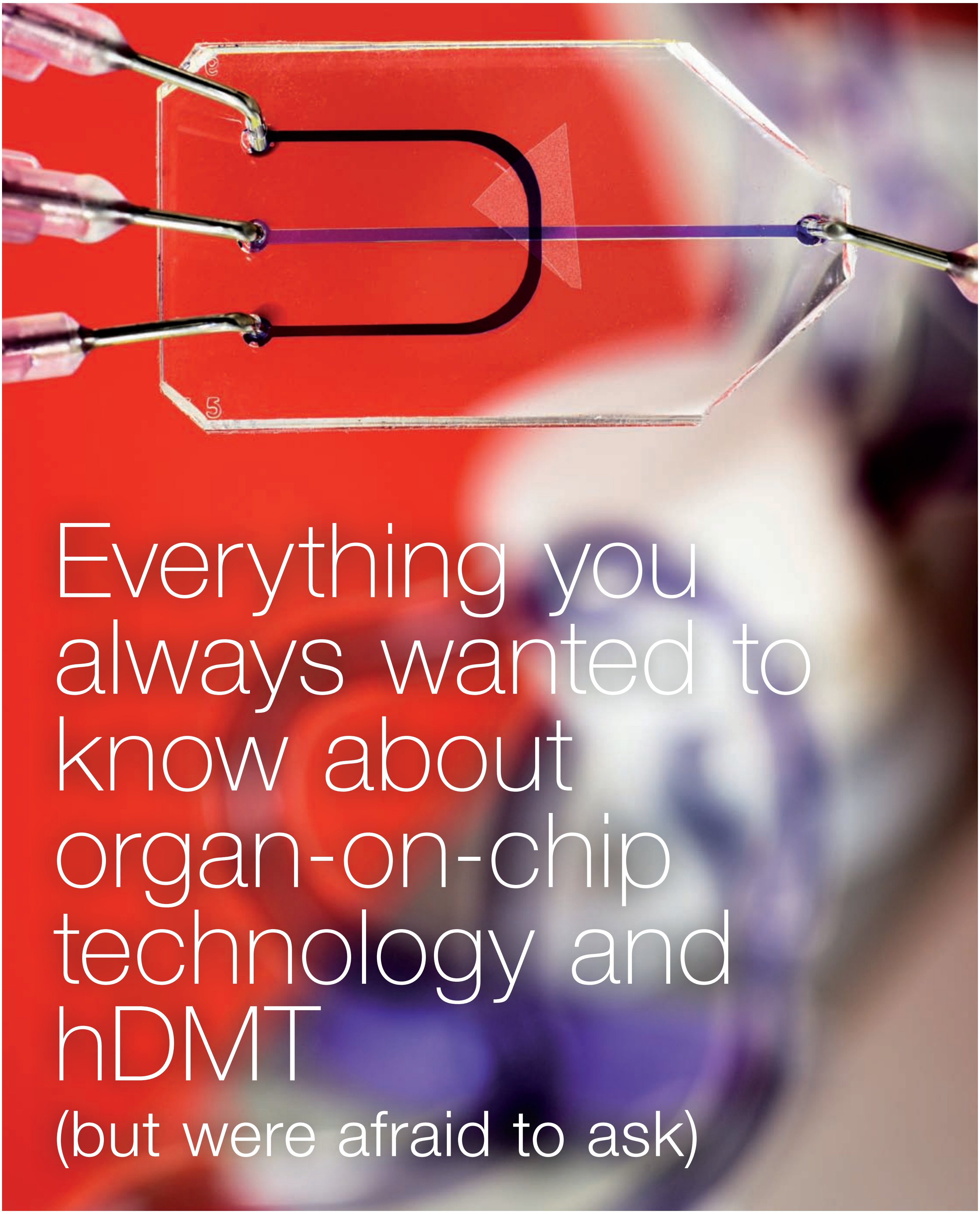

# Everything you always wanted to know about organ-on-chip technology and hDMT

(but were afraid to ask)

hDMT

HUMAN ORGAN AND DISEASE MODEL TECHNOLOGIES

## Why do we need organ-on-chip technology?

A major problem in developing new medicines is the limited availability of human model systems for preclinical research on disease target identification, drug efficacy and toxicity. This is still a major contributor of late (and expensive) drug failures in clinical trials. Laboratory animals or cells in standard tissue cultures, even if they are human, often do not respond to medication in the way cells in intact human organs in the body do. Organ-on-chip technology based on human cells may present solutions to this challenge of creating near-human test systems.

## How does organ-on-chip technology work?

Organs-on-chips are devices with one or more biocompatible microfluidic chambers (known as 'chips') containing multiple cell types in 3D culture; the living cells interact much as they might do in tissue as either miniature organs or miniature tumors. The chip design allows the cell cultures they contain to be continuously perfused and mechanically or electrically manipulated. This mimics normal organ physiology or can be used to induce disease pathology at the organ and tissue level. It is even possible to link chips containing different organ and tissue types; these might become especially valuable when one tissue (like the liver) processes a compound to a metabolite that causes an effect for example on kidney, brain or heart. This is particularly relevant for drug toxicity screening.

## What is so special about the chips?

1. The microfluidic chambers allow cell growth and maintenance under controlled, sterile conditions. The microfluidic flow can supply nutrients, drugs, immune cells, bacteria or viruses to the cell cultures inside the chips as necessary for the question to be addressed. Synthetic blood vessels can also be incorporated into the chip with real or synthetic blood flowing through.
2. The chips allow manipulation of the physical (micro) environment of cells. For example by varying the stiffness of the cellular environment (as in bone), varying pressure or stress (as in muscle or flowing blood), or causing vacuum-driven pressure oscillation (as in lung tissue or beating heart muscle). These mechanical cues are of crucial importance in the recreation of the mini-organs.
3. The chips allow molecular and functional monitoring, as well as real-time microscopic imaging of living cells.

## Might organs-on-chips reduce animal testing?

Yes indeed. Organs-on-chips support the 3Rs, the guiding principles of reduction, refinement and replacement of animal experiments.

## Why not build complete human test organs?

Because it is much easier and more reliable to do laboratory research on disease and drugs using miniature organs, or 'minimal functional (complex) tissue units'. Organs-on-chips are as simple as possible, yet as complex as necessary.

## How will organs-on-chips change the medical and pharmaceutical world?

It is expected that organ-on-chip models could result in a paradigm shift for biomedical research and the pharmaceutical industry, leading to new ways to identify effective drugs and improving the quality of medical care for many prevalent and severe diseases. They could provide near-human test systems for (pre)clinical trials with high relevance for individual patients. This would facilitate the development of novel treatment modalities, and allow assessment of the impact of inflammation and the immune system on treatments and disease. In turn, this could accelerate drug entry into the market and lower their costs. An example is the Cytostretch chip, on which human stem cell-derived heart cells stretch at the frequency of the beating heart at rest or during exercise. Exercise-induced arrhythmias precipitated by drugs – a common failure of clinical trials – could be detected early in the drug development process. Organs-on-chips will also make personalized medicine possible.

## How easy will it be to interpret the results?

Near-human models are not the same as the human body, so computational models will be needed to analyze the results from organs-on-chips.

## What will the economic impact of organs-on-chips be?

Organs-on-chips could significantly reduce the costs of healthcare, because they would allow drug development to become better, safer, faster and cheaper. Right now, the development of a new drug from start-to-market takes about 12 years, and costs minimally 1 billion euro per drug. This is due to inefficient drug development pipelines, with too many drugs failing late in development. Organs-on-chips will speed this up, thereby reducing costs. Drug repurposing – using a drug to treat a condition for which it was not originally developed – is considered an area most likely to benefit from these near-human models of organs-on-chips.

## Can organs-on-chips be used for personalized medicine?

Organs-on-chips can be tailored to the individual patient too, if they are made using the patient's own cells. This particular form of personalized medicine might ultimately yield:

- faster and cheaper drug development
- faster identification of drug targets
- better outcome of drugs in clinical trials
- fewer drug failures
- better drugs, without animal testing
- more effective treatments
- fewer negative side effects
- better and cheaper health-care
- better prediction of disease onset in individuals with inherited disease
- timely lifestyle adjustment or drug prescription to delay health decline
- better understanding of the mechanisms underlying complex diseases
- altogether, better quality of life

## For which diseases would organs-on-chips be good models?

Currently organs-on-chips are being developed for cancer, cardiovascular diseases, neurological and cognitive (brain) diseases, (auto)immune diseases, skin and a variety of others with complex genetic origins or with ethnic background impacting disease severity.

## What have stem cells got to do with organs-on-chips?

Stem cells can be used as the source from which to grow the miniature organs. These can be stem cells derived from healthy individuals or from patients. The resulting miniature organs are models that have the genetic characteristics of that particular individual. These could even be referred to as 'patients-on-chips'. These chips allow personalized analysis of drug responses and could thus facilitate identification of the most effective drug for an individual patient, before starting treatment. This would save time, money and unnecessary discomfort.

## What other research can be done with organs-on-chips?

It is not difficult to think of other interesting ways to use these near-human biological test systems. The possibilities include:

- discovering biomarkers for companion diagnostics
- discovering new treatment modalities for radiotherapy or hyperthermia
- determining the effects of environmental contaminants
- testing food additives and cosmetics for safety (this is of increasing importance because Europe completely banned the use of animals in testing cosmetics and their ingredients in 2013)

## What can hDMT contribute to advancing organ-on-chip technology?

Developing organs-on-chips means integrating different state of the art technologies. This requires creation of truly interdisciplinary research teams. The institute for human Organ and Disease Model Technologies (hDMT) is a consortium of internationally renowned scientists with backgrounds in biology, physics, chemistry, pharmacology, medicine and engineering. hDMT researchers work at academic research institutions, university medical centers and pharmaceutical companies in the Netherlands. In this 'laboratory without walls' multidisciplinary teams share their knowledge, expertise and facilities to deliver the human disease models of tomorrow.

## What are the plans of hDMT?

hDMT focuses on two kinds of research projects: the development of organ-on-chip technology platforms and of innovative human organ and disease models.

Technology platforms are important because of ongoing technological development, to address the scalability of device components to high throughput, and to enable reproducible manufacturability.

For innovative disease models, hDMT currently prioritizes four themes: vessels-on-chip, heart-on-chip, cancer-on-chip and brain-on-chip. Other models will be added in the near future, including the intestine, lifestyle models (skin and hair) and environmental models (nutrition and infection).

## What is hDMT?

hDMT is a precompetitive, non-profit technological R&D institute. hDMT will valorize organ-on-chip models developed through its biomedical and biophysical technologies to pharma companies and biotech, both in the Netherlands and internationally. hDMT also actively seeks collaboration with other researchers in the field of human organ and disease modeling worldwide, thus promoting open knowledge exchange and collaborations at the frontiers of organ-on-chip technology.

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