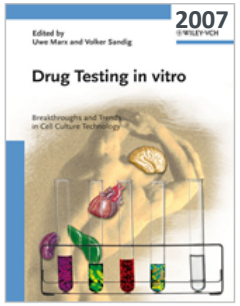
TISSUSE
Emulating Human Biology

UWE MARX, FOUNDER AND CSO

Biology-inspired MPS:

the asset of multi-organ co-cultures

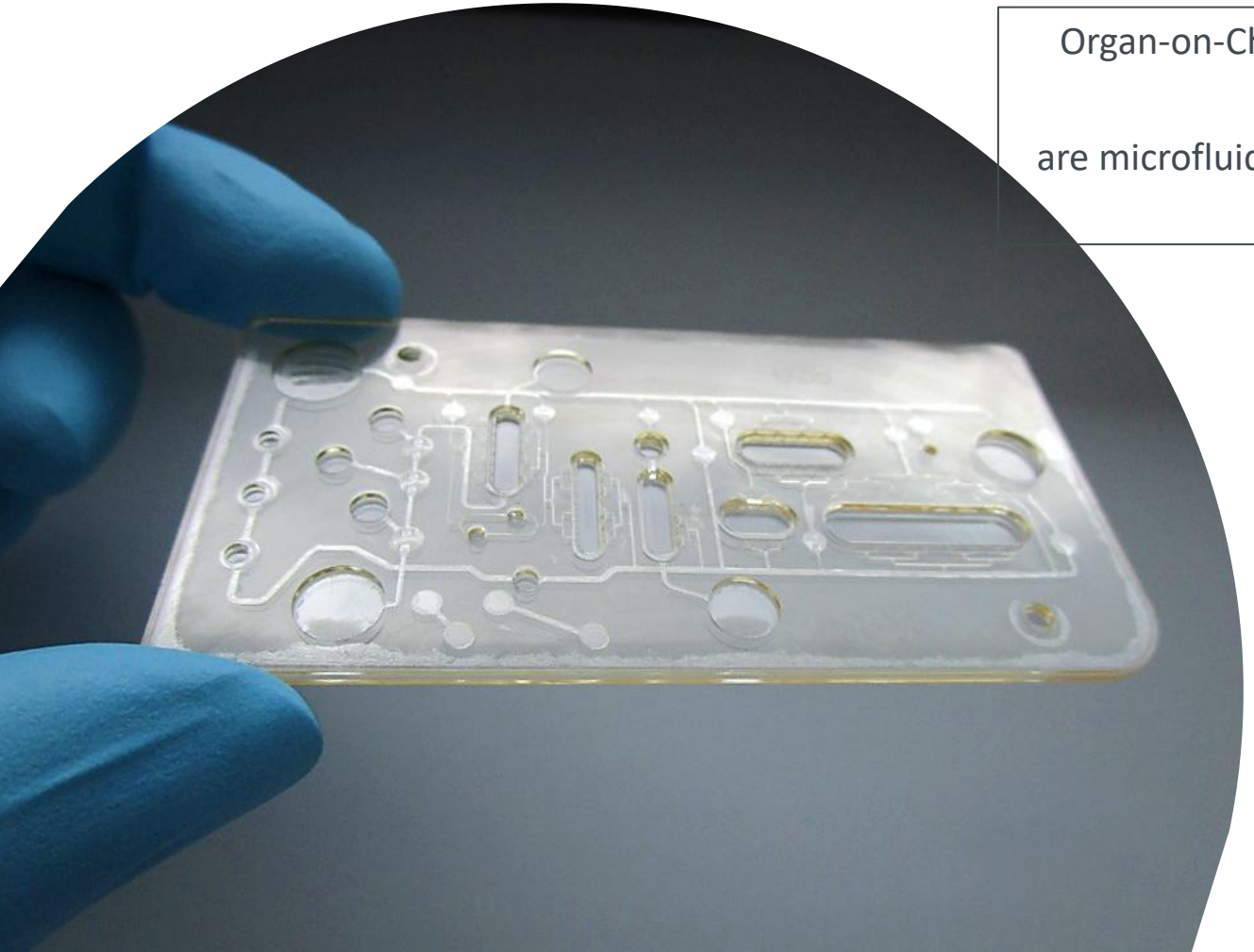
Founders Vision since 2010



“organoids”

“Human-on-a-Chip”

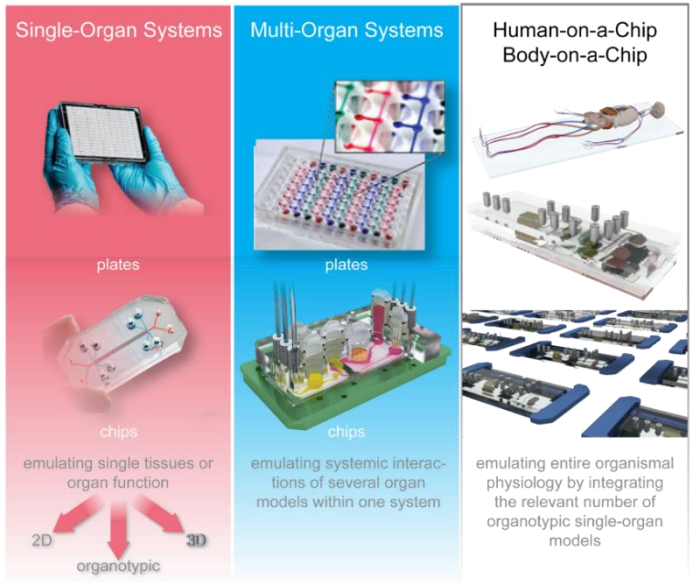
“Patient-on-a-Chip”



Organ-on-Chip, Body-on-Chip, Human-on-Chip, Patient-on-a-Chip collectively

Microphysiological systems (MPS)

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



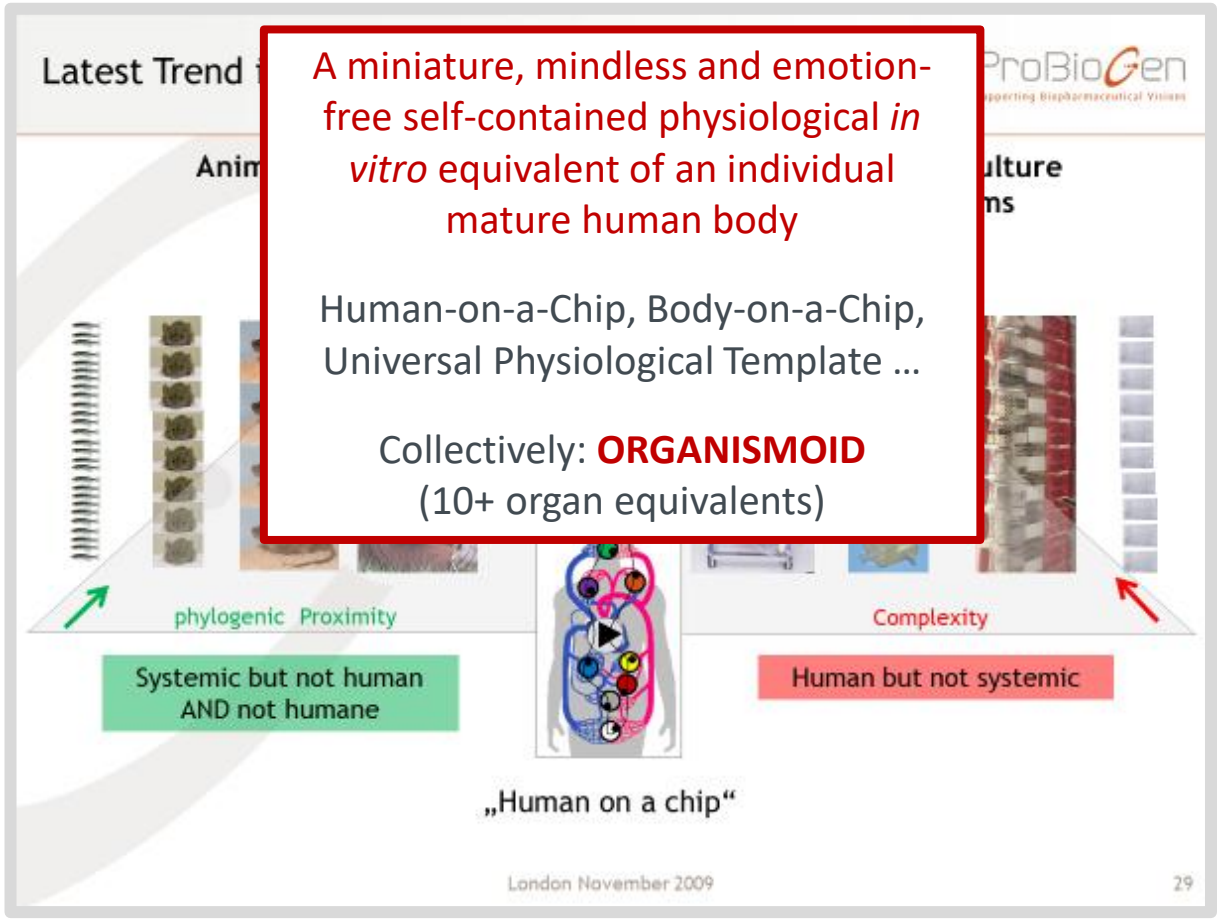
First MPS-Stakeholder Workshop 2015 in Berlin:
Marx et al., Biology-inspired Microphysiological System Approaches to Solve the Prediction Dilemma of Substance Testing. ***ALTEX 2016***

The ultimate alternative to testing in animals and human volunteers

THE ROYAL SOCIETY

Symposium Nov 19, 2009

Drug Discovery and Development in the 21st Century



A miniature, mindless and emotion-free self-contained physiological *in vitro* equivalent of an individual mature human body

Human-on-a-Chip, Body-on-a-Chip, Universal Physiological Template …

Collectively: **ORGANISMOID**
(10+ organ equivalents)

A 73kg human body

3.7×10^{13} cells
(4% turnover per day)

224 cell types

60/61 organs

10 systems

1. Circulatory
2. Respiratory
3. Digestive
4. Endocrine
5. Urinary
6. Integumentary
7. Musculoskeletal
8. Nervous
9. Immune
10. Reproductive

+ 2500 kcal/day = self-contained lifespan

2012: Marx et al. ***ATLA***

2012: Shuler, M.L. ***Annals of Biomed Eng***

2015: Abaci & Shuler, ***Integr Biol*** *(UK)*

2016: Marx et al. ***ALTEX*** *t4-report*

2020: Marx et al. ***ALTEX*** *t4-report*

2020: Dehne & Marx, **Curr Opin Toxicol**

2021: Marx et al. ***Frontiers in Medicine***

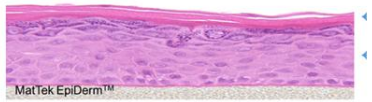
MPS within the human *in vitro* cell culture landscape

OECD

75 OECD guidelines for evaluation of the hazard potential and safety of chemicals

June 2020

TG 439 in vitro skin irritation



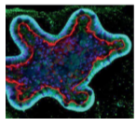
https://doi.org/10.1787/9789264242845-en

2009 Hans Clevers

Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature*

HUB ORGANOIDS

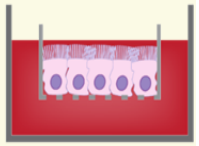
Personalized precision medicine approaches using patient-specific organoids *in vitro*



Degree of qualification for toxicity testing

static cell culture models

monolayer/suspension
(cell lines)



monolayer/suspension
(primary cells)

3D/artificial organoids
(stem cell-differentiated or assembled from primary cells)

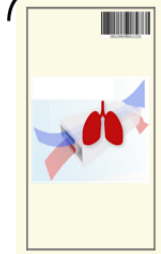
WC11 Sessions

S117
S152
S215

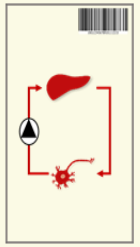
WC11 Sessions

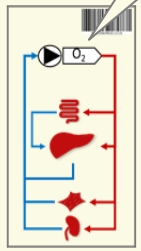
Don Ingber's Keynote
S115, S160, S162,
S235, S300, S302,
S304, S305, S308

microfluidic MPS models



single-organ





multi-organ

body-on-a-chip

Degree of emulation of human biology

>100 years

~20 years

~10 years

EUTOXRISK

2016 -2021
Prototyping and testing the first in history physiology-based four-organ chip for ADME profiling and evaluation of hazard potential of substances

ORGANISMOID THEORY

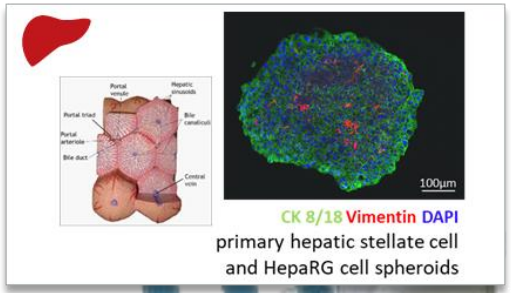
Marx et al.
Frontiers in Medicine
2021

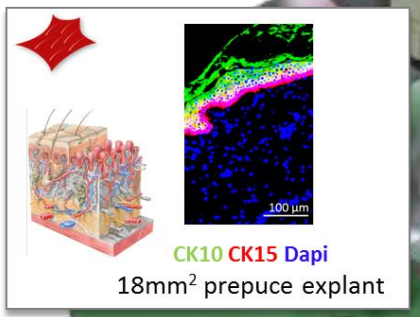
An individual patient's "body" on chips – how organismoid theory can translate into your personal precision therapy approach.

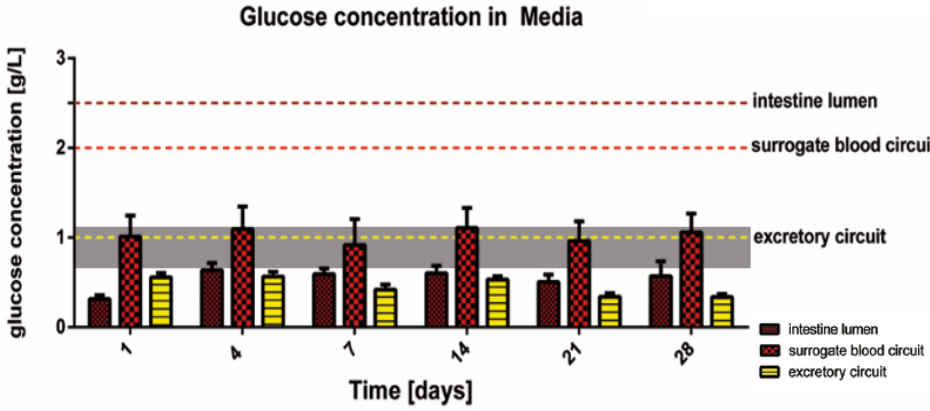
Adopted from Beilmann et al. Optimizing drug discovery by Investigative Toxicology: Current and future trends. ***ALTEX 2019***

Aiming for an ADME-Tox Chip since 2014

intestinal lumen: 250µl
surrogate blood circuit: 830µl
excretory circuit: 600µl

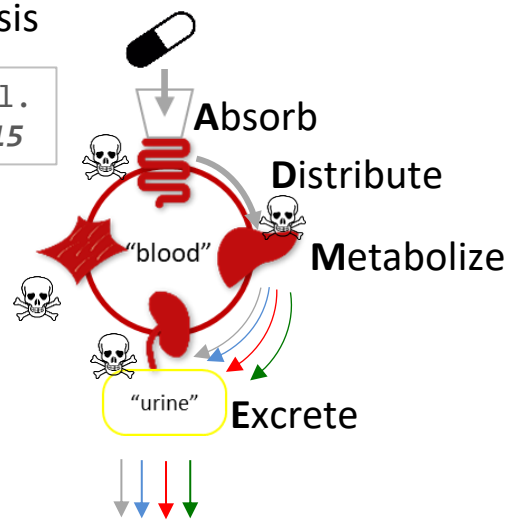






- normoglycemic blood glucose
- functional barriers
- 28-day homeostasis

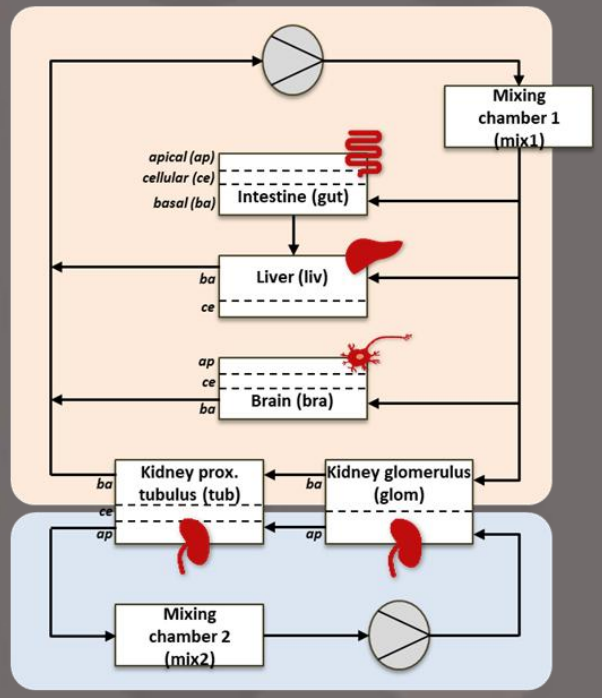
Maschmeyer et al.
Lab on Chip 2015

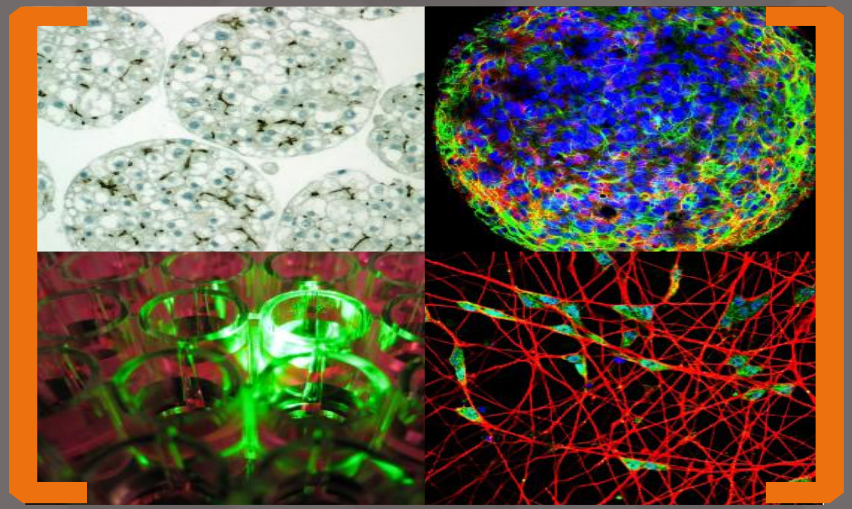


Toxicity Testing and Risk Assessment for the 21st Century

A physiology-based 4-Organ ADME – and Tox-Chip Redesign and prototyping followed by proof of concept for substance exposure.

1. physiological organ arrangement
2. physiological “blood” flow rates
3. brain compartment instead of skin
4. add a glomerulus compartment





Frederik Bois, INERIS, France

The human Physiology-based Chip4 for ADME- and Toxicity Studies

Dr. Beren Atac-Waggeg

Organ	Human Data*		Chip Data	
	Blood flow in L/h (L/min)	Ratio of blood flow in %	Simulation Proportion in %	Theoretical volumetric flow in µl/min**
Portal system: Pancreas/Intestine	64.3 (1.07)	35.3	35	10.6
Liver	82.0 (1.37)	45.2	45	13.6
- through portal vein	~64.3 (1.07)	35.3	35	10.6
- trough hepatic artery	~17.7 (0.30)	9.9	10	3
Kidney	61.1 (1.02)	33.7	34	10.3
X	38.6 (0.64)	21.1	21	6.4
Total (arterial blood)	181.7 (3.03)	100	100	30.3

D8.2. 36m

qualified cell-free prototype

commercial primary small intestine barrier (Transwell)

MatTek IN VITRO LIFE SCIENCE LABORATORIES

iPSC-derived
- glomerular cells
- proximal tubules line

TISSUSE Emulating Human Biology

VU

BIOTalentum

iPSC-derived neuronal spheroids

insphero Biomimetic Microtissue Technology

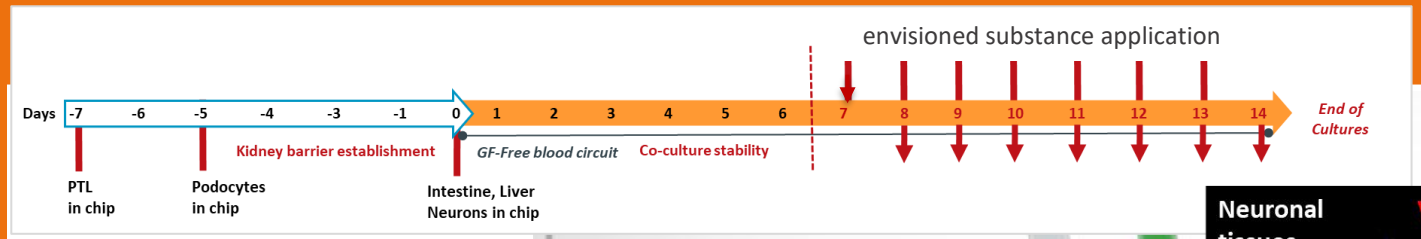
primary liver µ-tissues

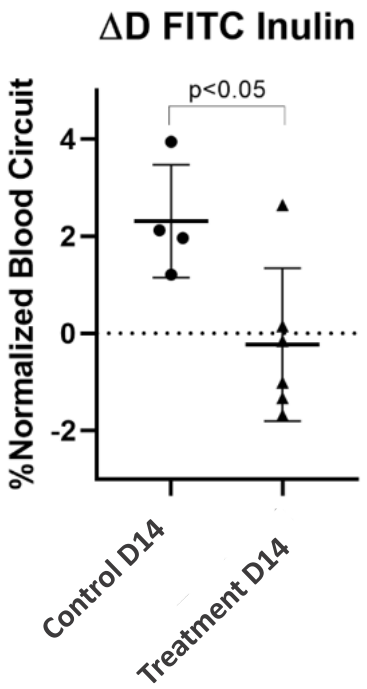
D8.5. 60m

ADME-"N" test system operational after model & assay qualification

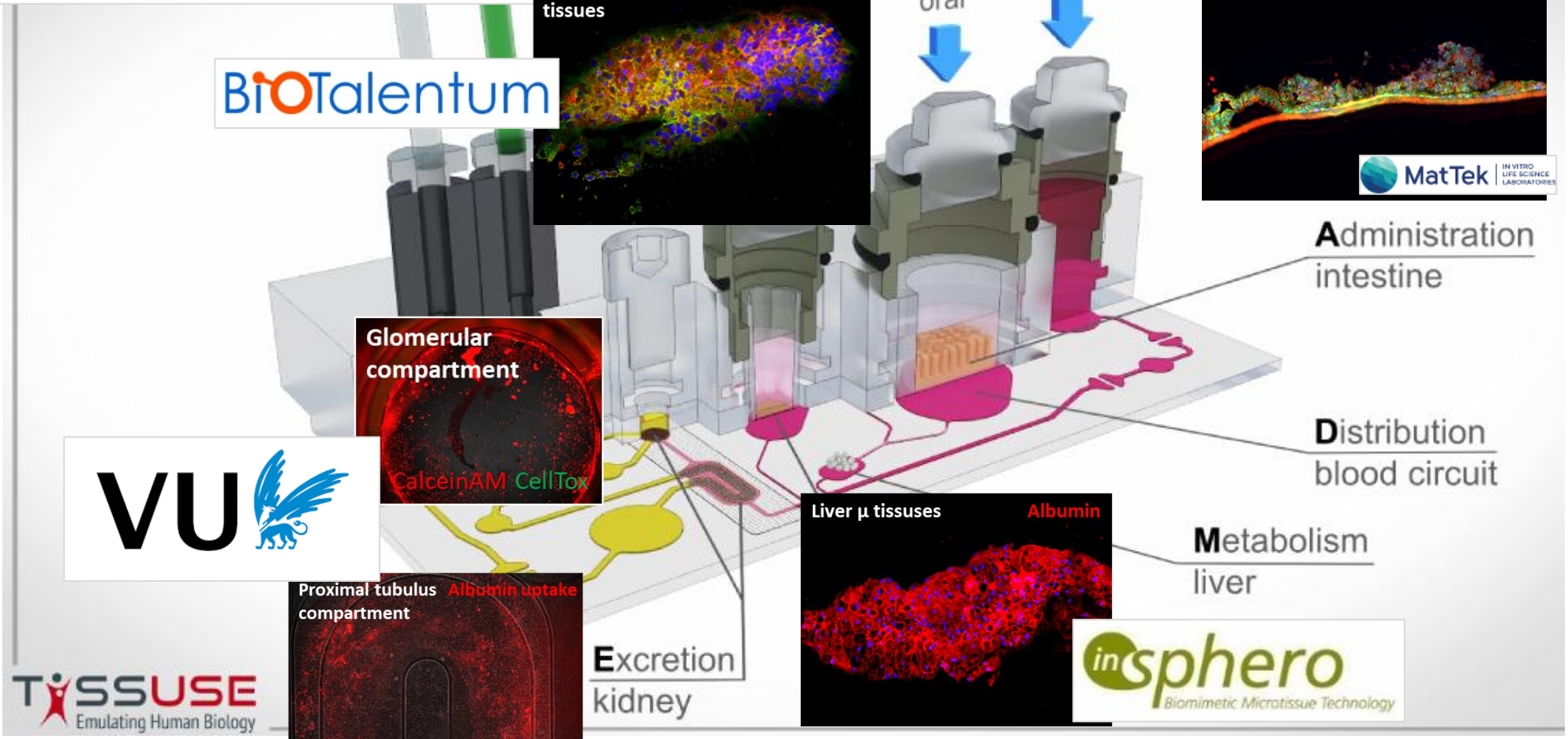
EUTOXRISK

Snapshot of Results: 14-day Organ Model Performance (non-exposed)



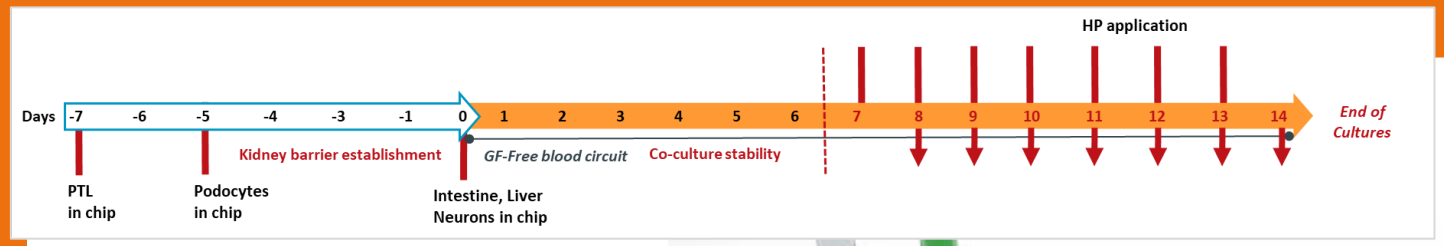


Feasibility: biological models



EUTOXRISK

Snapshots of Results: 7-day Substance Exposure

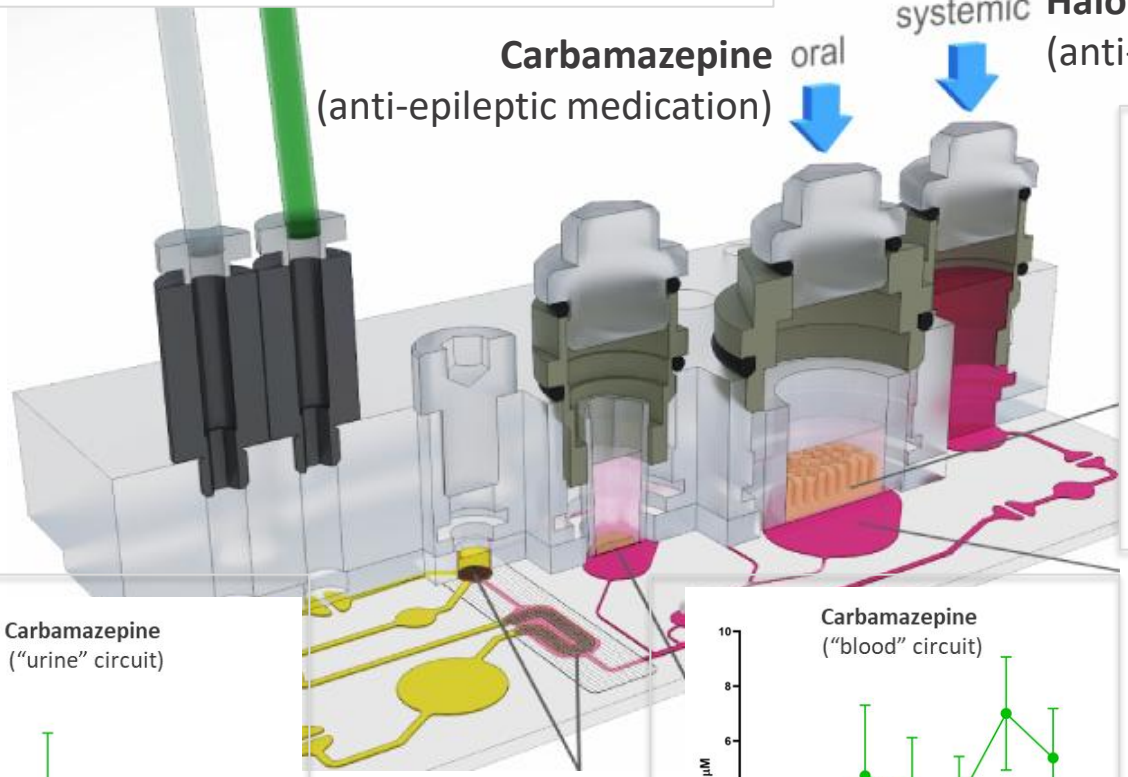


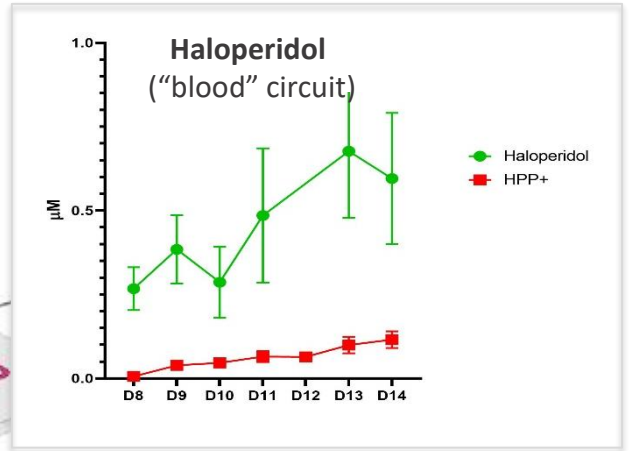
Carbamazepine
(anti-epileptic medication)

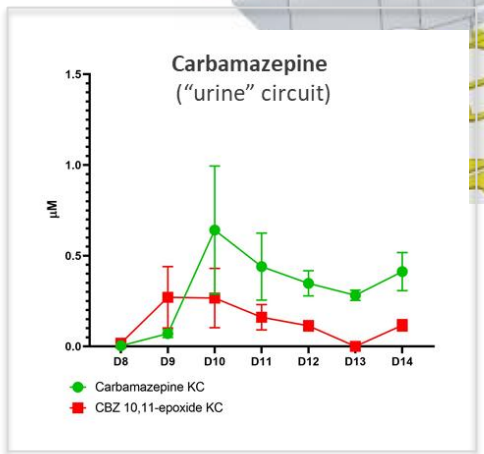
oral

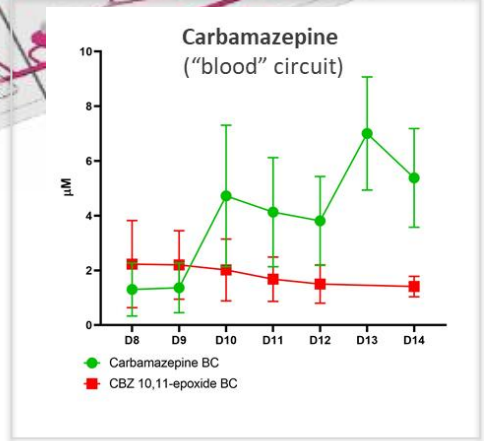
systemic

Haloperidol
(anti-psychotic medication)









D8.5. 60m
ADME-"N" test system operational after model & assay qualification

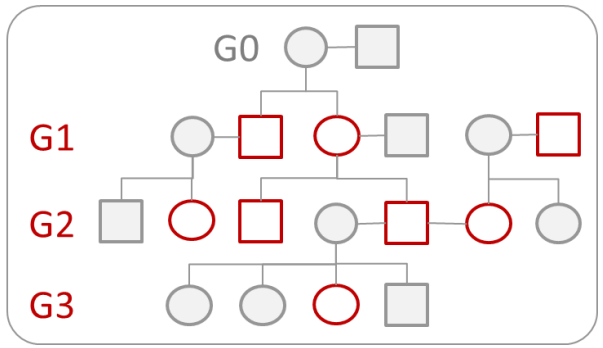
EUTOXRISK

Autologous Four-Organ-Co-culture to enable on-chip immune Competence

hPSCreg

Ramme et al.,
Stem Cell Research 2019

8 donors



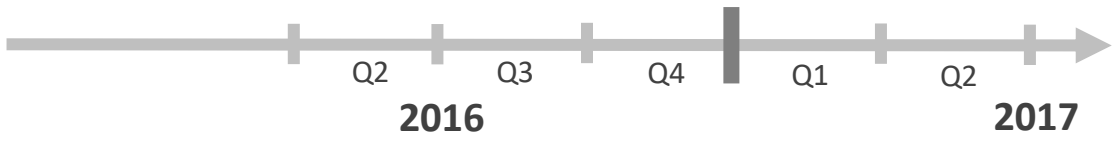
Ethikvotum
Eth 25/16
EU compliant legal background for commercial use

induced pluripotency

7 MCBs

QC release

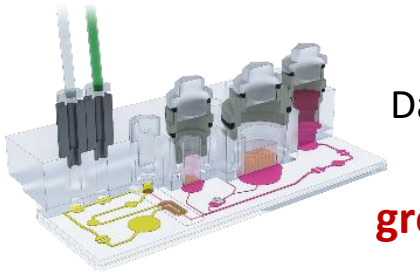
TISSUi001-A
Commercial Biobank



EUTOXRISK

Reproduction of the treatment scheme on autologous 14-day co-cultures including whole transcriptomic analysis

Ramme et al.
Autologous induced pluripotent stem cell-derived four-organ-chip.
Future science OA, 2019



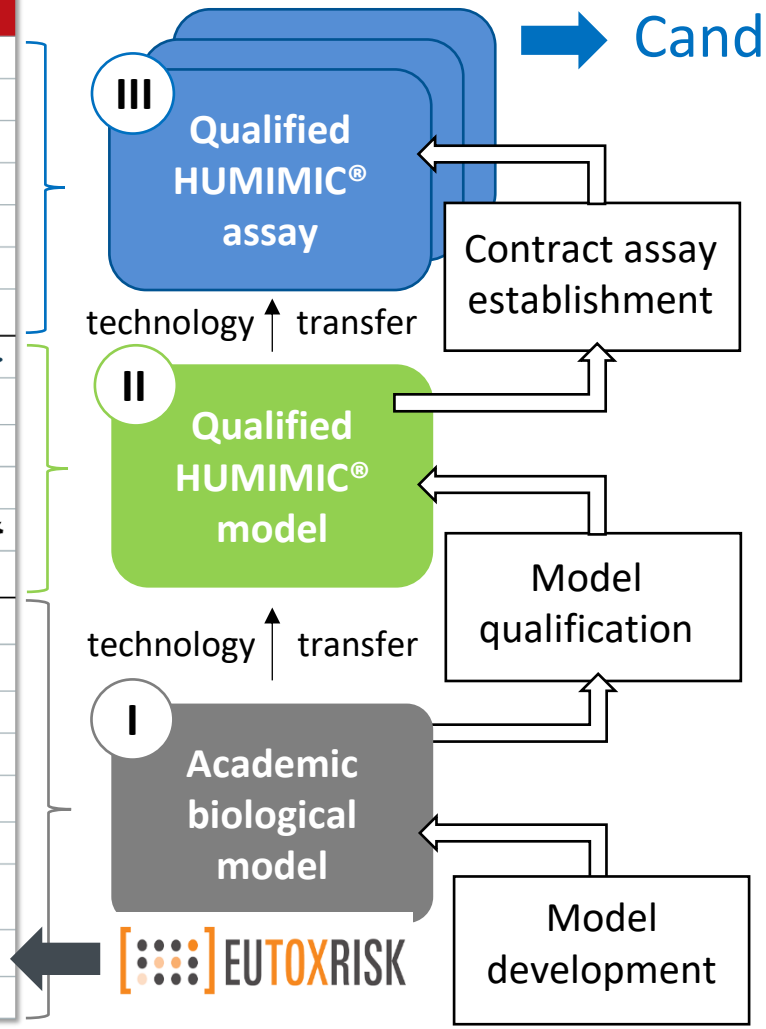
Day -6 — 0 14-day co-culture

growth factor-free medium with 5% human serum

The current assay portfolio and its levels of readiness

Nr.	Organ model	Schematic	Context of use	Level of readiness	Species
1	Bone marrow		Bone marrow toxicity	III	
2	Hair follicle		Hair growth agents	III	
3	Skin - Liver		Hazard identification, Tier 3	III	
4	Intestine - Liver		Absorption, metabolism	III	
5	Lung - Liver		Hazard identification	III	
6	Liver - Pancreas		Diabetes drug substances	III	
7	Skin - Tumor		Anti-tumor antibodies	III	
8	Thyroid - Liver		Hazard identification, safety	II	vs
9	Testis - Liver		Testicular toxicity	II	
10	Liver - Neuro		Metabolite neurotoxicity	II	
11	Skin - Leukocytes		Allograft rejection therapies	II	
12	Intestine - Muscle		Muscle growth agents	II	vs
13	vasc. Pancreas - Tumor		Anti-tumor therapy	II	
14	Bone		Nanoparticle toxicity	I	
15	Bone marrow		Erythropoiesis	I	
16	Skin - Hair follicles		Hair growth agents	I	
17	Liver - Cardio		Metabolite cardiotox	I	
18	Liver - Kidney		Kidney toxicity	I	
19	Skin - Lymph node		Hazard identification, Tier 3	I	
20	vasc. Intestine – Lymph node - Tumor		Immuno-Oncology	I	
21	ADME-axis + 1		ADME-profile, PBPK, Tox	I	
22	Blood-Brain-Barrier		Permeability & Neurotoxicity	I	

III - Assay established, available for testing/assay transfer
II - Model qualified, available for assay establishment
I - Proof of Concept, available for joint model & assay development



ISO 9001:2015 certified

Quality Management System

DEKRA certified

23 Assays for internal Pharma Decision Making (as of October 2019)

MPS-based Organ/Tissue model	Nr. of cases	Area of usage (drug development phase)	MPS-Supplier	End user	Reference (if available)
Blood Vessel, Vasculature	5	Target identification, validation and compound selection	AIST	Daiichi-Sankyo	Satoh et al., 2016
		Discovery (scleroderma)	Mimetas	Galapagos	-
		Systems toxicology for consumer products	Mimetas	Philip Morris	Poussin et al., 2019
		Pharmacokinetics and pharmacology	Mimetas	undisclosed	-
		Target identification and validation	Mimetas	NovoNordisk	-
Bone Marrow	4	Preclinical safety	TissUse	AstraZeneca	Sieber et al., 2018
		Preclinical safety	Emulate	AstraZeneca	Chou et al., 2018
		Preclinical safety	TissUse	Roche	-
		Preclinical safety	TissUse	Bayer	-
Gut Epithelium	4	Discovery (inflammatory bowel disease)	Mimetas	Galapagos	Beaurivage et al., 2019
		Discovery	Mimetas	Roche	-
		Clinical development	Mimetas	Roche	-
		Preclinical Safety	Emulate	Roche	-
Lung	3	Discovery (alveolus)	Wyss	undisclosed	Huh et al., 2012
		Drug efficacy (epithelium)	Wyss	Pfizer, Merck USA	Benam et al., 2016
		Preclinical safety	Emulate	Roche	-
Liver	2	Pharmacological and toxicological effects	Emulate	AstraZeneca	Foster et al., 2019
		Preclinical safety – assessment of species (Rat, Dog & Human)	Emulate	J&J, AstraZeneca	Jang et al., 2019
Ocular compartment	1	Discovery	Fh IGB / EKUT	Roche	Achberger et al., 2019
Kidney Epithelium	1	Pharmacokinetics and pharmacology	Mimetas	undisclosed	Vormann et al., 2018
Liver-Pancreas	1	Target validation / identification	TissUse	AstraZeneca	Bauer et al., 2017
Liver-Thyroid	1	Preclinical safety – assessment of species-specificity (Rat and Human)	TissUse	Bayer	Kuehnlenz et al., 2019
Skin-Tumor	1	Preclinical safety & efficacy	TissUse	Bayer	Huebner et al., 2018

∑ = 23 cases

Second MPS-Stakeholder Workshop 2019 in Berlin:
Marx et al., Biology-inspired Microphysiological Systems to Advance Medicines for Patient Benefit and Animal Welfare. ***ALTEX 2020***

2018

Sieber et al.,
Bone marrow-on-a-chip: Long-term culture of human haematopoietic stem cells in a three-dimensional microfluidic environment

Tissue Eng Regen Med

Recolin et al.
Using a bone marrow MPS to inform oncology drug-combination scheduling
Poster 387 at WC11,
Aug 27, 2021

2017

Bauer et al.,
Sci Rep

Casas et al.
Integrated experimental-computational analysis of a liver-islet mps for human-centric diabetes research
BioRxiv 2021

2019

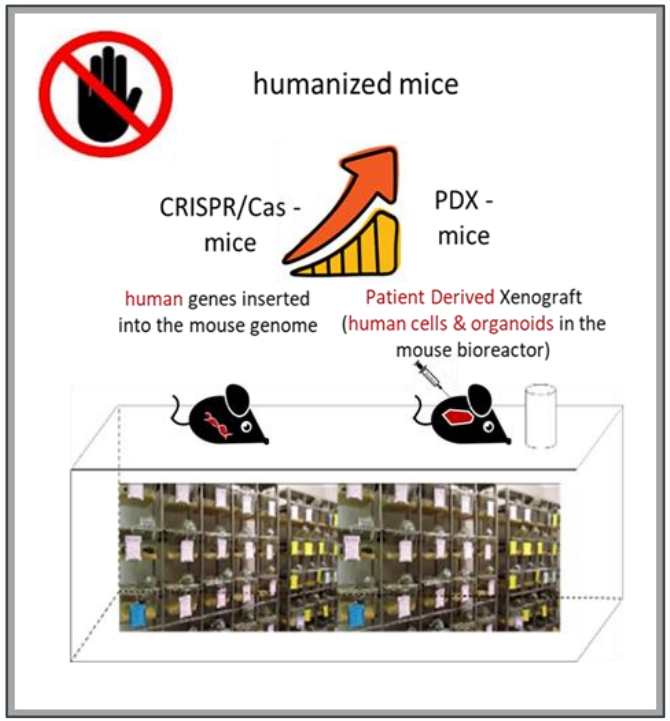
Kühnlenz et al.,
Toxicol Lett *(Abstract)*

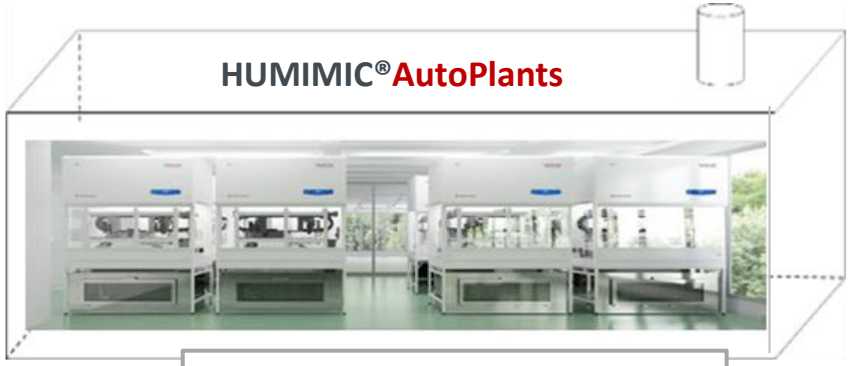
2018

Hübner et al.,
Sci Rep

Patient's benefit and animal welfare – an outlook for the next decades

Replace humanized animal models





Precli… …nced thera… …ment

- automation … …chip assays
- preclinical e… …ed therapies
- evaluation c… …ways of chemicals
- (pre)clinical … …ip" trials (MoA, PK, Pl… …)
- early evalua… …predisposition …

Science Perspective 17 Sep 2021

Human MPS for drug development

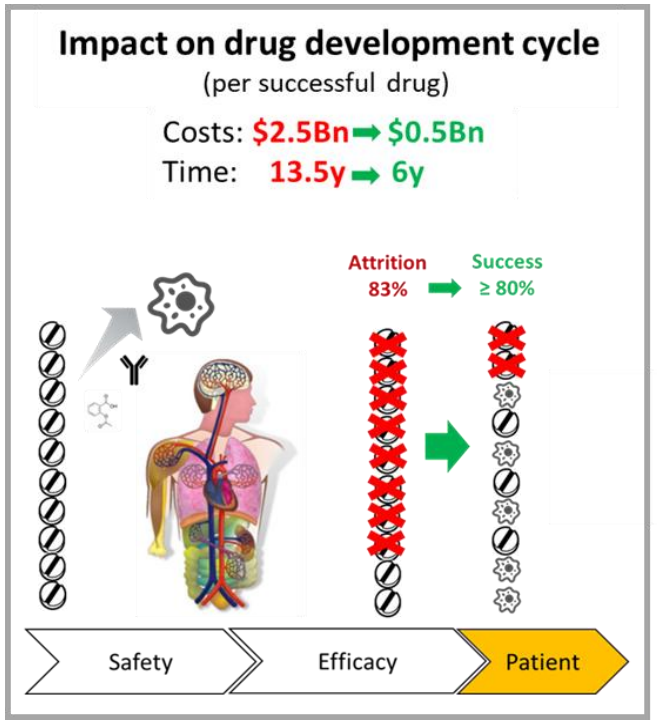
Adrian Roth and MPS-WS Berlin 2019

DOI: 10.1126/science.abc3734

EUTOXRISK

Replacing 70-80% of current laboratory animals

Turn current attrition rate into success



TISSUSE
Emulating Human Biology

Thank you!

Dr. Uwe Marx
CSO
+49 (0)30 5130 264 00
uwe.marx@tissuse.com

TissUse GmbH
Oudenarder Str. 16
13347 Berlin | Germany
Website: www.tissuse.com
Social Media: