

Microphysiological systems – from scientific models towards industrial adoption of qualified assays and their regulatory acceptance

*Uwe Marx,
Founder & CSO of TissUse, Germany*

The team is the key to innovation



- ISO 9001:2015 certified QMS
- revenue-based product and service business
- solid customer basis in Pharma and Academia
- 9 patent families with > 140 granted patents
- 16 human on-chip organ models established,
- 12 multi-organ combinations proven,
- 22 assay formats available

Organ-on-Chip, Multi-Organ-Chip, Body-on-Chip,
Human-on-Chip, collectively

Microphysiological systems (MPS)

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

For detailed definitions, please refer to:

- **Suzanne Fitzpatrick's presentation** (next one)
- **Recent MPS stakeholder report** (ALTEX, 2020, open access)

MPS-based **models, tests** and **methods**

MPS-based **qualified assays**

MPS-based **validated assays**

2nd MPS-stakeholder workshop: Berlin, June 18-20, 2019

Regulatory bodies – Acceptance through regulatory science, global harmonization



User industry - Validation and fit-for-purpose use



Supplier industry

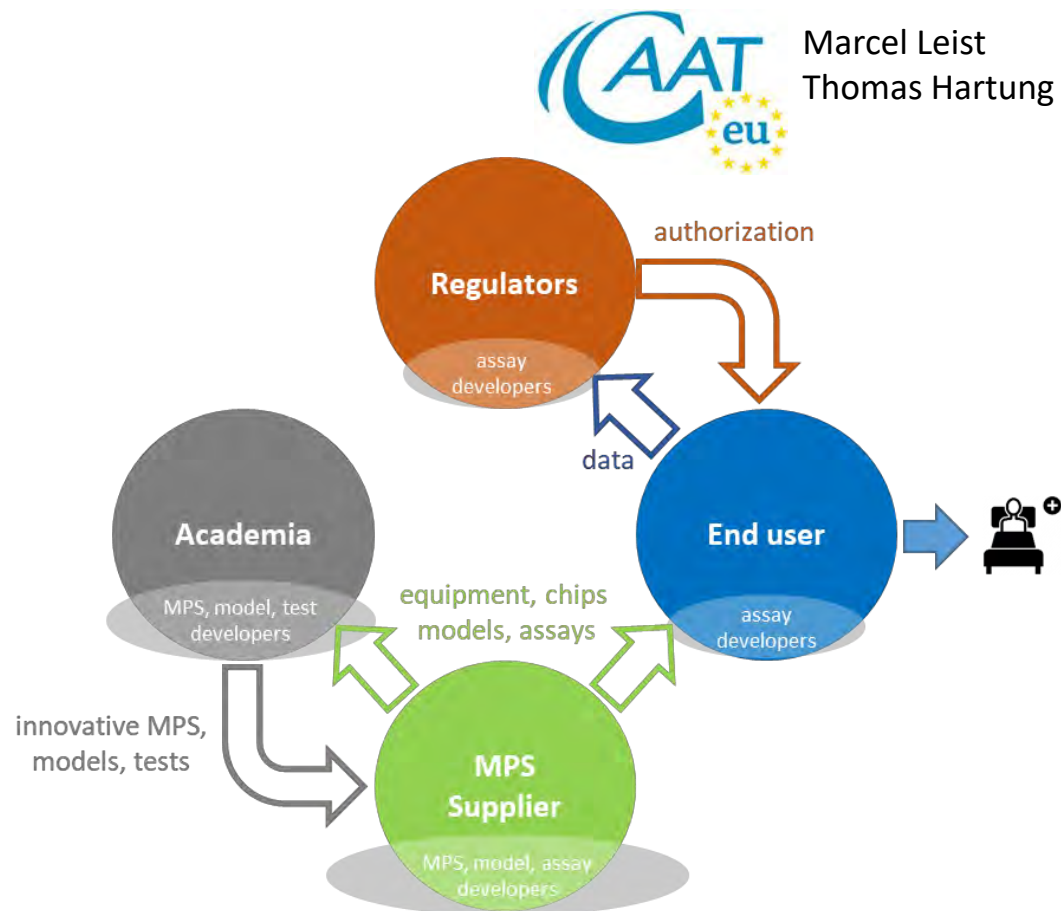
Translation into industrial adoption and regulatory acceptance



Academia – R&D roadmap, Body-on-a-chip definition



Deliverable



Marcel Leist
Thomas Hartung

Think Tank Report on:

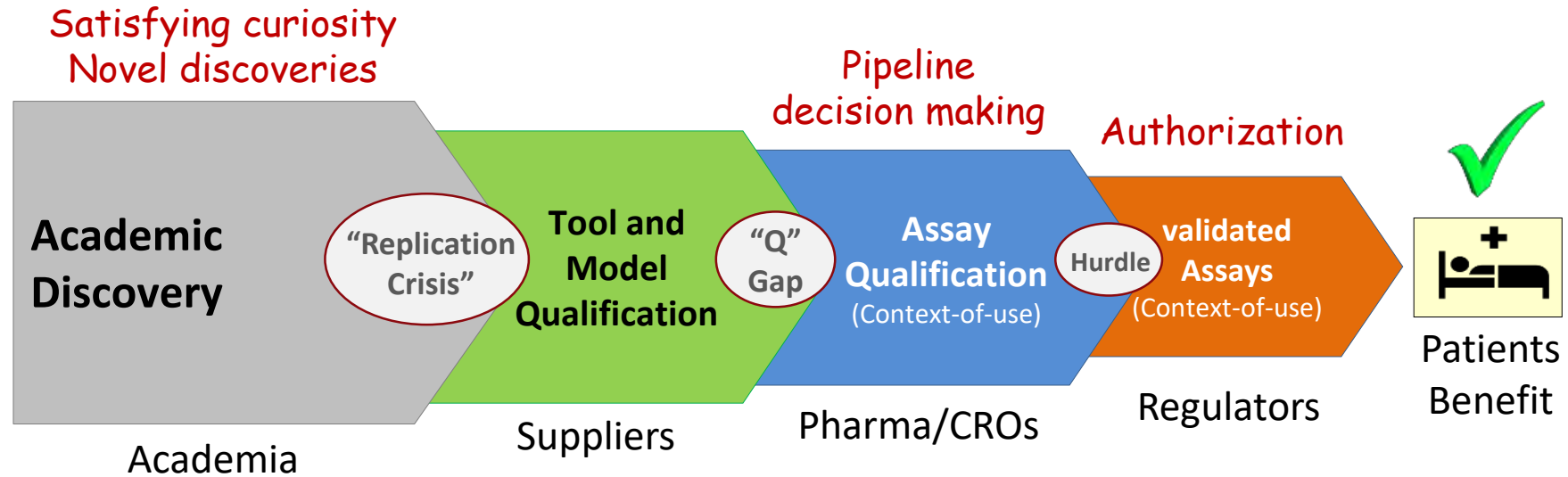
Biology-inspired Microphysiological Systems to Advance Medicines for Patient Benefit and Animal Welfare

Marx et al. *ALTEX* 2020, 37, 3; <https://doi.org/10.14573/altex.2001241> (open access 4.0)

Status quo + 20-year roadmap: short/mid term at higher resolution (10 ys) + long term goals and visions (20+ ys)

The key to industrial adoption and regulatory acceptance is a functional value chain

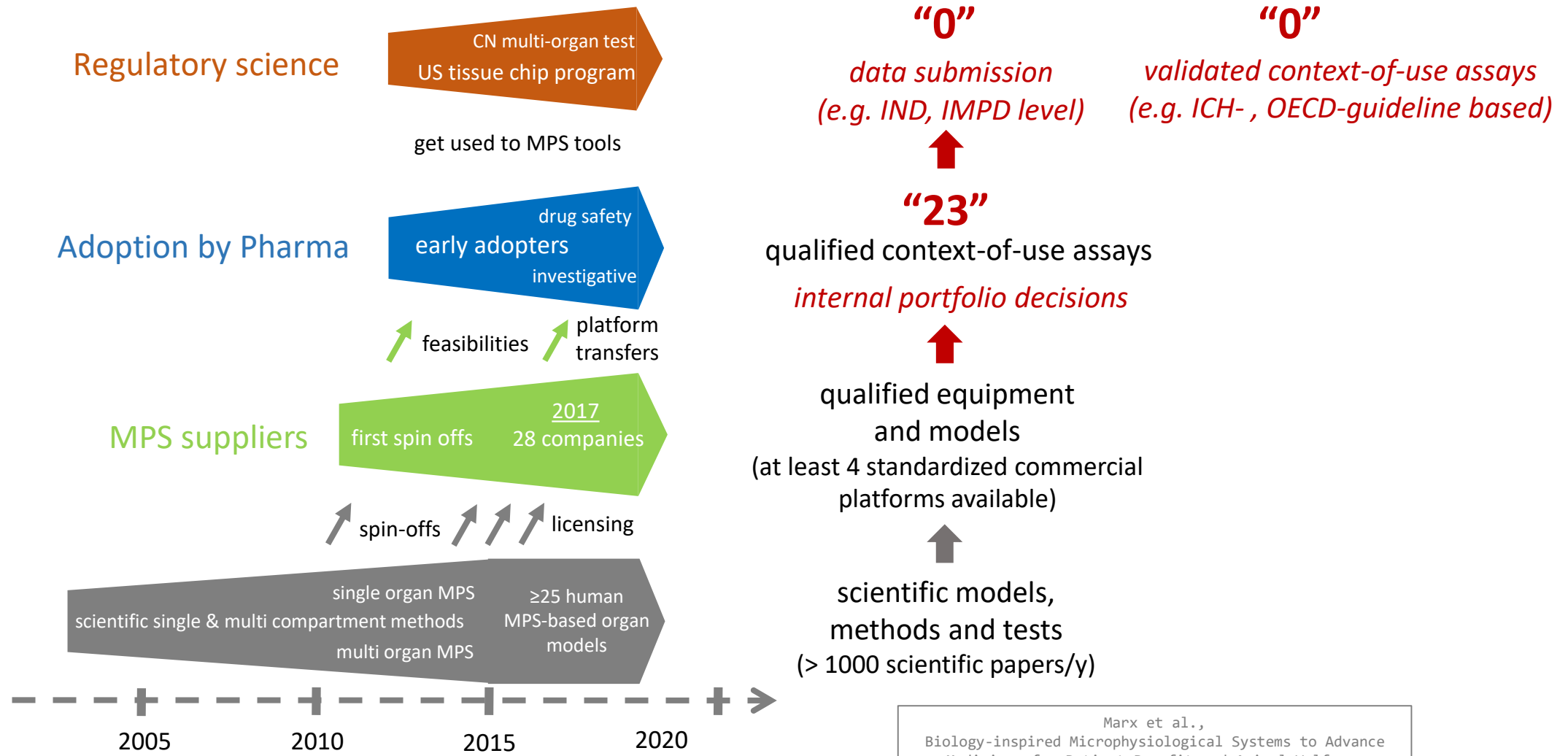
MPS-based assay value chain



Nature 2013 Begley et al.
Reproducibility: Six red flags for suspect work.

PLoS Med 2016 Ioannidis et al.
Why Most Clinical Research Is Not Useful.

Establishment of a stakeholder community for MPS



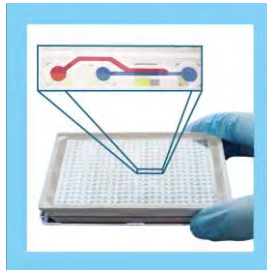
At least four commercially available MPS platforms

Test throughput
Single tissue/organ models

Biological complexity
Multi tissue/organ models



OrganoPlate®



Human Emulation System



PhysioMimix™



license



HUMIMIC®



Our 10-year KPI's for translational success

KEY PERFORMANCE INDICATORS

Pharma End Users ○ 4 decision making assays at 6 sites



A
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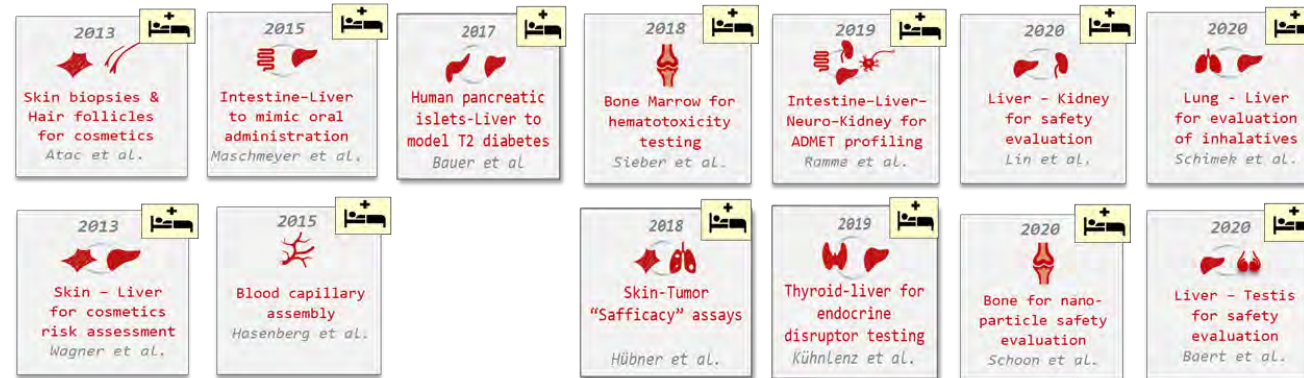


Supplier
2010

○ 16 human organ models ○ 12 multi-organ-models ○ 22 assays 2020

**2010
Academia**

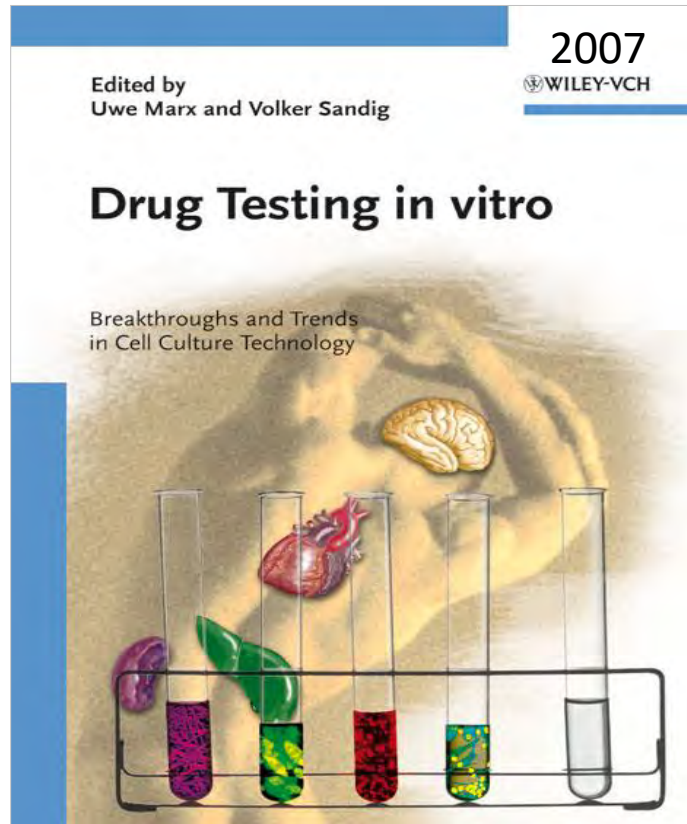
○ 47 Master Thesis ○ 14 PhD's, 9 Postdocs ○ 45 peer-reviewed papers 2020



13 papers targeted aspects of industrial adoption for patient's benefit and animal welfare



Working hypotheses for the HUMIMIC® technology platform

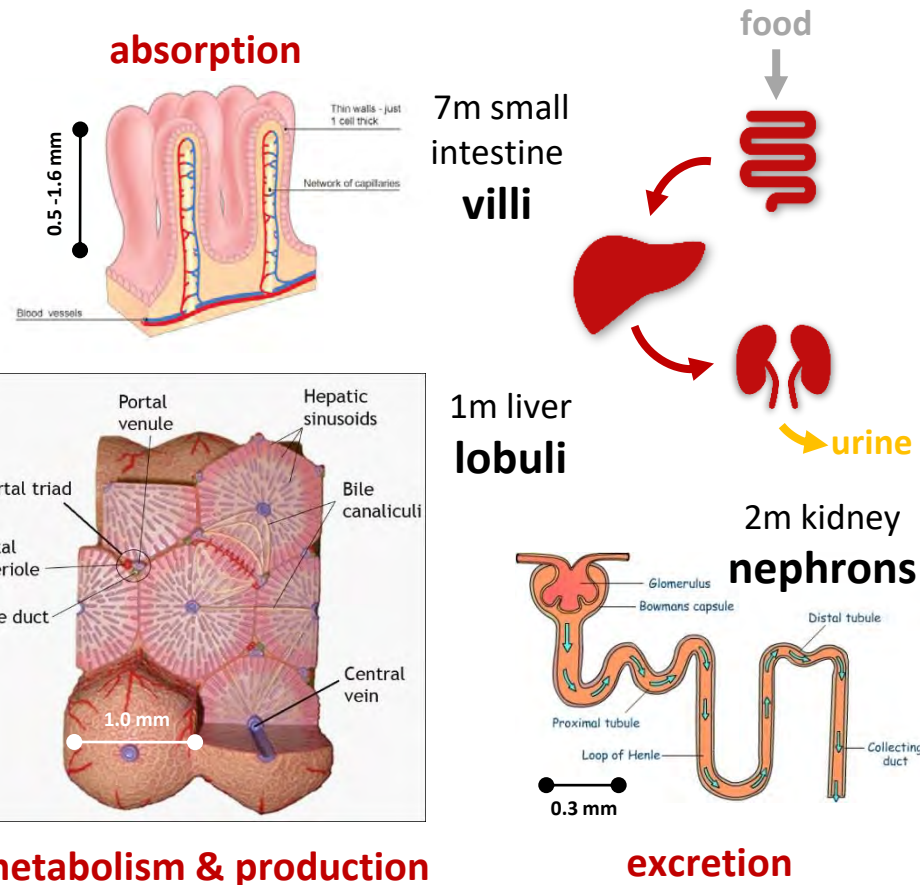


Chapter 11

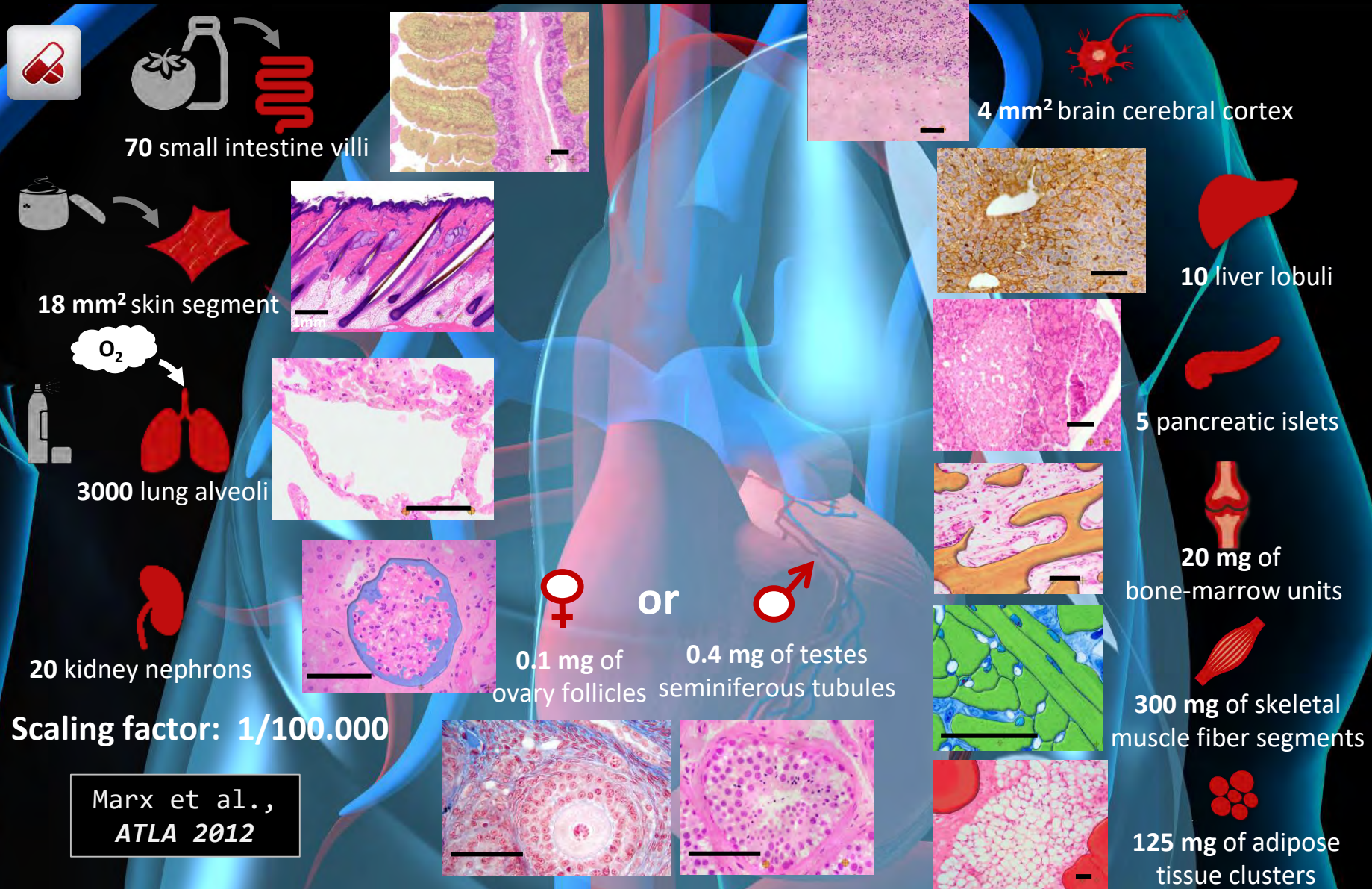
“How drug development of the 21st century could benefit from human micro-organoid in vitro technologies”

© 2007 Wiley VCH Weinheim, ISBN: 978-3-527-31488-1

- Organs are built up by multiple, identical, functionally self-reliant structural organoids
- Organoids are evolutionarily conserved and subject to genetically encoded self-assembly



Downscaling a human body: How small can we go?



Components of the HUMIMIC® MPS platform

Commercial Equipment

European IQ, OQ, PQ standards



HUMIMIC Starter
(4-8 circuits)



HUMIMIC AutoLab
(24-48 circuits)



HUMIMIC XX/XY

Rapid prototyping



HUMIMIC Chip2



HUMIMIC Chip3



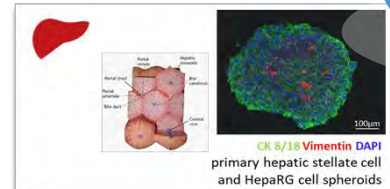
HUMIMIC Chip4

Qualified Biological Models

GCCP standards

Pamies et al.

ALTEX 2018



D1 ... D14 ... D28



Qualified Assays (Context-of-Use)

GCCP standards

Administration, Exposure time,
Dosing regimen, Controls

Organ model	Assay	Context of Use	Level of evidence	Assay
Brain (mouse)	Brain (mouse) model	Brain (mouse) model	1	1
Brain (human)	Brain (human) model	Brain (human) model	2	2
Brain (human)	Brain (human) model	Brain (human) model	3	3
Brain (human)	Brain (human) model	Brain (human) model	4	4
Brain (human)	Brain (human) model	Brain (human) model	5	5
Brain (human)	Brain (human) model	Brain (human) model	6	6
Brain (human)	Brain (human) model	Brain (human) model	7	7
Brain (human)	Brain (human) model	Brain (human) model	8	8
Brain (human)	Brain (human) model	Brain (human) model	9	9
Brain (human)	Brain (human) model	Brain (human) model	10	10
Brain (human)	Brain (human) model	Brain (human) model	11	11
Brain (human)	Brain (human) model	Brain (human) model	12	12
Brain (human)	Brain (human) model	Brain (human) model	13	13
Brain (human)	Brain (human) model	Brain (human) model	14	14
Brain (human)	Brain (human) model	Brain (human) model	15	15
Brain (human)	Brain (human) model	Brain (human) model	16	16
Brain (human)	Brain (human) model	Brain (human) model	17	17
Brain (human)	Brain (human) model	Brain (human) model	18	18
Brain (human)	Brain (human) model	Brain (human) model	19	19
Brain (human)	Brain (human) model	Brain (human) model	20	20

End users

Portfolio decision making

- internal portfolio decision making
- hazard identification, tier 3
- supportive data for IND/IMP

Regulators

Registrations,
Approvals

Regulatory-acceptable
options to validate assays

Academia

Animal-free
discovery

Features of the HUMIMIC[®] platform, supporting easy transfer

CE



HUMIMIC Starter



HUMIMIC AutoLab



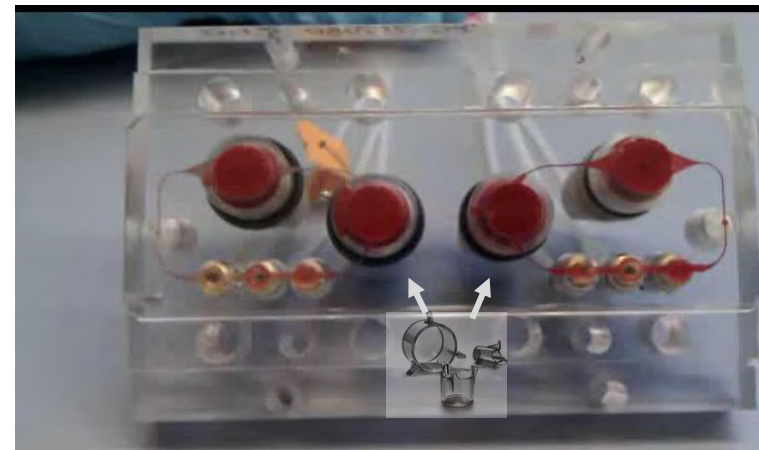
HUMIMIC Chip2



HUMIMIC Chip3



HUMIMIC Chip4



Cell culture inserts (96-/12-/24-well format)















































Manufacturing:

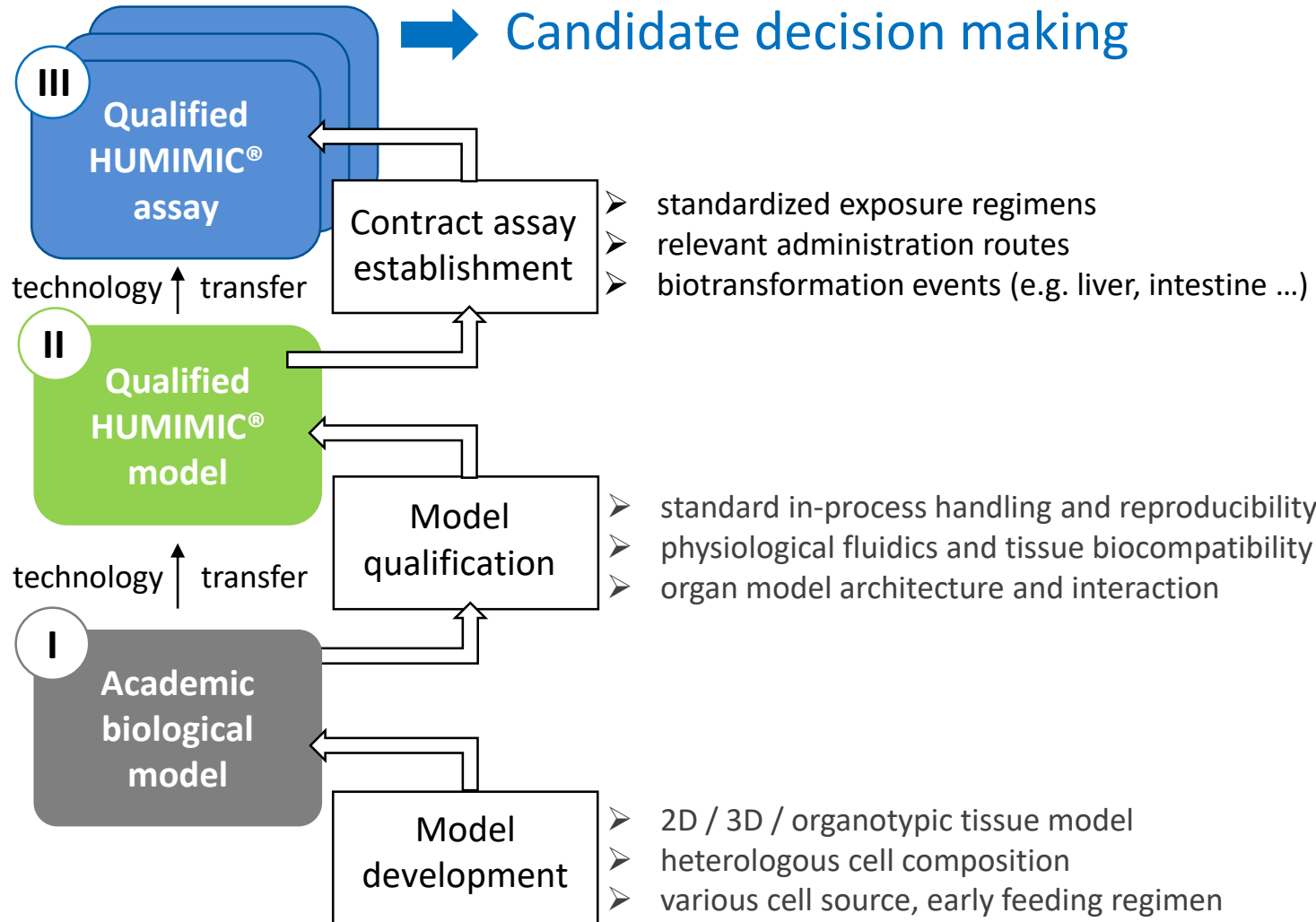
- In-house manufacturing of equipment
- HUMIMIC Starter: 4x HUMIMIC Chip2
- HUMIMIC AutoLab: 24x HUMIMIC Chip2
- Dedicated chip manufacturing environment
- Rapid prototyping for customer specific solutions

Features:

- Size of a standard microscope slide
- On-chip micro-pump enabling pulsatile flow
- Suitable for primary and iPSC-derived cells, 3D constructs, biopsies and cell lines
- Compatible with live tissue imaging
- Plug-in option for insert-based barrier models

The 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	



MPS assays used for internal portfolio decision-making in drug development

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

$\Sigma = 23$ cases

Marx et al.,
Biology-inspired Microphysiological Systems to Advance
Medicines for Patient Benefit and Animal Welfare.
ALTEX 2020

Korean Webinar, 05.03.21

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

2017

Bauer et al.,
Sci Rep



2019

Kuehnlenz et al.,
Toxicol Lett (Abstract)

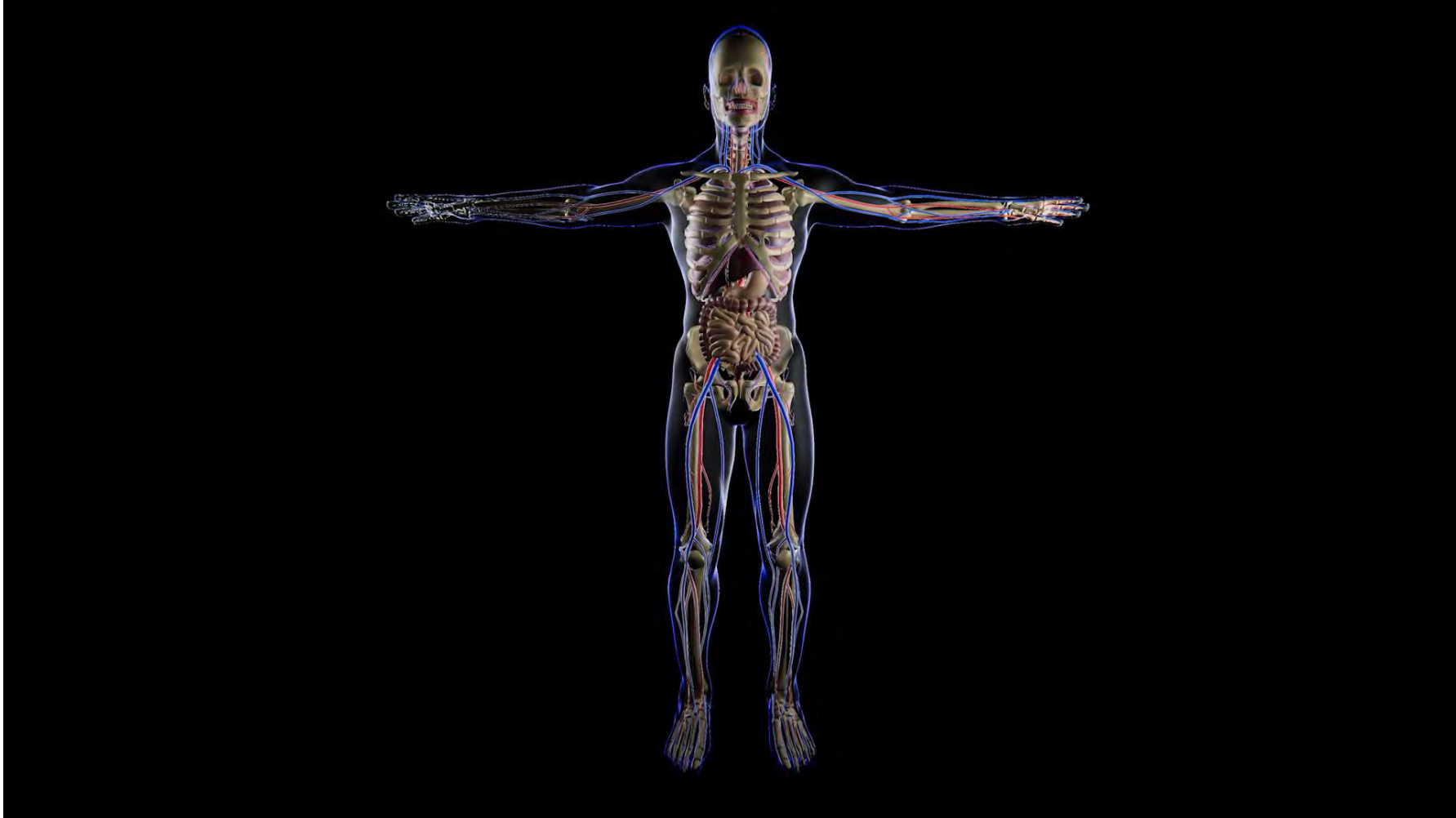


2018

Hübner et al.,
Sci Rep



Modelling the human bone marrow unit



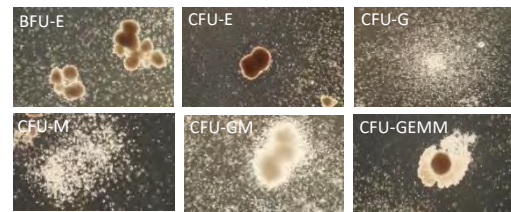
Hematopoietic potential of the HUMIMIC® bone marrow chip

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 2018

four-week MOC culture



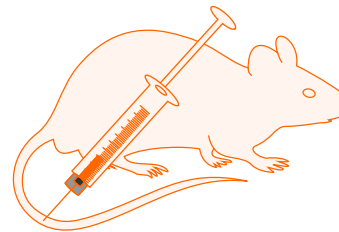
HUMIMIC Chip2



colony-forming unit assays

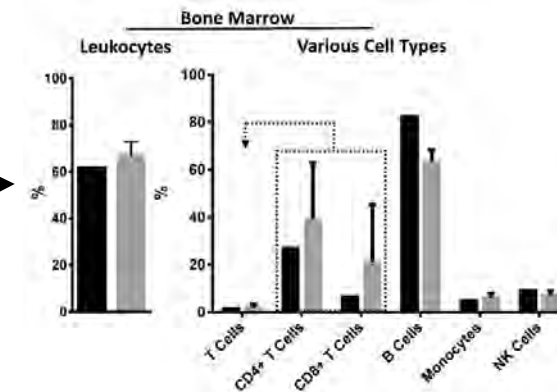
Type	Isolated HSCs	Day 28 (n=7)
BFU-E	9	9 ± 4
CFU-E	10	7 ± 2
CFU-G	9	23 ± 7
CFU-M	6	14 ± 5
CFU-GM	3	4 ± 2
CFU-GEMM	11	5 ± 2

bone-marrow repopulation of irradiated NOG mice

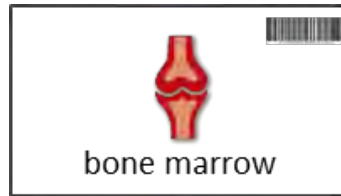


Korean Webinar, 05.03.21

Human cell engraftment
(20 weeks after injection)



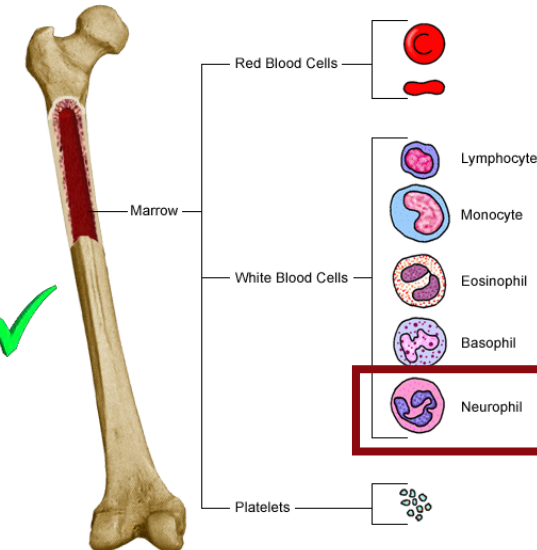
Industrial adoption for a specific context of use - a 2-year process



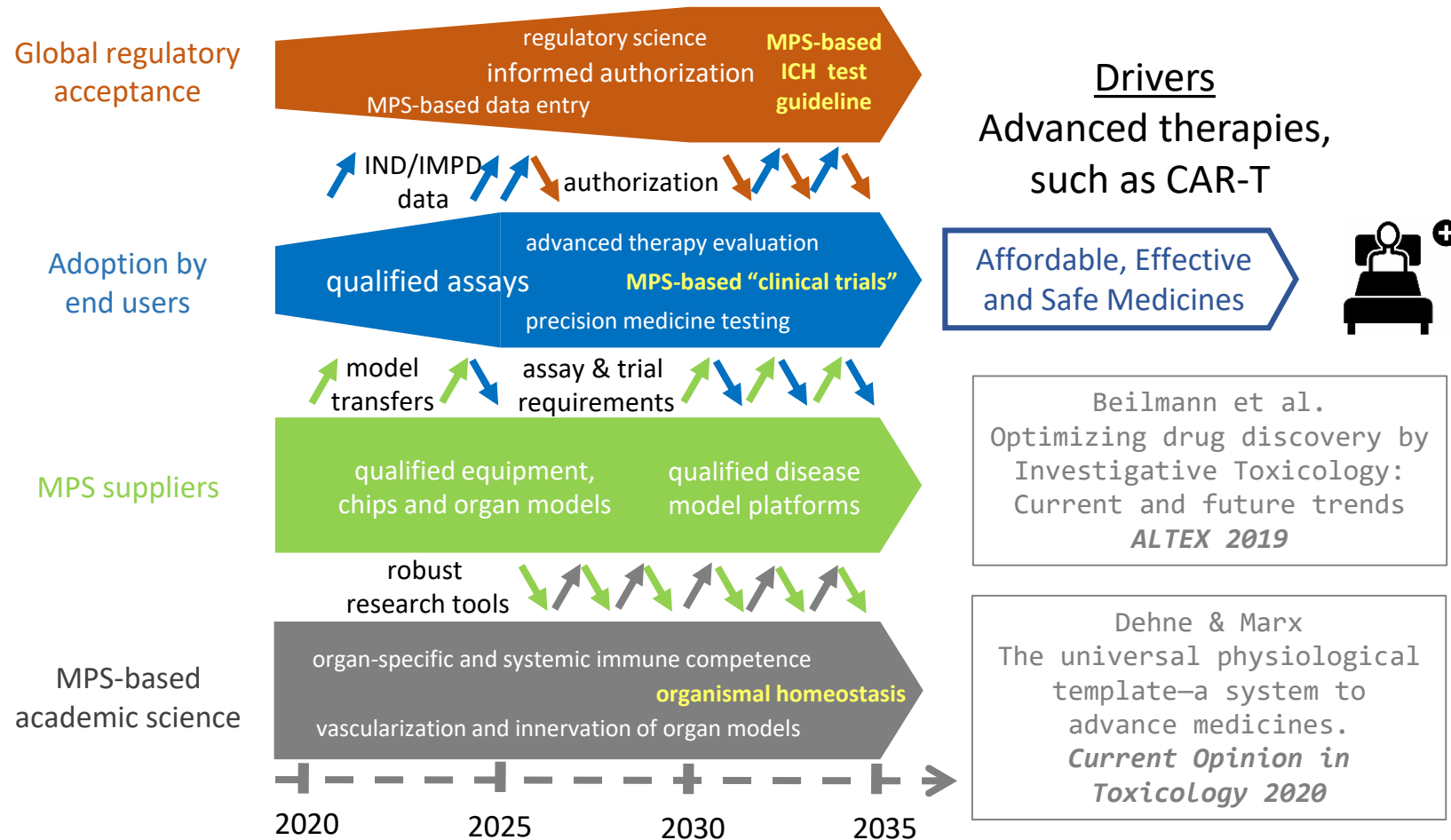
Rationale: Use for human repeated dose hematopoietic lineage toxicity testing (scheduling)

- Prolongation of culture period (eight weeks) ✓
- Commercial cell source supply secured ✓
- Process optimization for cost reduction ✓
- In-depth model characterization (resident vs. circulating cells) ✓
- Inter-laboratory qualification ✓

technology transfer ✓



The MPS Roadmap into the future



Conclusion

At academic level MPS-based **scientific models, methods and tests** support new discoveries and add to the investigation of mode of action of drug candidates and therapies



Qualified MPS- based single- and multi-organ-models can provide **qualified context of use assays** for safety and efficacy testing of for candidate drugs and advanced therapies.



The US FDA is the frontrunner in establishing frameworks for the end-users to **validate such context of use assays** within regulatory approval processes.



Please, refer to the next presentation of Suzanne Fitzpatrick, US FDA

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4	Intestine - Liver		Absorption, metabolism	III	
5	Lung - Liver		Hazard identification	III	
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For further information on any available product, model or assays ...

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Kuehnlenz et al.,
Toxicol Lett (Abstract)

2018



Hübner et al.,
Sci Rep

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Thank you!

Academic support



Industrial adoption



others

Fostering approaches for regulatory acceptance of MPS-based assays



Korean Webinar, 05.03.21

