Organoids, an industry perspective

Patrick Guye

Co-founder and Partner, Trilliome

https://www.linkedin.com/company/trilliome
https://consulting.trilliome.com

About myself

Mammalian SynBio
hES/hiPS reprogramming
Directed differentiation
Engineered 3D models
Liver / Tumor / Neural

R&D, PM, Services
3D systems for:
Oncology
Diabetes
Liver Diseases
Liver Tox
MPS/BOC Systems

UNI BASEL 2007 | Massachusetts Institute of Technology 2014 | 2016 insphero 2019 TRILLIOME

PhD | Academia in US | Pharma | Biotech | Consulting

Molecular
Infection
Biology

Cell Therapy and DD
hiPSC to Pancreatic Tissue
Cell engineering for
biologics production

Organoids/3D Systems
CGT with focus on SynBio
Immuno-Oncology/Inflam.
Digital Medicine
Microbiome

Organoids: applications & challenges

- Basic research
- Drug discovery & development
- Personalized medicine
- Cell therapy / regen. med.
- Cultured meat / agritech

- Delivering value – where and how
- Manufacturing
  - Cell sources
  - Required complexity
  - Growth/Assembly
  - Maturation
  - Scalability
- Reproducibility
  - Long-term availability
  - Diseasability
- Composition
- Validation
- Consent
- Endpoints/Information extraction
- Distribution
- Summary

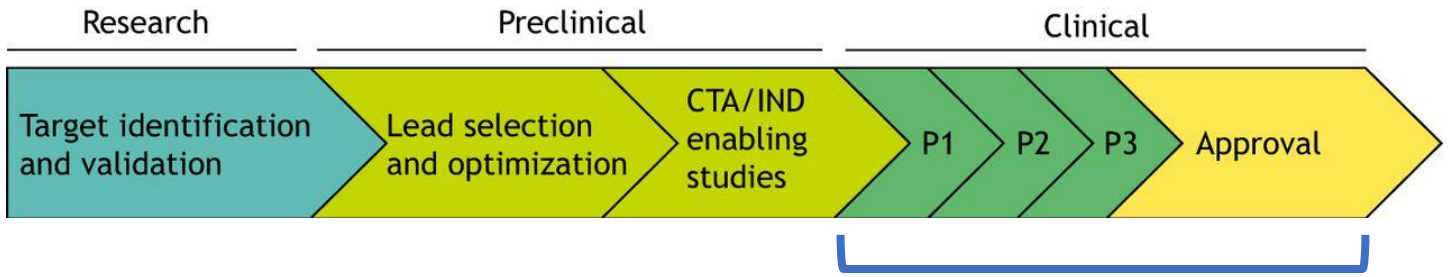
Where drug discovery & dev. needs a fix

Simple in-vitro models

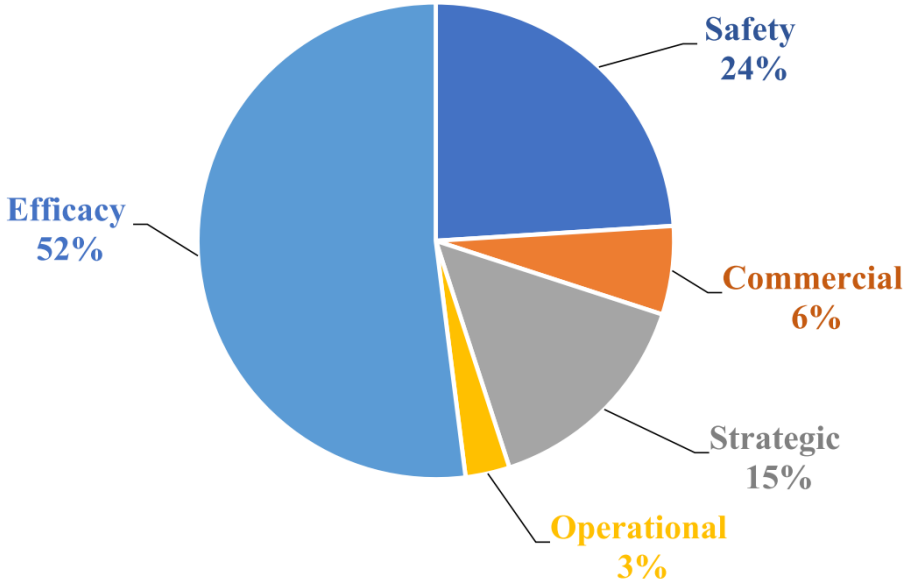
Animal models

Humans

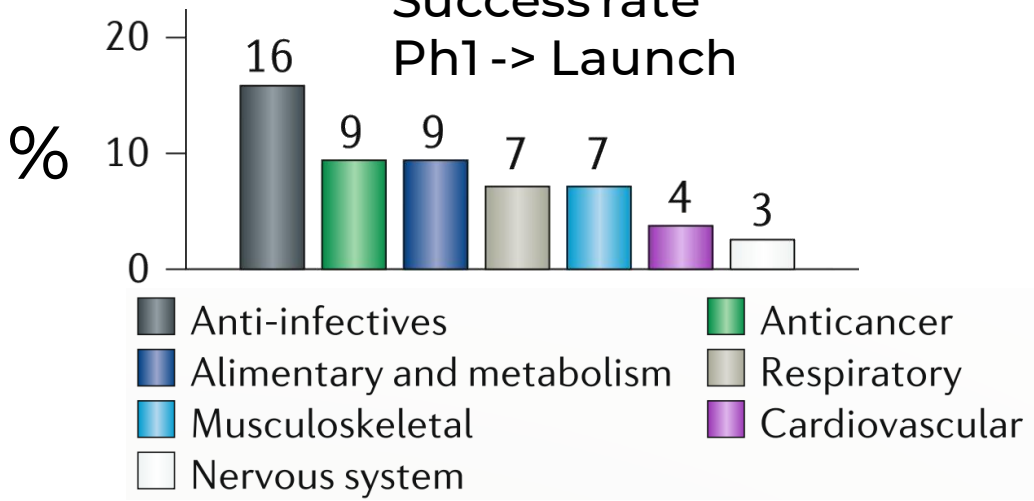
13 years
USD 2-3 B



Reasons for failure

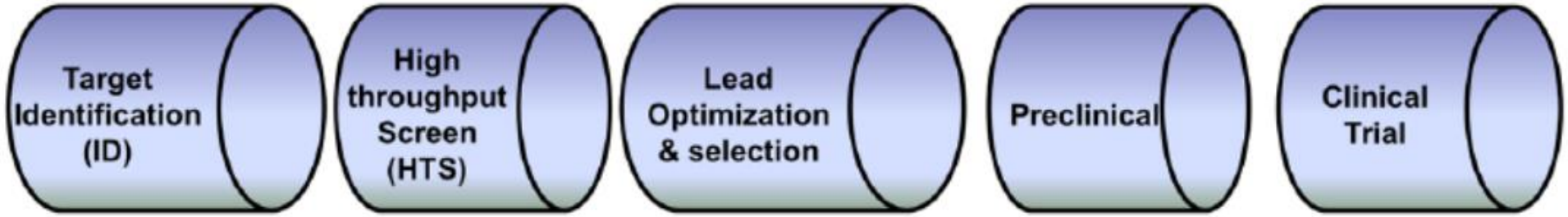


Success rate
Ph1 -> Launch



https://doi.org/10.1038/d41573-019-00074-z
https://doi.org/10.1186/s43094-020-00047-9

Three-Dimensional Cell Cultures in Drug Discovery and Development



Disease modeling
- Spheroids (82,83,84,85,86,87)
- Organoids (81,90,91,92,93,94,95)
- Organs-on-chips (55,56,57)

Target ID
- Spheroids (99)
- Organoids (81)
- Organs-on-chips (59)

HTS
- Spheroids (105,106)
- Scaffolds
- Hydrogels
- Organoids (107)

Efficacy profiling
- Spheroids (113)
- Organoids (112)
- Organs-on-chips (114)

Toxicity profiling
- Spheroids (117,118)
- Organoids (30,116,117)
- Organs-on-chips (60,61, 57)
- 3D bioprinting (62)

Pharmacokinetics

Pharmacodynamics
- Liver spheroids (116)
- Liver organoids
- Body-on-chip (63,64,65,66)

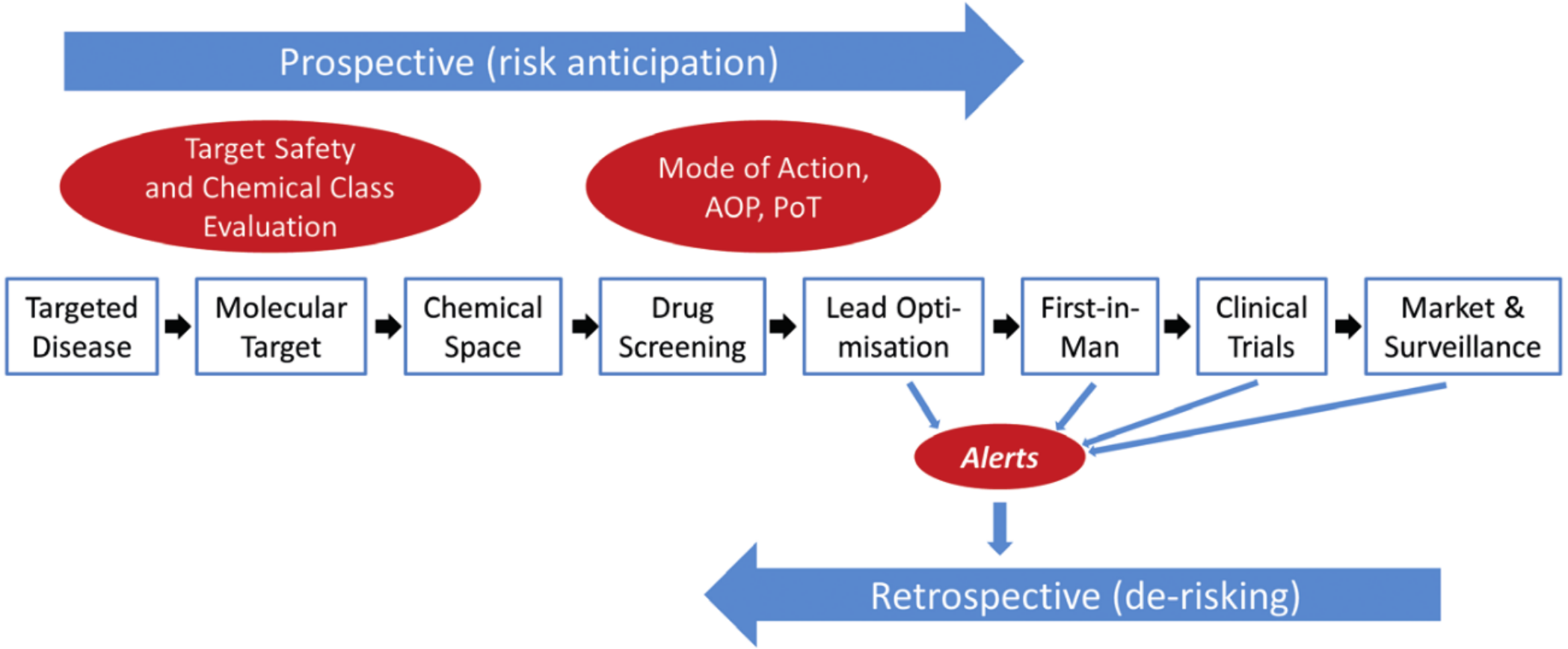
Regenerative medicine
- Stem cell spheroids (132,133)

Transplantation
- Organoids (136)
- 3D bioprinted tissues/organs (137)

Precision medicine
- Patient derived spheroids (112)
- Patient derived organoids (112)

https://doi.org/10.1177/1087057117696795

Prospective and retrospective

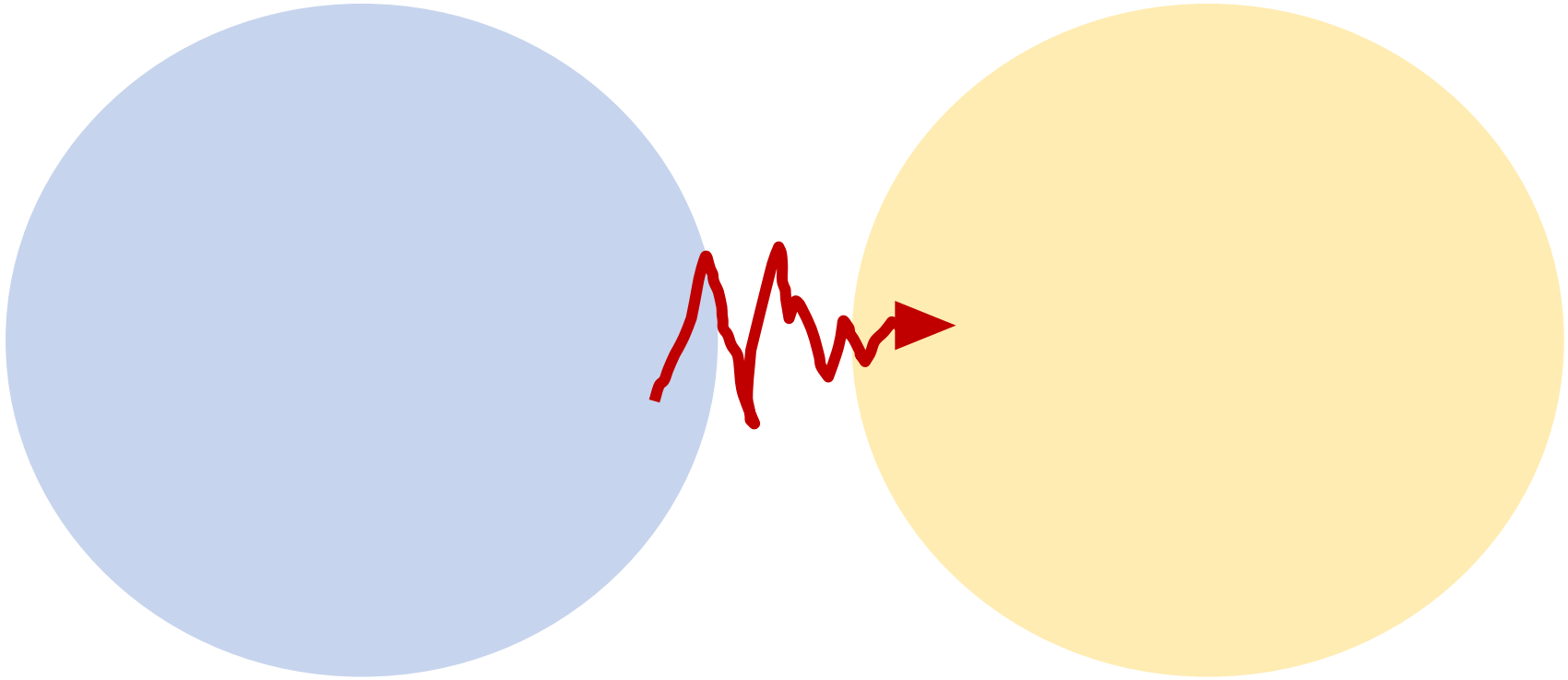


https://doi.org/10.14573/altex.1808181

Before complex 3D models

Experimental Models

Human patients



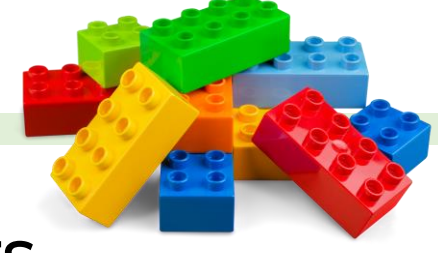
The promise of complex 3D models

Experimental Models

Human patients

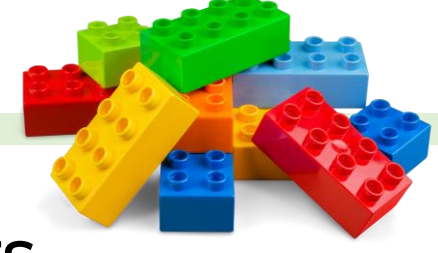
Challenges

Cell Sources



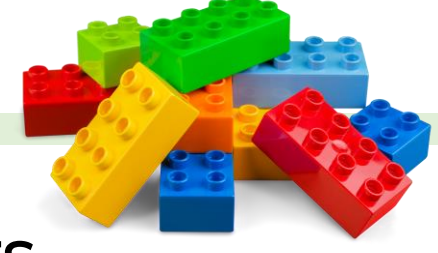
	LIMITATIONS	ADVANTAGES
Cells from donors	• Limited availability • Donor-donor variation • Difficult to genetically modify	• Excellent performance (mature, adult cells)
Adult stem cells		
iPSC’s		

Cell Sources



	LIMITATIONS	ADVANTAGES
Cells from donors	• Limited availability • Donor-donor variation • Difficult to genetically modify	• Excellent performance (mature, adult cells)
Adult stem cells	• Generating mostly epithelial tissues – missing other cell types • Difficult to genetically modify	• Established simple protocols (e.g. Clevers method) • Unlimited source
iPSC's		

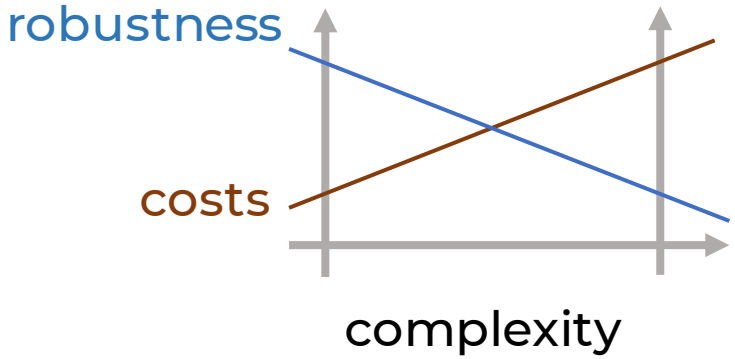
Cell Sources



	LIMITATIONS	ADVANTAGES
Cells from donors	• Limited availability • Donor-donor variation • Difficult to genetically modify	• Excellent performance (mature, adult cells)
Adult stem cells	• Generating mostly epithelial tissues – missing other cell types • Difficult to genetically modify	• Established simple protocols (e.g. Clevers method) • Unlimited source
iPSC's	• Labour- and QC-intense differentiation protocols needed • Resulting cells mostly embryonic/fetal in nature	• Potential for generating any cell type, tissue or organ • Unlimited source • Easy to genetically modify

Required Complexity

homotypic | heterotypic | Multi-germ layers | MPS/BOC-compatible | Complex tissue structure | Non-human components (e.g. microbiome)

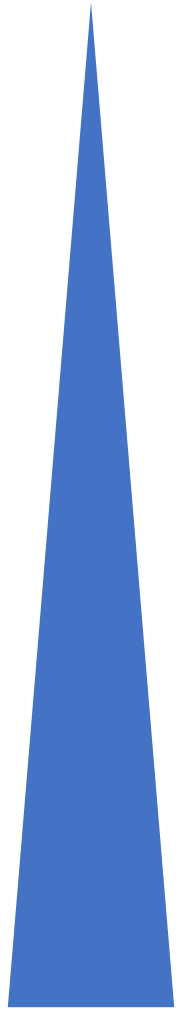


“As Simple as Possible, as Complex as Necessary”

“Fit for purpose”

Required Complexity

2D Hepatocytes	OK for acute tox studies (24 – 48h)
3D Hepatocytes	OK for simplified chronic tox studies (up to a month)
3D Hepatocytes + Stellate Cells	OK for simplified hepatic fibrinogenesis
3D Hepatocytes + Kupffer Cells	OK for better chronic tox studies (up to a month)
3D Hepatocytes + Kupffer Cells + CD4+ T-cells	OK for simplified immune-mediated tox studies (e.g. checkpoint inhibitors)
3D Hepatocytes + Stellate Cells + Kupffer Cells + Endothelial Cells	OK for complex, chronic, inflammation-mediated diseases (e.g. MAFLD)



Costs
Complexity
Physiological Relevance

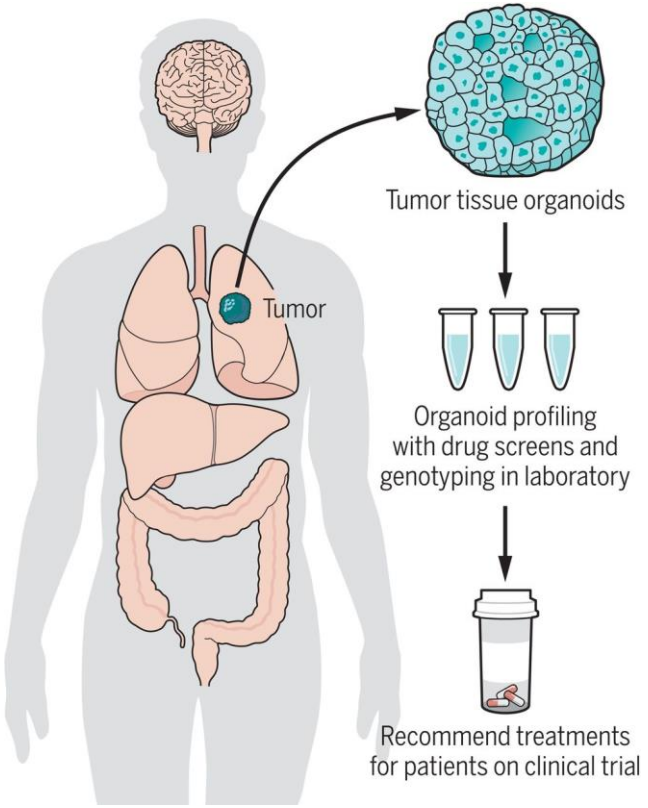
Good enough in oncology?

Immortalized cells in 2D

Immortalized cells in 3D

Immortalized cells in 3D + Fibroblasts

Immortalized cells in 3D + Fibroblasts + Immune cells



PDX-derived In 3D

PDX-derived In 3D + Fibroblasts

PDX-derived In 3D + CAFs

PDX-derived In 3D + CAFs + Immune cells

Primary, direct

Just PBMCs or tumor-resident immune cells?

Lymph nodes??

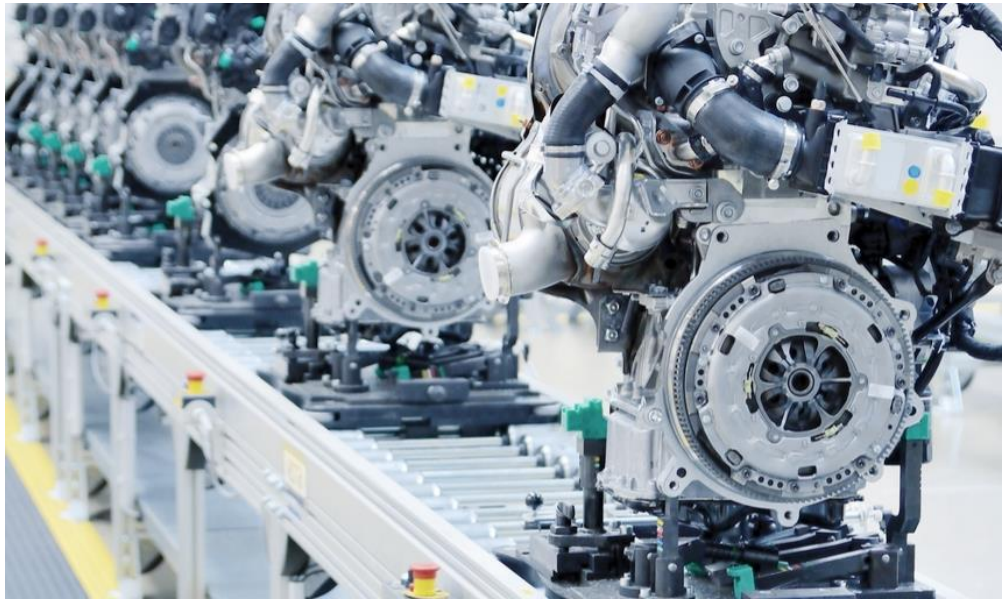
Physiological relevance

https://doi.org/10.1126/science.aaw6985

Scalability: from art to industrial process

Work of Art

That’s fine for model development
or highly explorative basic research



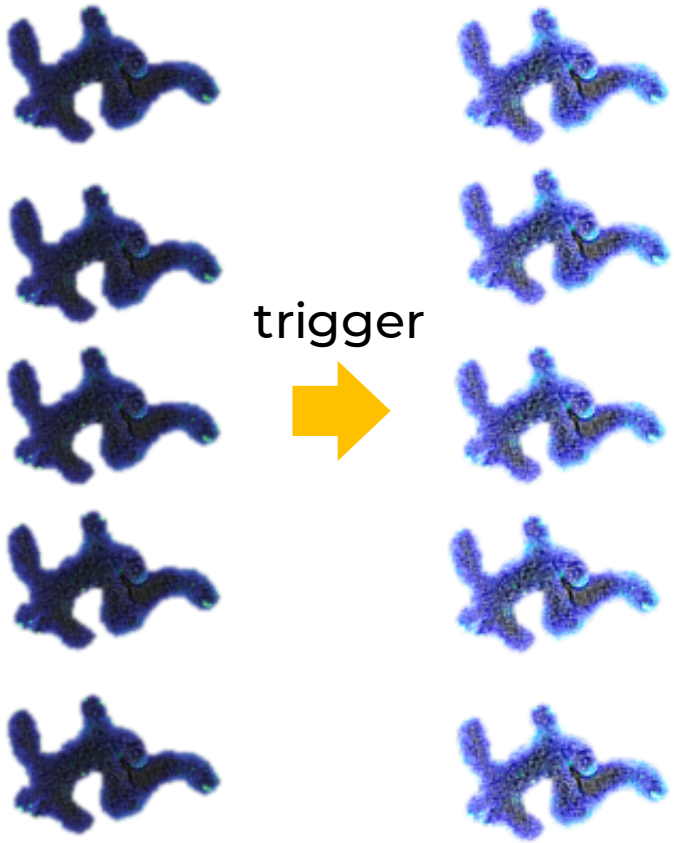
Industrial process

That’s necessary for everything afterwards

Max Hauri Art / Saffron Interactive

Diseasibility

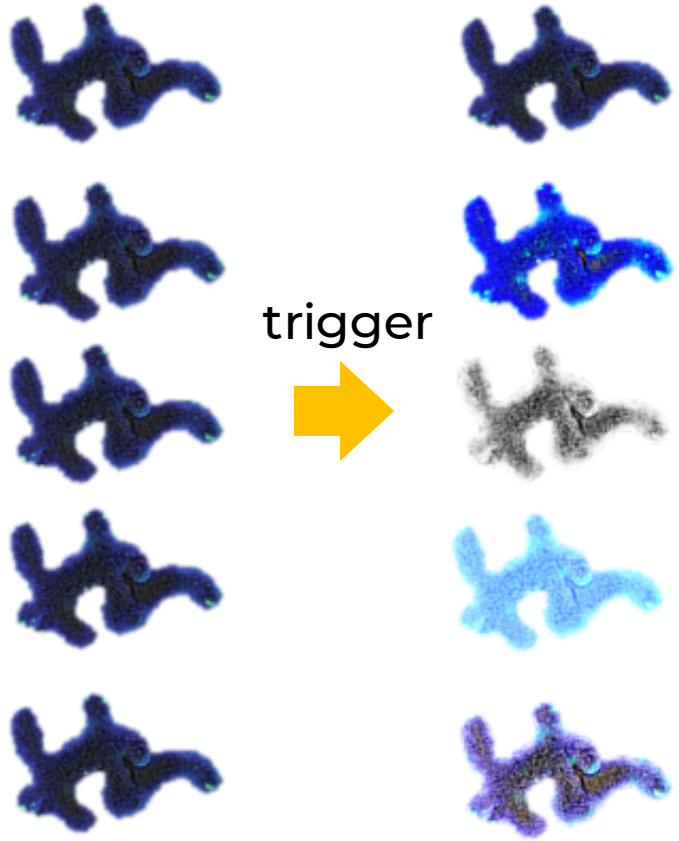
What is wished for



Healthy Organoids

Diseased Organoid

How it often looks like

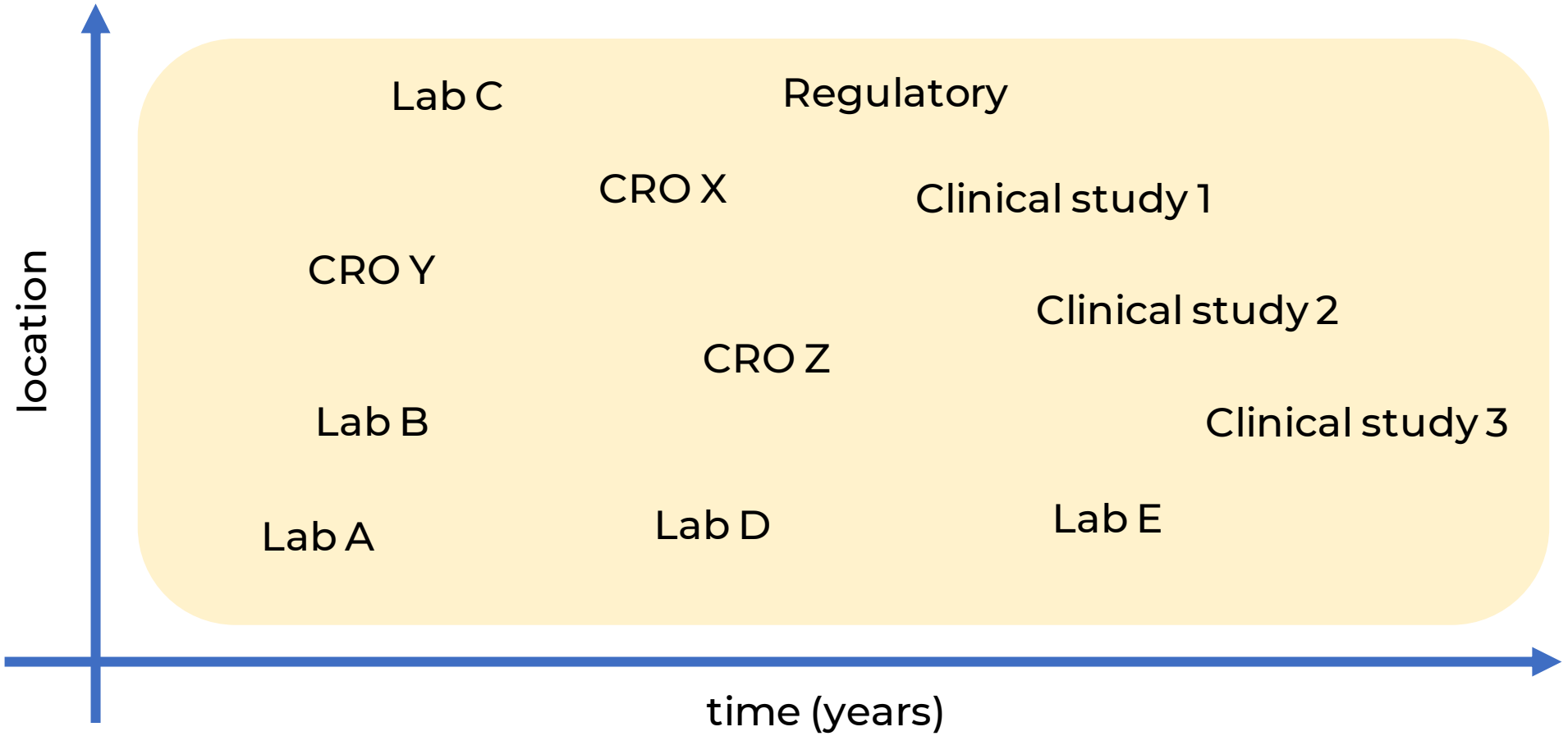


Healthy Organoids

Diseased Organoid

384w plate, https://per-form.hu

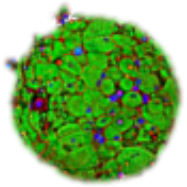
A perfect 3D model…



Cell sources
Biobanking
Cell culture media
Cell culture hardware
Expansion systems
Experts/technicians
Protocols
QC's / Performance
Delivery

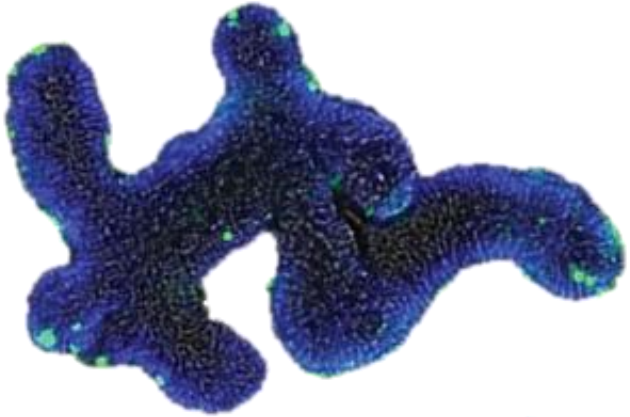
Growth / Assembly

- Self-aggregation



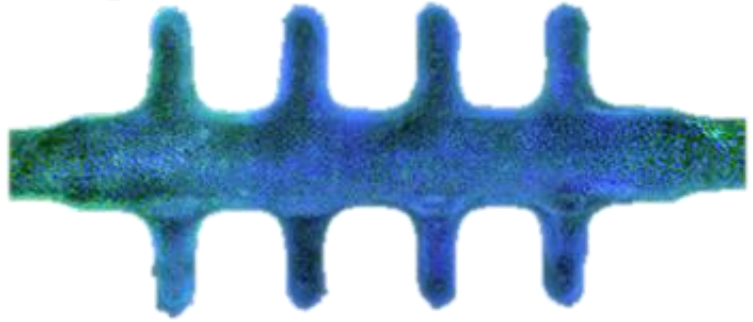
Highly scalable, reproducible
Limited complexity

- Self-assembly



Quite scalable, quite variable
Higher complexity

- Guided assembly



Less scalable, more reproducible
Higher complexity

Spheroid: InSphero
Intestinal Organoid, freestyle: Stem Cell Technologies
Intestinal Organoid, patterned: M. Lutolf, EPFL

Regulatory Efforts

https://www.fda.gov/media/144891/download

Commercial Liver MPS in late 2020

MPS	Chip supplier	Design	Content[a]	Throughput[b]	Cells	Key characteristics
vLAMPS[56]	Micronit	Two-channel with membrane	High	Med	PHH, LSEC, THP-1, HSC	ECM: collagen and LECM; Material: Glass, PC; physiological zonation
Liver-Chip[37,200]	Emulate	Two-channel with membrane	High	Med	PHH, LSEC	ECM: Matrigel; Limitation: PDMS material[c] and PC; automated platform
LAMPS[59]	NortisBio	One-chamber	High	Med	PHH, HMVEC or LSEC, THP-1, HSC	ECM: collagen and LECM; Limitation: PDMS material[c]; single oxygen zones
ExVive[201,202]	Organovo	Bioprinting on array of 24-well Transwell membranes	High	Med	PHH, HUVEC, HSC plus KC[203]	ECM: Novogel; Material: PS, PC; Limitation: static
Organo-Plate[50,204]	Mimetas	Array of 96 two-channel chips, phase-guide, rocker-driven flow	Med	High	HepG2, iPSH, HMVEC, THP-1	ECM: collagen; Material: glass and PS; Limitation: bidirectional perfusion
PREDICT96 (REF.[79])	Draper	Array of 96 two-channel chips, with membrane, 96 pump array	Med	High	PHH	ECM: collagen, fibronectin; Material: COC, PC
LiverChip[66,74,109,205]	CNBio Innovations LLC	Array of 12 bioreactors with cells cultured on 3D PC scaffold	Med	Med	PHH, HK and HSC or NPC	ECM: collagen; Material: PS, PU, PC, self-assembly, integral perfusion; Limitation: no imaging until end of study
Microliver[206,207]	HμRel	Array of four chambers	Med	Med	PHH, NPC	ECM: collagen; Material: PC and elastomer
HemoShear Chip[65,208]	HemoShear	Two-channel with membrane, cone-plate to induce flow stimulation	Med	Low	PHH, HSC, HM	ECM: collagen; Material: Plastic, PC

PHH: primary human hepatocytes
LSEC: liver sinusoidal endothelial cells
THP-1: monocyte cell line
HSC: hepatic stellate cells
HMVEC: human microvascular end. cells
KC: Kupffer cells
HepG2: hepatocyte cell line
NPC: non-parenchymal cells

https://doi.org/10.1038/s41575-020-00386-1

Information Extraction / Endpoints

Non-destructive

Biochemical sensors
Genetic sensors
Live reporters (XFP / Luc)
Imaging (limited)
Electrodes in system
Proteomics (supernatant)
Lipidomics (supernatant)
ELISA (supernatants)
Electronic Chips
…

Destructive

Transcriptomics
Imaging on fixed tissue
Proteomics (in-cell)
…

Image: Perkin-Elmer

Biobanking in Precision Medicine

passive donors

‘consent or anonymize’ paradigm

active donors

‘consent for governance’ model
‘dynamic consent’ model
….

- specific characteristics of future research are unknown at the time of consent
- Full de-identification might be at odds with the patient’s need

https://doi.org/10.1242/dev.177972

What does a customer get?

- An empty MPS chip with guidance?
- An empty MPS chip, separately with cells/microtissues/organoids?
- An MPS chip pre-filled with cells/microtissues/organoids?
- A service (off-site)

Players

Big Pharma

Academia

CROs

Biotech (Producer)

NIH / NCATS

Biotech (Consumer)

FDA

Expert Forums

Potential and Challenges

- Making drug development faster and more successful
- Patient cohorts in an incubator
- Personalization of therapies (focus Oncology)
- Spare parts (cells, tissues) for regenerative medicine
- Animal meat w/o the animal

- Cell sourcing
- Reproducibly & reliability
- Manufacturing & scaling
- Harmonization, Regulation
- Performance metrics/datasheets
- Cost-efficiency
- Biobanking
- Modern consent rules

Thanks!

Questions, Comments?

patrick.guye@trilliome.com

https://www.linkedin.com/company/trilliome
https://consulting.trilliome.com

Regenerative medicine / CGT

REPORT

Cholangiocyte organoids can repair bile ducts after transplantation in the human liver

Fotios Sampaziotis[1,2,3,*], Daniele Muraro[1], Olivia C. Tysoe[1,4], Stephen Sawiak[5], Timothy E. Beach[4], Edmund M. …

+ See all authors and affiliations

Science 19 Feb 2021:
Vol. 371, Issue 6531, pp. 839-846
DOI: 10.1126/science.aaz6964