPs of candidates, which failed
in late phases or post marketing



years

-13.5 Discovery | -11 Lead optimization | -9 Pre-clinics | -8 Phase I | -6.5 Phase II | -4 Phase III | -1.5 Sub-mission | 0 Patients Market

laboratory animal studies - *in vitro* testing - clinical trials -

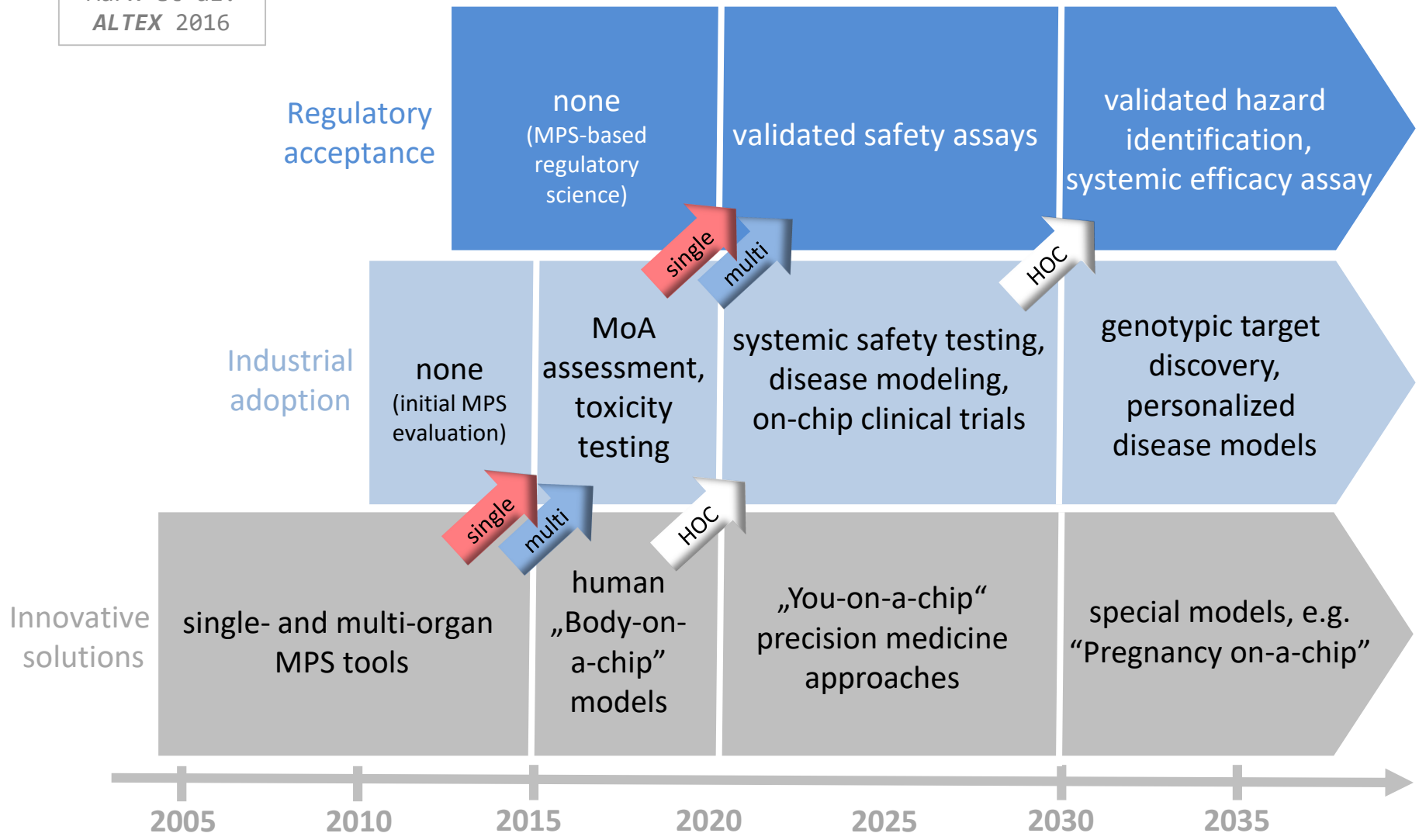
“Patient-on-a-chip”

>2030

Preclinical phase | Validation in patients | Sub-mission | Patients

A roadmap towards MPS-based decision-making

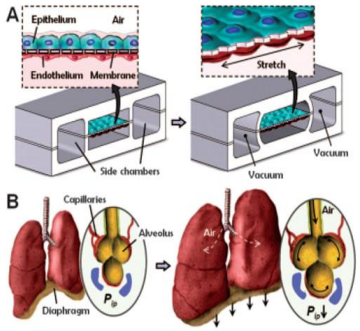
Marx et al.
ALTEX 2016

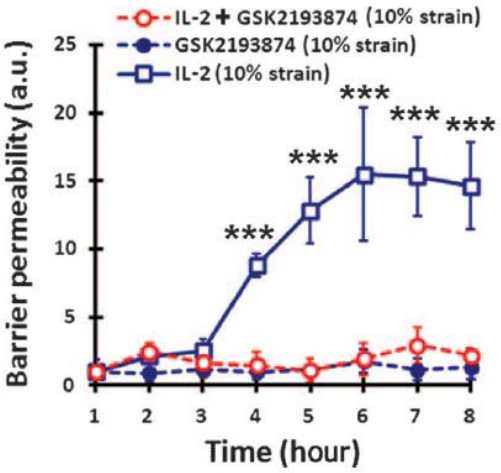


MPS-based research highlights

WYSS INSTITUTE

Pulmonary Edema in a Lung-on-a-Chip



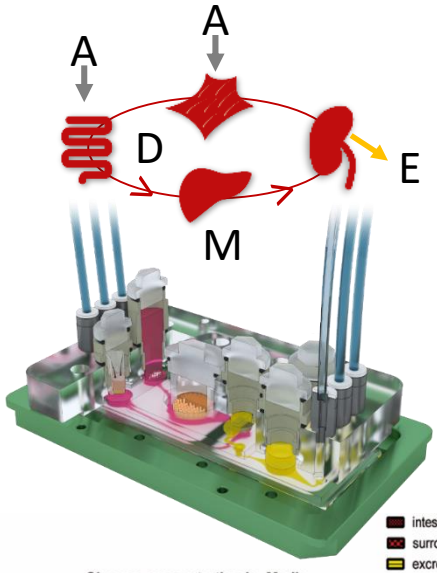


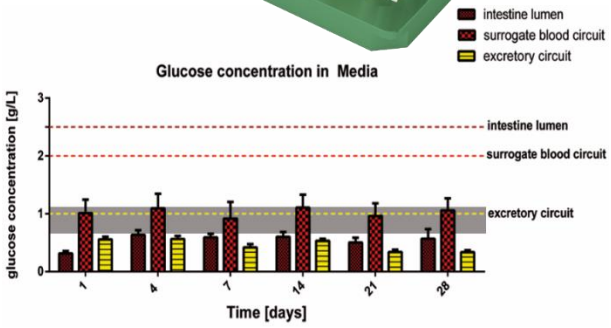
TRPV4 inhibitor blocks IL2-induced edema

Huh et al. Science 2010
Huh et al. Sci. Transl. Med. 2012

Technische Universität Berlin

Four-Organ-ADMET-Chip



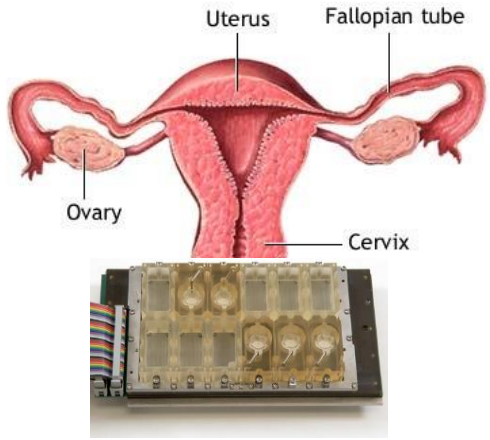


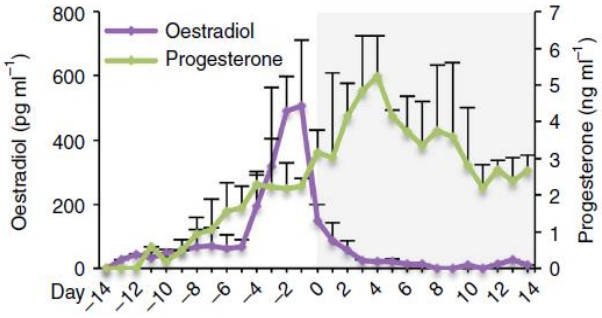
homeostatic 28-day downregulation of glucose

Maschmeyer et al. LabChip 2015

Northwestern University

Female Reproductive Tract-on-a-Chip

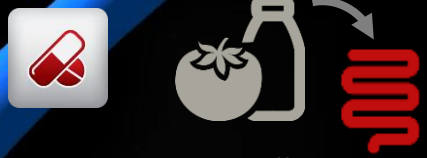




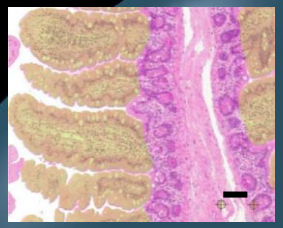
modeling menstrual cycle and „pregnancy“

Xiao et al. Nature Communications 2017

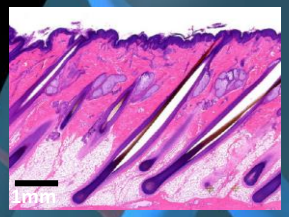
Downscaling a human body: How small can we go?

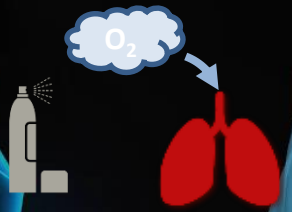


70 small intestine villi

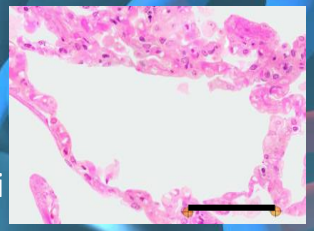


18 mm² skin segment

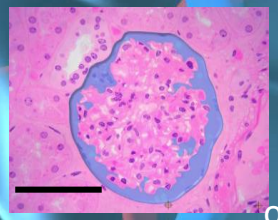




3000 lung alveoli



20 kidney nephrons



Scaling factor: 1/100.000

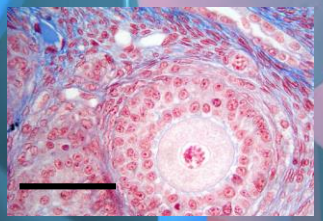
Marx et al. (2012)
ATLA 40, 235-257

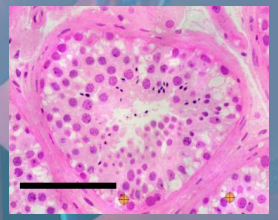
Bars: 100 µm

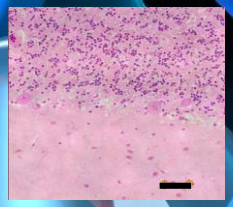
0.1 mg of ovary follicles

or

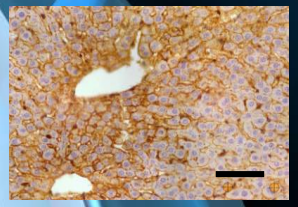
0.4 mg of testes seminiferous tubules



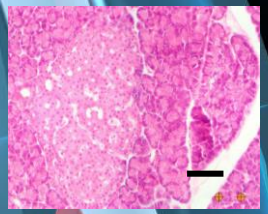




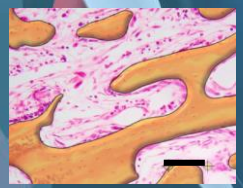
4 mm² brain cerebral cortex



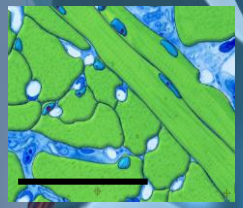
10 liver lobuli



5 pancreatic islets



20 mg of bone-marrow units

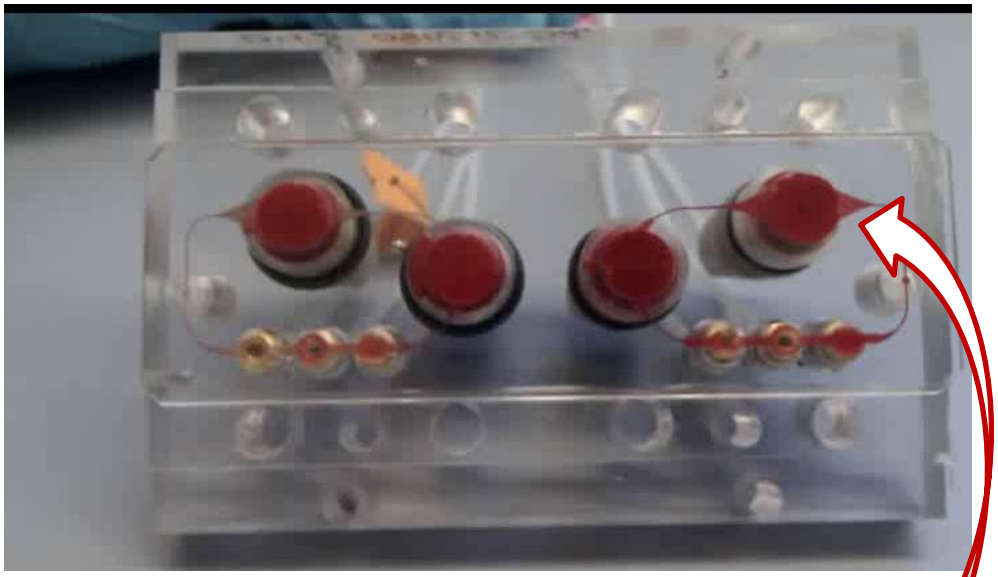


300 mg of skeletal muscle fiber segments

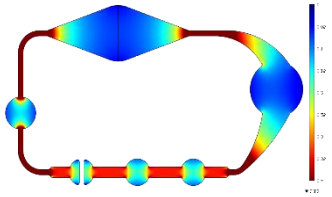
125 mg of adipose tissue clusters

The MOC technology

touchscreen-based benchtop



COMSOL Multiphysics® 5.2.



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

MOC features:

- area of a microscopic slide
- on-chip micropump enabling pulsatile flow
- suitable for primary cells, 3D tissues and cell lines
- compatible with live tissue imaging
- plug-in option for insert-based barrier models

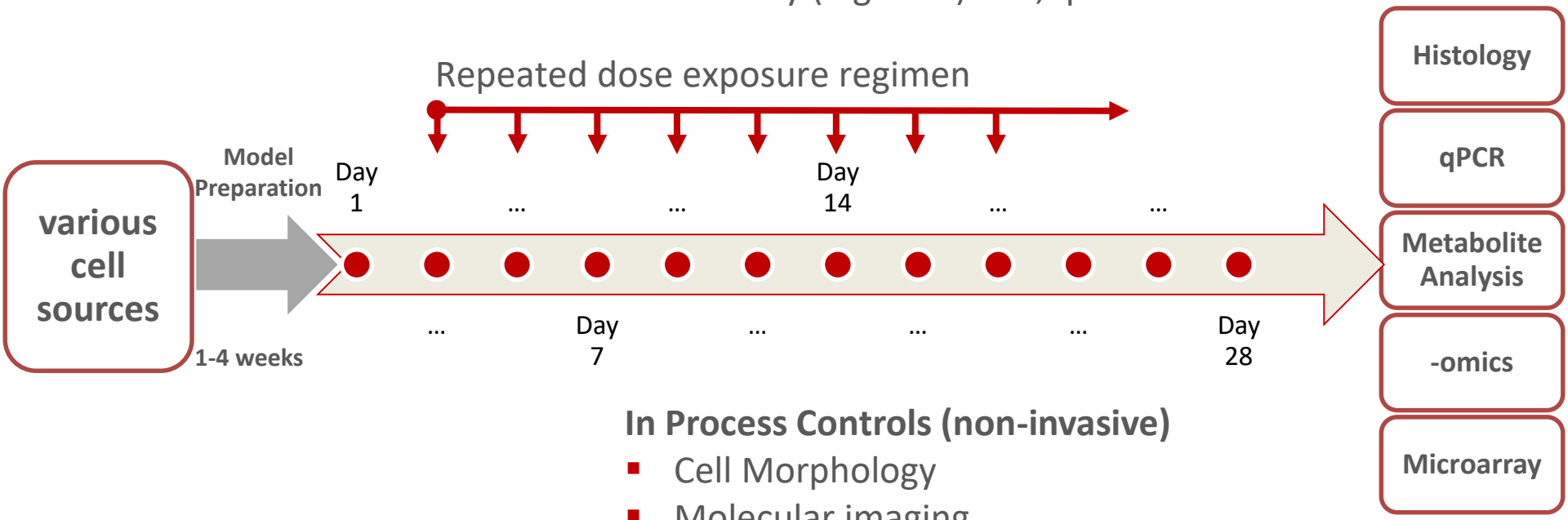
https://www.youtube.com/watch?v=whsqNvj9vdU

TISSUSE Emulating Human Biology

Multi-Organ-Chip Assays

In Process Controls (Sampling) ~250µl/sample

- Blood Surrogate Analysis
- Metabolism (e.g.Glucose/Lactate) ~6µl
- Viability (e.g. LDH) ~12,5µl

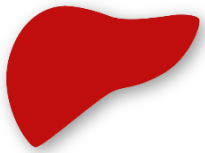


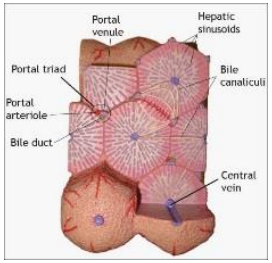
In Process Controls (non-invasive)

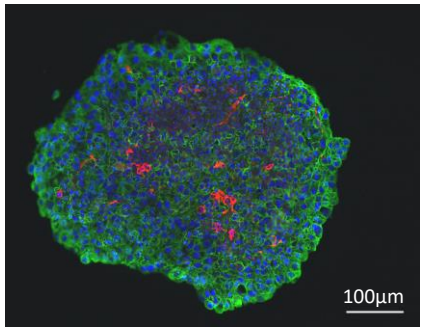
- Cell Morphology
- Molecular imaging
- Others

TISSUSE Emulating Human Biology

Preformed human organ equivalents

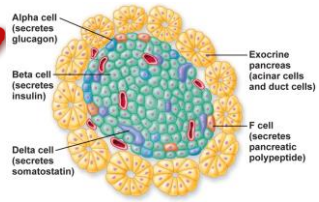


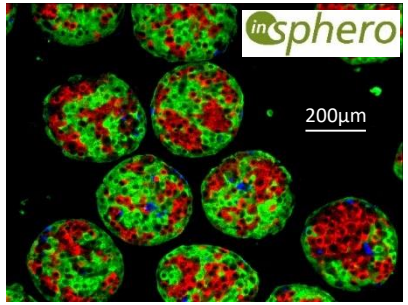




CK 8/18 Vimentin DAPI

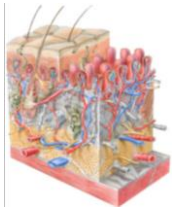
primary hepatic stellate cell and HepaRG cell spheroids

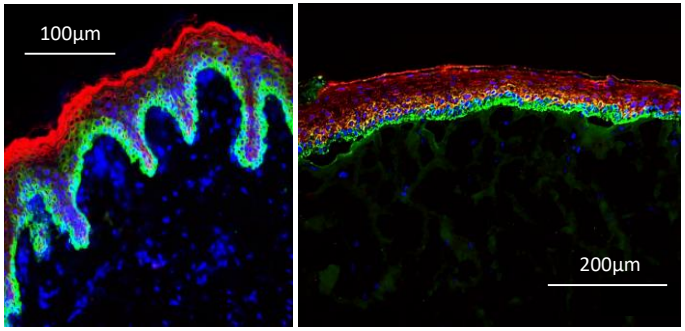




Glucagon α Insulin β Somatostatin δ

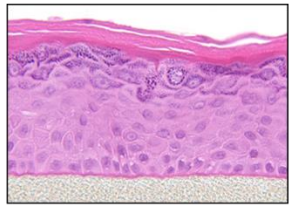
primary pancreatic islet cell spheroids

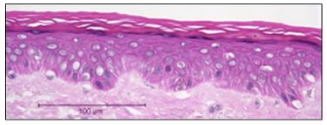




CK10 CK15 Dapi

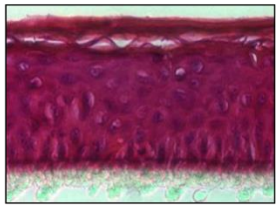
prepuce explants and primary keratinocyte/ fibroblast-based skin equivalents



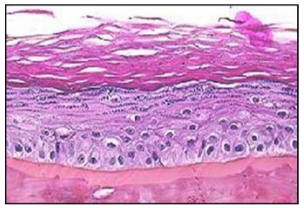


Native human skin

MatTek Corp. EpiDerm™ (EPI-200)



Cell Systems epiCS®

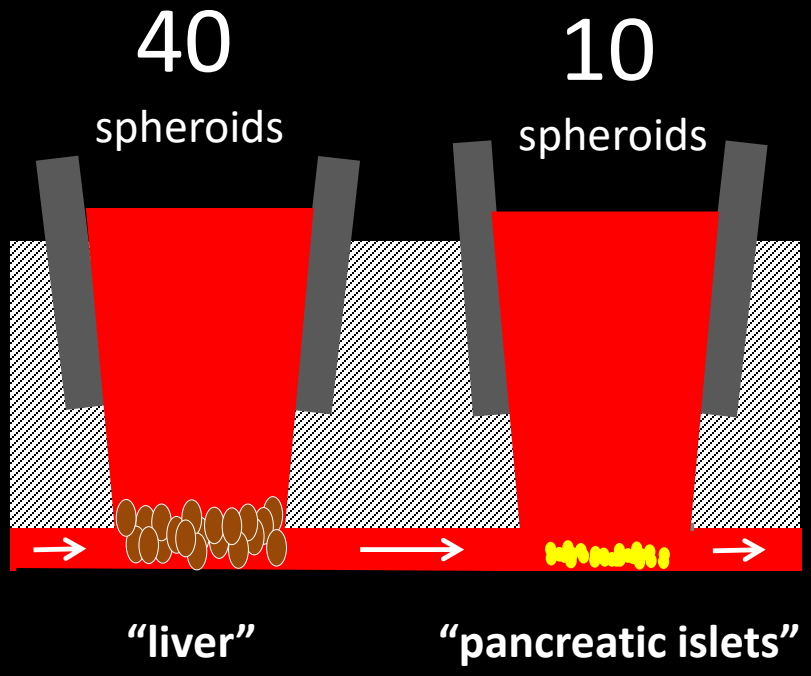


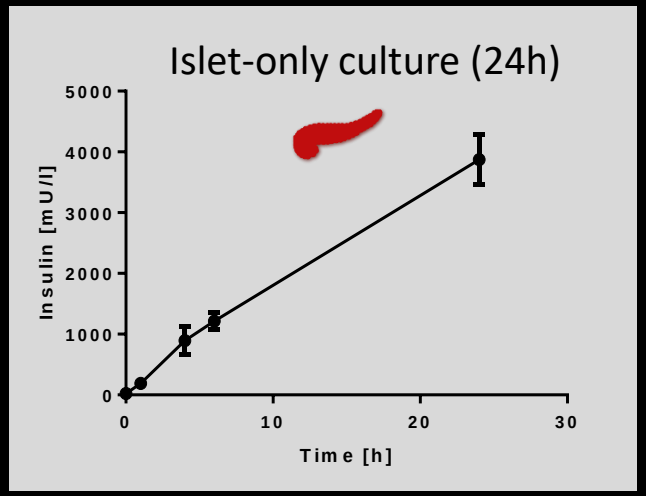
EpiSkin™ (SM)

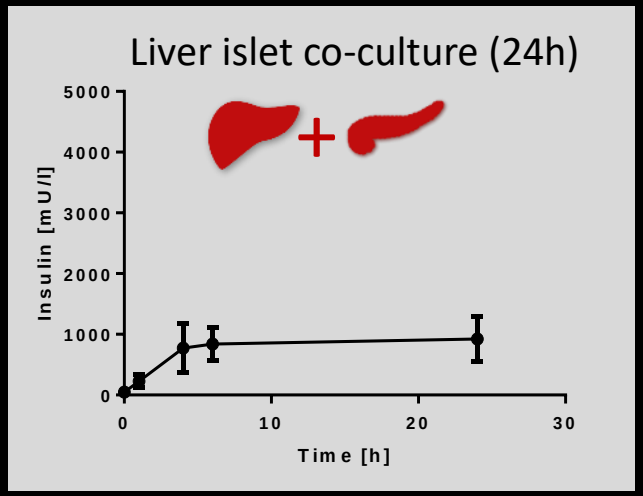
V - validated commercially available 3D models

Liver-islet chip: insulin responsiveness

Bauer et al.
Scientific Reports
in press



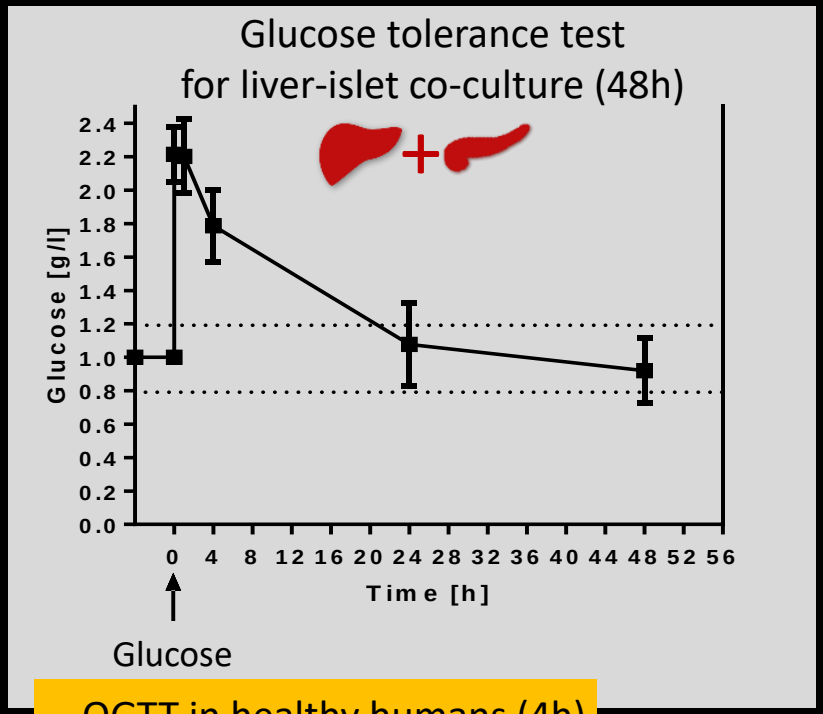


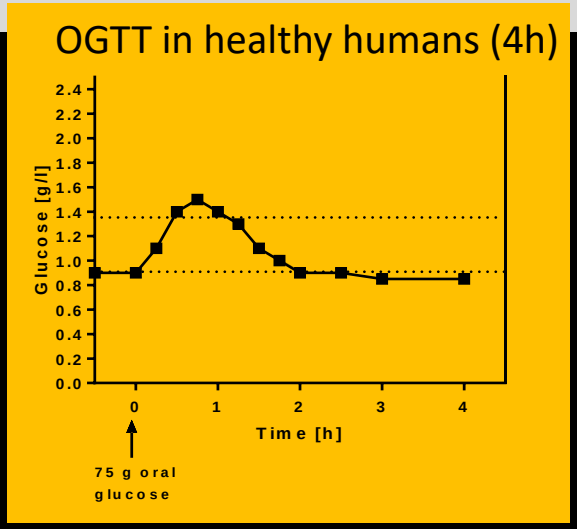


Regulated physiological insulin secretion

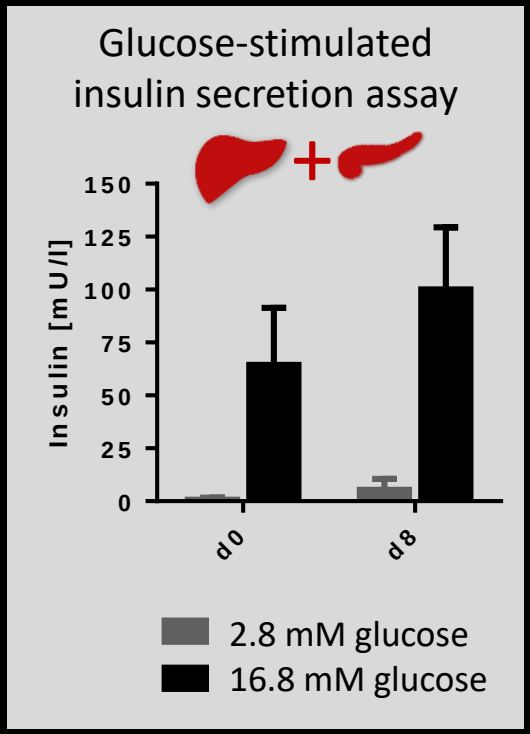
Liver-islet crosstalk to ensure glucose homeostasis

Bauer et al.
Scientific Reports
in press





8-day liver islet co-culture



Long-term homeostasis and crosstalk

Industrial adoption of liver-islet MOC

R&D, Innovative Medicines

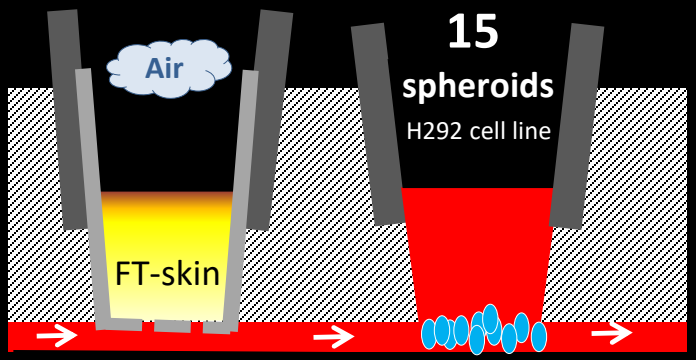
Rationale: establish Type 2 diabetes model for drug testing

- Model transfer and inter-lab validation
- Commercial cell source supply secured
- On-chip insulin resistance induction in progress

tech transfer ✓

TISSUSE Emulating Human Biology

Application of a skin-tumour model in the pharma industry



10,000 ng/ ml
100 ng/ ml
10 ng/ ml

Bay1a

5-d skin-tumour co-culture

readouts: histology, gene expression …

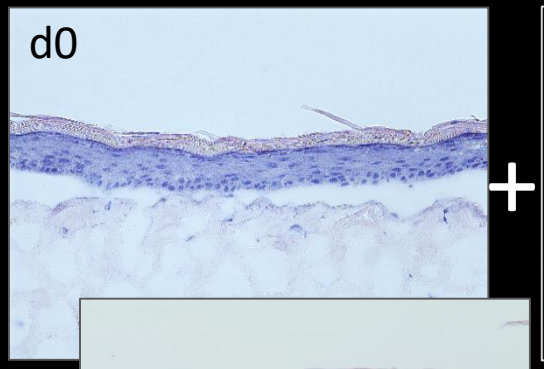
Rationale

Establish a combined safety and efficacy ("safficacy") assay for cancer drug candidates

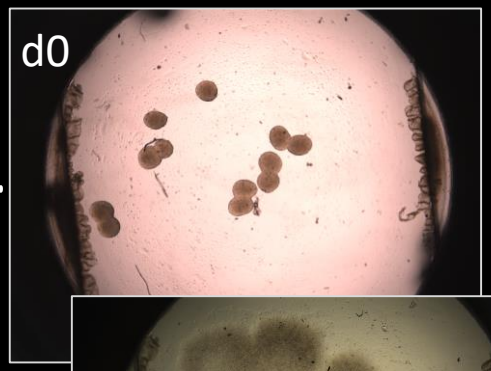
Qualification tool

Bay1a, a drug effective on lung tumour cells but causing severe skin toxicity in primates

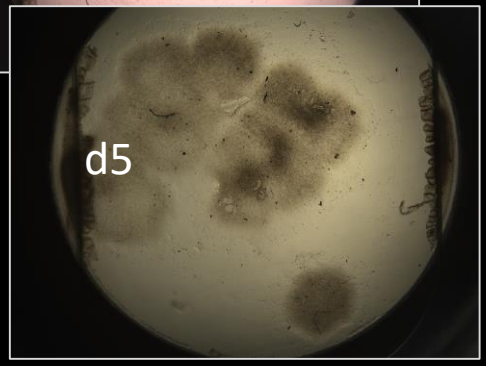
Could an in vitro co-culture serve to screen for candidates with a better profile before going in vivo?



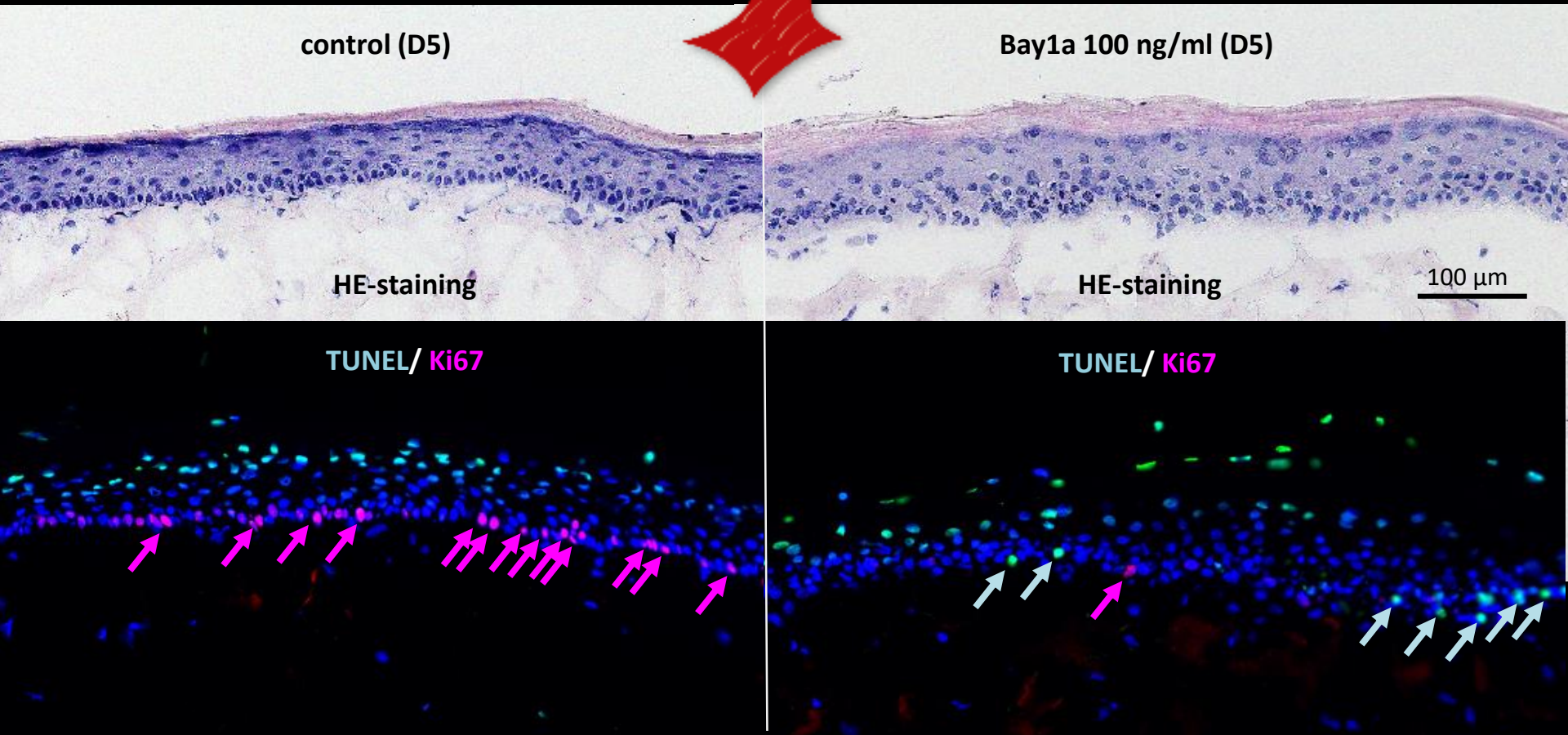
+



+



Status quo of the “safficacy” assay



- reproducible human 3D tumour-skin co-culture in place
- skin side effects observed but no tumour effects yet detected
- various hurdles to be solved for feasibility completion

with permission of Dr. Thomas Steger-Hartmann

Current challenges

- Secure reliable cell sources
- Increase level of similarity to human biology
- Regulatory acceptance to foster the paradigm shift

Our 3D organoid engineering pipeline 2017

	tissue explants	primary cells	cell lines
Liver 1.	–	✓	✓
Intestine 2.	–	Ⓥ	✓
Kidney 3.	–	–	✓
Brain 4.	–	✓	✓
Pancreas 5.	islets	Ⓥ	–
Skeletal muscles 6.	–	✓	✓
Adipose tissue 7.	subcutaneous explants	✓	–
Skin 8.	punch biopsies	Ⓥ	–
Hair 9.	follicular unit extraction	✓	–
Lung 10.	–	Ⓥ	–
Bone-marrow 11.	punch biopsies	✓	–
Lymph node* 12.	–	✓	–
Vasculature 13.	–	✓	–
3D Lung tumor	–	–	✓

selected context of use

↑

fit for purpose assays

- duration of 5 days to 8 weeks
- repeated dose exposure
- NCEs, NBEs, chemicals …

↑

12 multi-organ combinations

↑

13 single organ models

(as of September 2017)

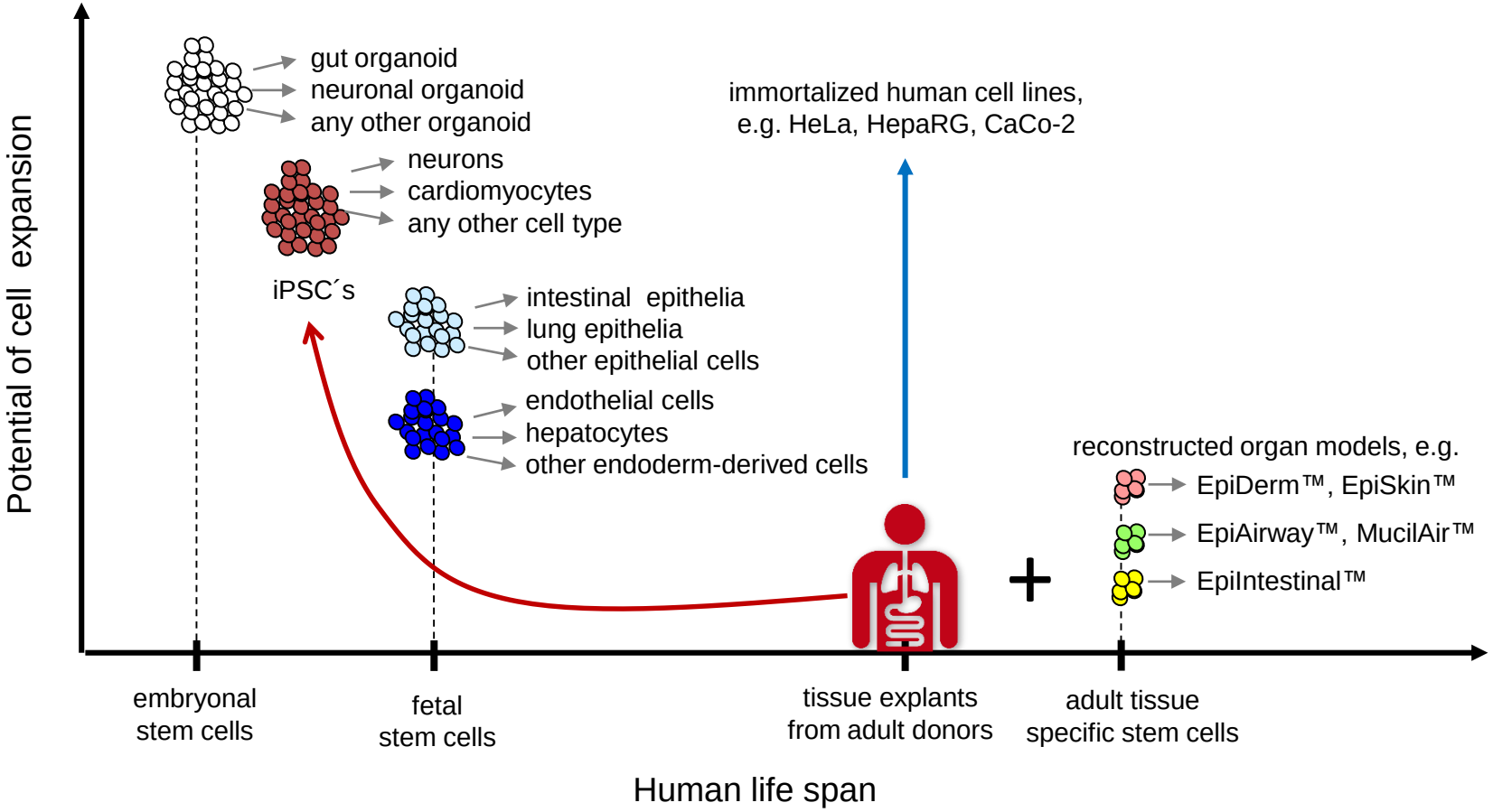
*in collaboration with ProBioGen, Germany

Ⓥ - validated commercially available 3D models

TISSUSE
Emulating Human Biology

Secure reliable cell sources

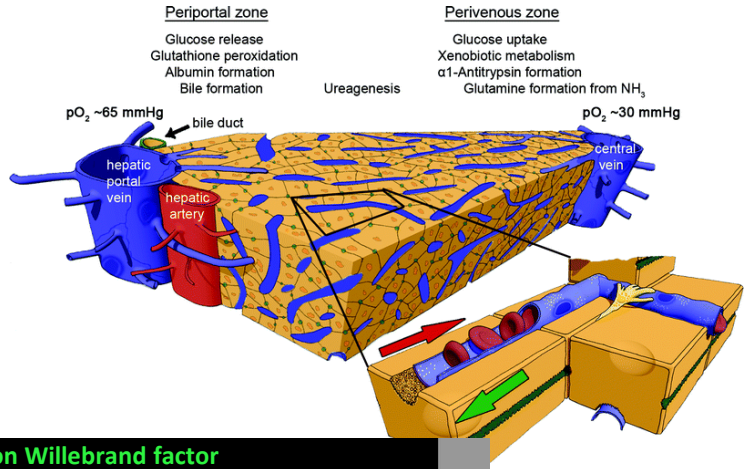
Marx et al.
ALTEX 2016



Level of similarity to human biology

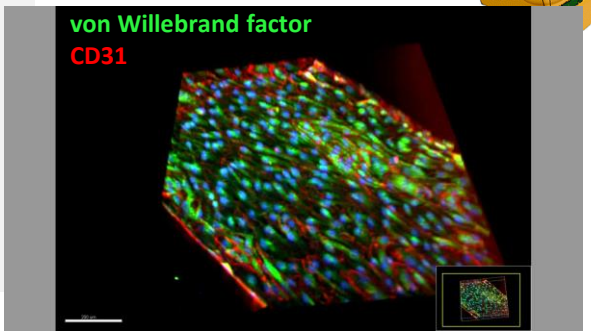
- segregate bile from liver equivalents and add entero-hepatic “recirculation”

Materne et al. ***Lab Chip,*** 2013,
Chip-based liver equivalents for toxicity testing – organotypicalness versus cost-efficient high throughput



- vascularize channels and organ equivalents

Schimek et al. ***Lab Chip*** 2013,
Integrating biological vasculature into a multi-organ-chip microsystem.
Hasenberg et al. ***J Biotechnology*** 2015,
Emulating Human Microcapillaries in a Multi-Organ-Chip Platform.
Knezevic et al. ***Frontiers in Bioeng Biotech*** 2017,
2017: Engineering blood and lymphatic microvascular networks in fibrin matrices.



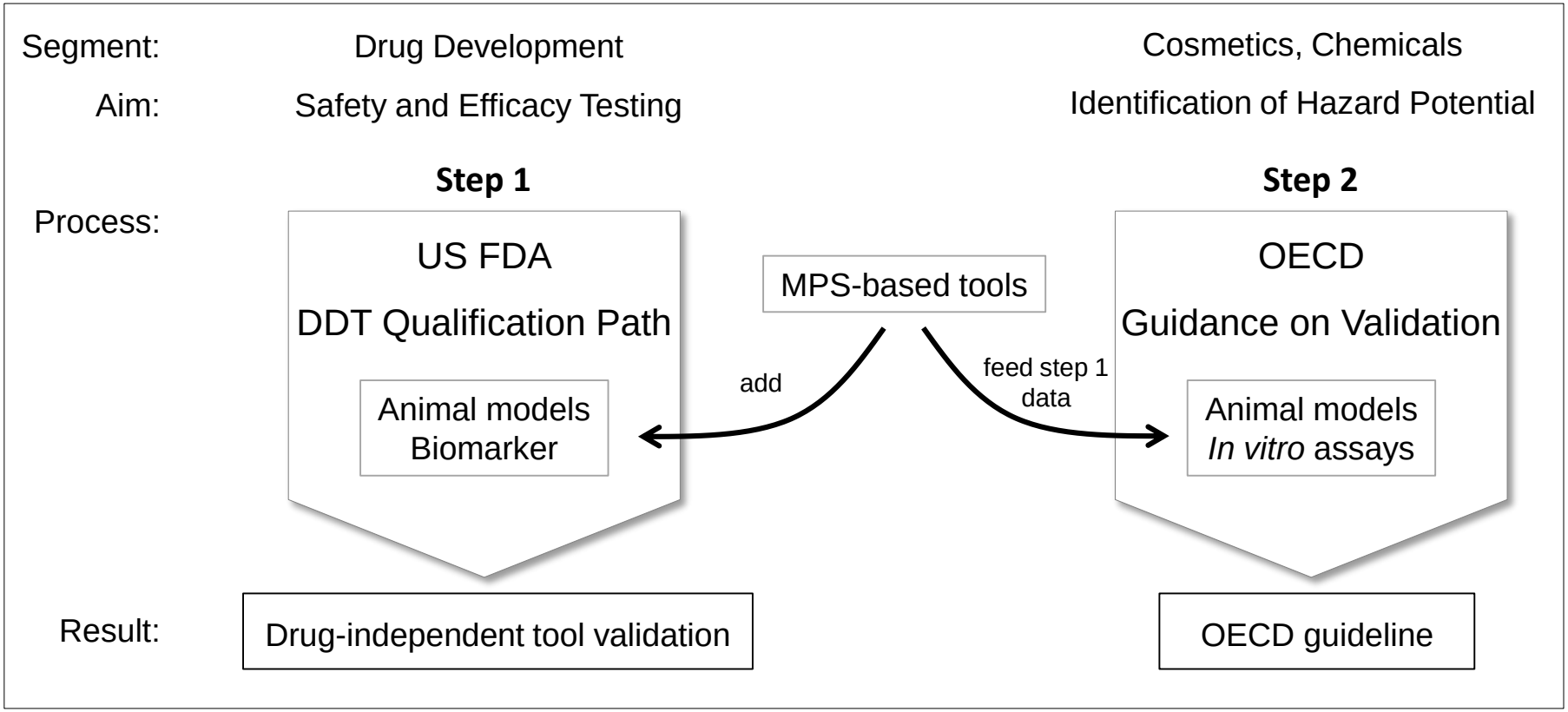
- apply plasma/blood perfusion and integrate innate and adoptive immunity

Giese and Marx, ***Adv. Drug Deliv. Rev.***, 2014,
Immunity in vitro — solving immunogenicity and more.

Regulatory acceptance =

Marx et al.
ALTEX 2016

Regulatory science + Validation strategy



Eds. Eskes and Whelan: Validating Alternative Methods for Toxicity Testing. Vol 856 of the series Advances in Experimental Medicine and Biology pp 299-316 ***Springer***, 2016, Chapter 12: Rebelo et al; Validation of bioreactor and human-on-a-chip devices for chemical safety assessment

Thank you

Fraunhofer IGB

Bundesministerium für Bildung und Forschung

GO-Bio

HiPSTAR

eurostars

EUTOXRISK

THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION
HORIZON 2020

uwe.marx@tissuse.com

CAAT eu

next workshop: Berlin, Germany, June 17th – 19th 2019

"Biology-Inspired Microphysiological System Approaches to Solve the Prediction Dilemma of Substance Testing"

Institute of Biotechnology
Berlin Institute of Technology
Medical Biotechnology

TISSUSE
Emulating Human Biology