The 3Rs: are Human Stem Cells and Organs on Chip alternatives?

Towards precision medicine in future healthcare

Christine Mummery

Leiden University Medical Centre
University Twente
hDMT
Three kinds of human stem cells

- Pluripotent Stem cells
  - Derived from human embryos
  - Can form all cells in the body
  - ‘Reprogramming’

- Adult stem cells
  - From bone marrow, gut, lung, liver, pancreas (as organoids), etc.
  - Form cell types of the tissues from which they are derived
    - From skin, blood, urine etc.

- Induced pluripotent stem cells
Pluripotent stem cells can be derived from skin, blood, urine, teeth ... and differentiate to (patient or healthy) heart, brain, liver, pancreas cells... in just a few months. Organoids can be formed from all gastrointestinal organs, prostate....

Human iPS cells and adult stem cell organoids are ethically widely accepted.

Genetically identical to the donor so capture all of their inherited characteristics.
Drug research is expensive and costs are rising

In silico, cell lines, animal models

discovery

preclinical testing

phase I clinical trial

phase II & III

FDA/EMA approval

Average time: 12 years

market

Average costs: $3.4-5.5 billion per drug to market

~85% of new drugs fail in first trials in humans

Little incentive to develop drugs for rare diseases
Cost-cutting in drug development for common diseases challenging

Source: Innothink Center for Research in Biomedical Innovation; FactSet Systems; FDA
Human heart cells in drug research

- Heart disease: high mortality and morbidity
- Market value: 141.3 billion €
- Increasing market due to aging population and prolonged survival after cancer treatment
- No new drugs for heart failure in the “pipeline”
- 20% of drugs are not suitable for clinical use because of side effects on the heart
- Can we use bioassays based on human stem cells derived cardiovascular cells for safety pharmacology, drug repurposing and lead compound discovery?
Drug Toxicity

Micro Electrode Array (MEA) analysis of drugs on cardiomyocytes from human pluripotent stem cells

Field potential "ECG" measurement + correlation with clinical data

Induction of cellular arrhythmias

Heart cells from healthy stem cells

Heart cells from patient stem cells

MEA Chip

Control

Dofetilide

Beat-to-beat variability

EADs

Braam et al 2010, 2013

FDA will adopt this kind of assay for safety pharmacology for the heart: CiPA initiative 2017
DRUG EFFECTIVITY

Forskolin-induced swelling of organoids from intestinal biopsy of healthy control and cystic fibrosis (CF) patients

Combination of drugs restores normal swelling as in healthy controls
Organ-on-chip: a way forward in human bioassays?

Summary of the problem:
• Limited availability of human model systems for preclinical research
• Multiple failures/removal from market of drugs because of poor prediction of clinical effectivity in humans + unexpected toxicity

Animal models are not always sufficiently predictive of human disease and toxicity

There is a need for:
1. *Human* disease models (including the immune response) to develop new treatments
   - Medicines/drugs and other treatments
   - New medicines and “off-label” use of existing medicines
2. *Human* organ models for toxicity screening and safety pharmacology of drugs, cosmetics, foods and supplements, industrial and agricultural products
Organ-on-chip bioassays

What are organs-on-chip?

The smallest functional unit/structure of healthy or diseased tissues or organs cultured in 3D on a chip under controlled conditions
What do organs-on-chip look like?

“Microfluidic” currents to mimic e.g. blood flow

“double layer chips to mimic the blood-brain barrier between the circulation and the central nervous system

Under the microscope

Lung-on-chip

- Lung disease mimic
  - Pneumonia
  - Inflammation caused by inhalation of (nano)particles
  - Astma
- Drug delivery via inhalation
- Drug-induced toxicity of the lung
Brain-op-chip for inherited (including cognitive) diseases

MicroElectrodeArray measurements on nerve cells

Axon ingrowth and “synapse formation” on a chip

Schizophrenia: iPSC neurons and oligodendrocytes-on-chip

Kanagasabapathi, Decré, van de Stolpe, Philips Research Eindhoven

Kushner, ErasmusMC; MIMETAS, Leiden

Gezond

Patient

Meer “potholes” in breinscan
Pluripotent stem cells from an ALS patient: use of anti-epileptic drug Retigabine (drug “repurposing” may need no additional animal experiments)

Cell Reports 7, 1–11, April 10, 2014

Kevin Eggan, Harvard
What might be impossible?

• Accurate pharmacokinetics (half-life, turnover, clearing from the body)
• Multi-generation reproductive toxicology and fertility
• Effects on cognition
• ..........??
Stem cells and engineered 2D and 3D devices towards the future of personalized treatments and responses to toxic compounds

Adapted from Milena Bellin et al., 2012