A revolution like the microchip

Dr. Felix Wöhrle, DMG, Germany

In cooperation with Queensland University of Technology, Queensland, Australia

https://www.pexels.com/de-de/video/abstrakt-weiss-rauch-dampf-9694240/

DMG – medical device development & production

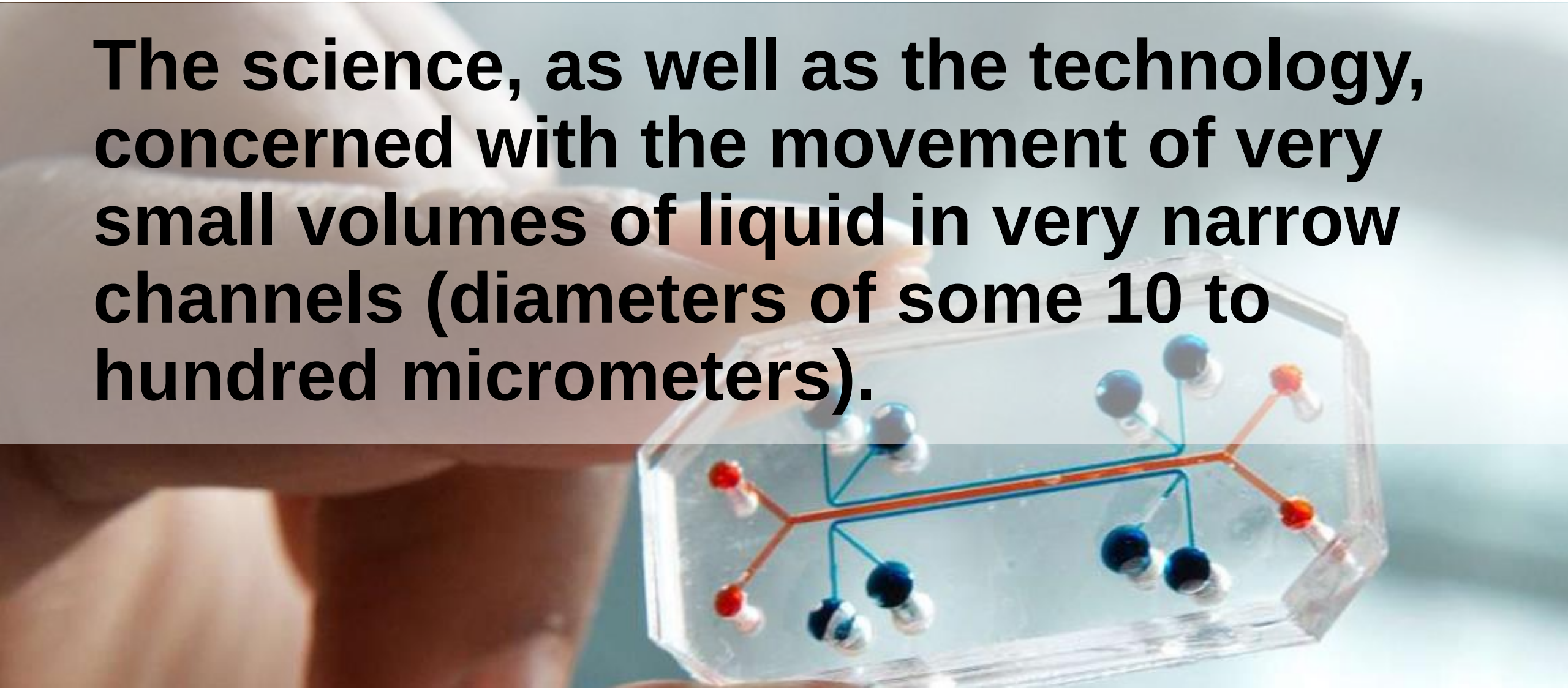
Brisbane

Queensland University of Technology (QUT) is a major Australian university with a truly global outlook. Home to nearly 50,000 students, we're providing real-world infrastructure, learning and teaching, and graduate skills to the next generation of change-makers.

https://www.qut.edu.au/about

Microfluidics

The science, as well as the technology, concerned with the movement of very small volumes of liquid in very narrow channels (diameters of some 10 to hundred micrometers).



https://www.malvernpanalytical.com/de/products/technology/microfluidics;https://nara.getarchive.net/media/how-organs-on-chips-and-computer-modeling-are-changing-2c2c5b

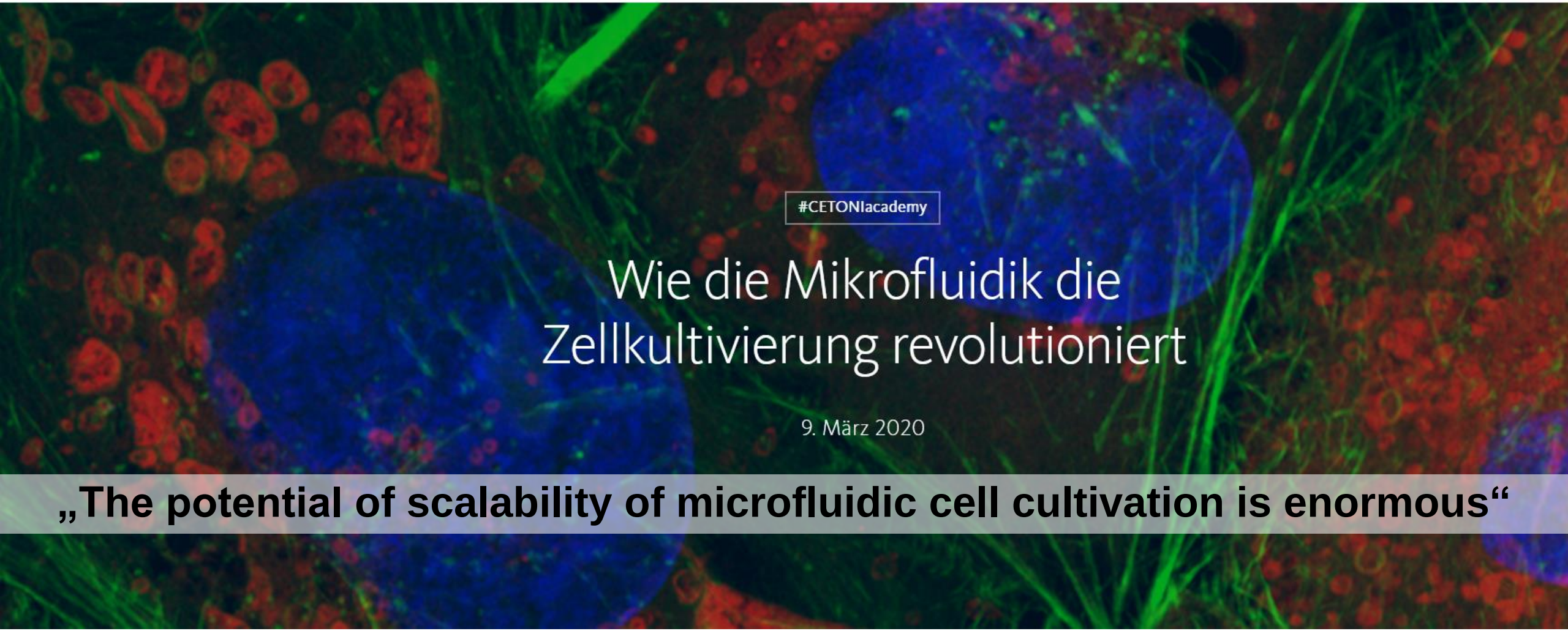
Covid

Photo from Sarah Blocksidge: https://www.pexels.com/de-de/Photo/papier-negativ-flatlay-coronavirus-11048535/

Lab-on-a-chip: Personalized therapies

CETONI

Flow Systeme Cobomation Solution Consulting



„The potential of scalability of microfluidic cell cultivation is enormous“

https://cetoni.de/wie-die-mikrofluidik-die-zellkultivierung-revolutioniert/

Organ-on-a-chip

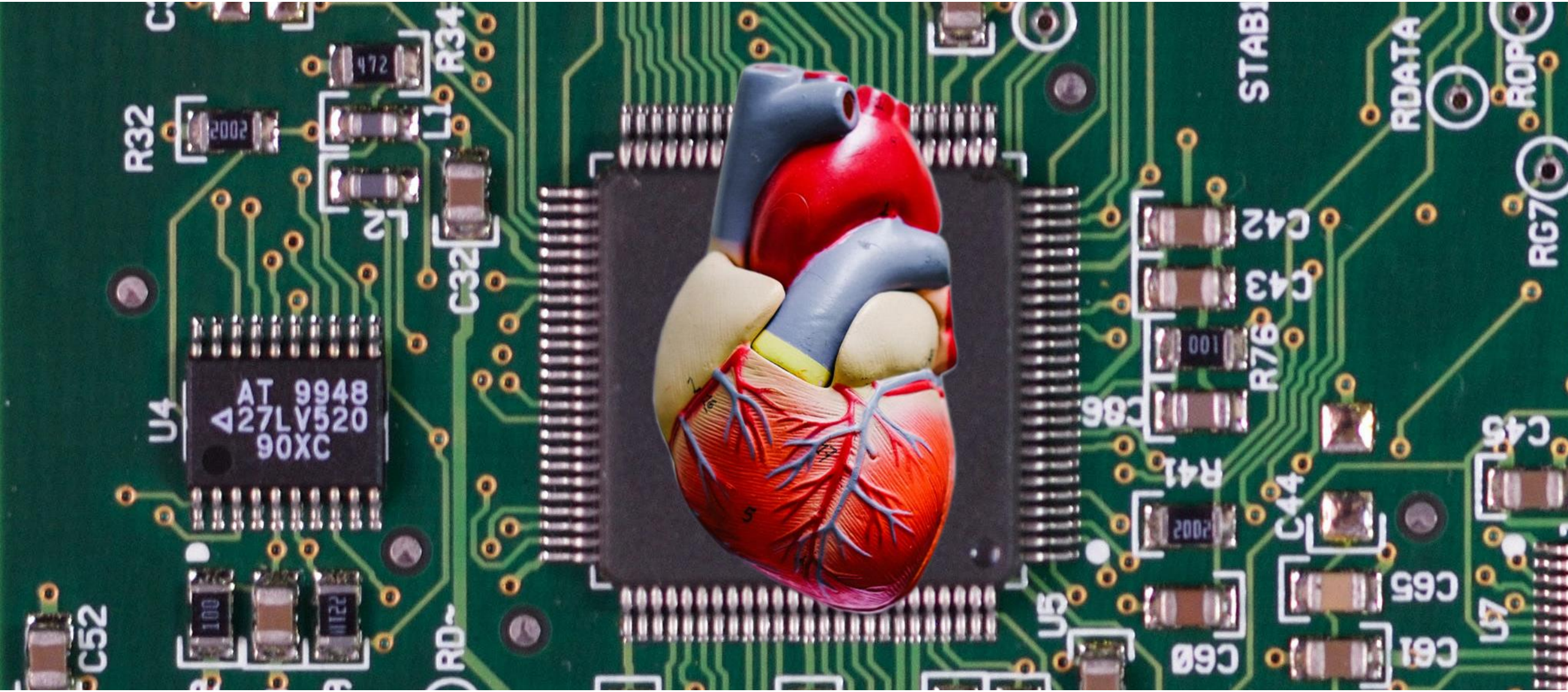
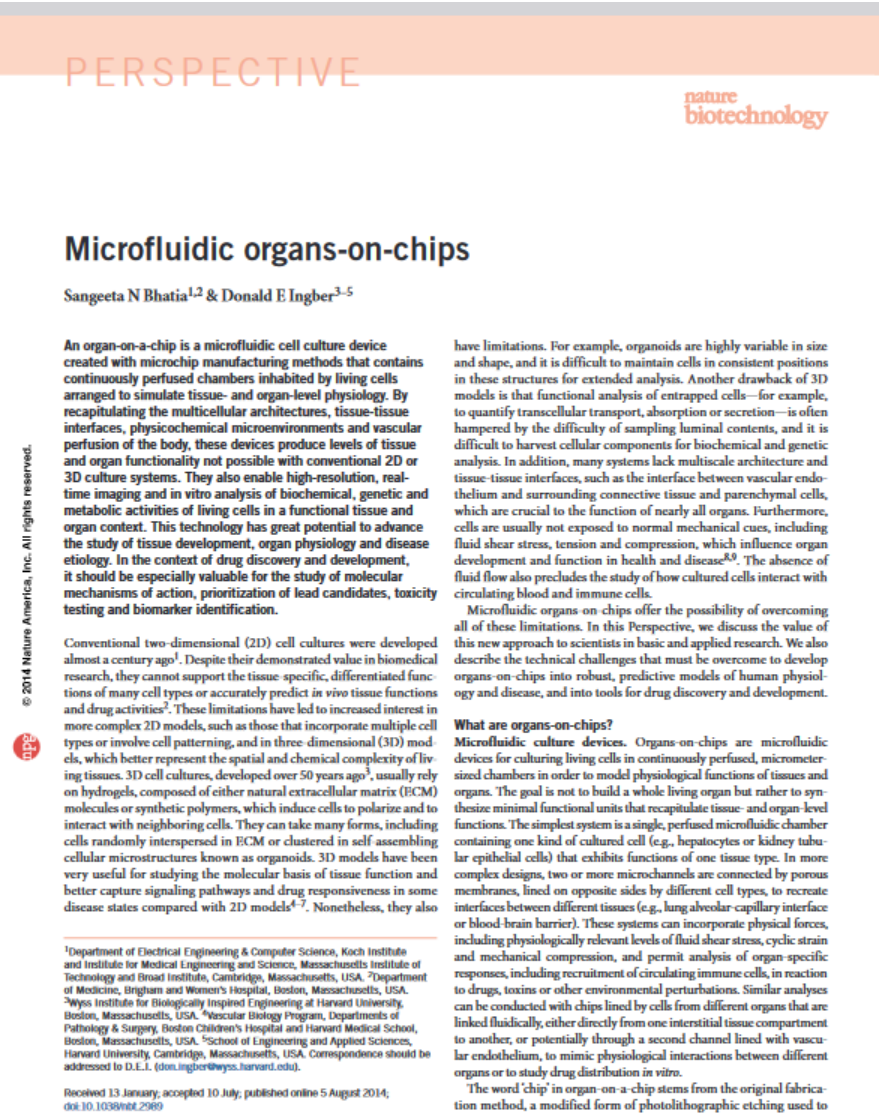


Photo from Miguel Á. Padriñán: https://www.pexels.com/de-de/Photo/grune-leiterplatte-343457/ /Kenny Eliason auf Unsplash

Organ-on-a-chip = microfluidic cell culture device



PERSPECTIVE

nature biotechnology

Microfluidic organs-on-chips

Sangeeta N Bhatia[1,2] & Donald E Ingber[3–5]

An organ-on-a-chip is a microfluidic cell culture device created with microchip manufacturing methods that contains continuously perfused chambers inhabited by living cells arranged to simulate tissue- and organ-level physiology. By recapitulating the multicellular architectures, tissue-tissue interfaces, physicochemical microenvironments and vascular perfusion of the body, these devices produce levels of tissue and organ functionality not possible with conventional 2D or 3D culture systems. They also enable high-resolution, real-time imaging and in vitro analysis of biochemical, genetic and metabolic activities of living cells in a functional tissue and organ context. This technology has great potential to advance the study of tissue development, organ physiology and disease etiology. In the context of drug discovery and development, it should be especially valuable for the study of molecular mechanisms of action, prioritization of lead candidates, toxicity testing and biomarker identification.

Conventional two-dimensional (2D) cell cultures were developed almost a century ago[1]. Despite their demonstrated value in biomedical research, they cannot support the tissue-specific, differentiated functions of many cell types or accurately predict *in vivo* tissue functions and drug activities[2]. These limitations have led to increased interest in more complex 2D models, such as those that incorporate multiple cell types or involve cell patterning, and in three-dimensional (3D) models, which better represent the spatial and chemical complexity of living tissues. 3D cell cultures, developed over 50 years ago[3], usually rely on hydrogels, composed of either natural extracellular matrix (ECM) molecules or synthetic polymers, which induce cells to polarize and to interact with neighboring cells. They can take many forms, including cells randomly interspersed in ECM or clustered in self-assembling cellular microstructures known as organoids. 3D models have been very useful for studying the molecular basis of tissue function and better capture signaling pathways and drug responsiveness in some disease states compared with 2D models[4–7]. Nonetheless, they also have limitations. For example, organoids are highly variable in size and shape, and it is difficult to maintain cells in consistent positions in these structures for extended analysis. Another drawback of 3D models is that functional analysis of entrapped cells—for example, to quantify transcellular transport, absorption or secretion—is often hampered by the difficulty of sampling luminal contents, and it is difficult to harvest cellular components for biochemical and genetic analysis. In addition, many systems lack multiscale architecture and tissue-tissue interfaces, such as the interface between vascular endothelium and surrounding connective tissue and parenchymal cells, which are crucial to the function of nearly all organs. Furthermore, cells are usually not exposed to normal mechanical cues, including fluid shear stress, tension and compression, which influence organ development and function in health and disease[8,9]. The absence of fluid flow also precludes the study of how cultured cells interact with circulating blood and immune cells.

Microfluidic organs-on-chips offer the possibility of overcoming all of these limitations. In this Perspective, we discuss the value of this new approach to scientists in basic and applied research. We also describe the technical challenges that must be overcome to develop organs-on-chips into robust, predictive models of human physiology and disease, and into tools for drug discovery and development.

What are organs-on-chips?

Microfluidic culture devices. Organs-on-chips are microfluidic devices for culturing living cells in continuously perfused, micrometer-sized chambers in order to model physiological functions of tissues and organs. The goal is not to build a whole living organ but rather to synthesize minimal functional units that recapitulate tissue- and organ-level functions. The simplest system is a single, perfused microfluidic chamber containing one kind of cultured cell (e.g., hepatocytes or kidney tubular epithelial cells) that exhibits functions of one tissue type. In more complex designs, two or more microchannels are connected by porous membranes, lined on opposite sides by different cell types, to recreate interfaces between different tissues (e.g., lung alveolar-capillary interface or blood-brain barrier). These systems can incorporate physical forces, including physiologically relevant levels of fluid shear stress, cyclic strain and mechanical compression, and permit analysis of organ-specific responses, including recruitment of circulating immune cells, in reaction to drugs, toxins or other environmental perturbations. Similar analyses can be conducted with chips lined by cells from different organs that are linked fluidically, either directly from one interstitial tissue compartment to another, or potentially through a second channel lined with vascular endothelium, to mimic physiological interactions between different organs or to study drug distribution *in vitro*.

The word 'chip' in organ-on-a-chip stems from the original fabrication method, a modified form of photolithographic etching used to

[1]Department of Electrical Engineering & Computer Science, Koch Institute and Institute for Medical Engineering and Science, Massachusetts Institute of Technology and Broad Institute, Cambridge, Massachusetts, USA. [2]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA. [3]Wyss Institute for Biologically Inspired Engineering at Harvard University, Boston, Massachusetts, USA. [4]Vascular Biology Program, Departments of Pathology & Surgery, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA. [5]School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts, USA. Correspondence should be addressed to D.E.I. (don.ingber@wyss.harvard.edu).

Received 13 January; accepted 10 July; published online 5 August 2014; doi:10.1038/nbt.2989

It contains continuously perfused chambers inhabited by living cells arranged to simulate tissue- and organ-level physiology.

By recapitulating the multicellular architectures, tissue-tissue interfaces, physicochemical microenvironments and vascular perfusion of the body, these devices produce levels of tissue and organ functionality not possible with conventional 2D or 3D culture systems

They also enable high-resolution, real-time imaging and *in vitro* analysis of biochemical, genetic and metabolic activities of living cells in a functional tissue and organ context.

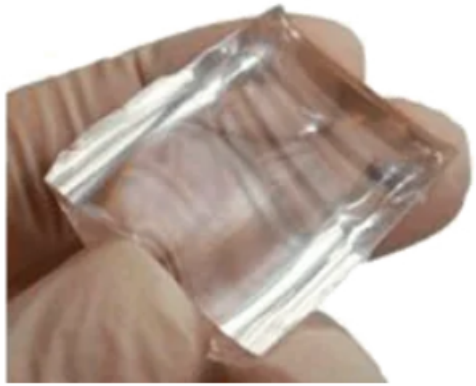
https://www.nature.com/articles/nbt.2989

Current chip materials - complicated

MICROFLUIDIC REVIEWS

PDMS: a review

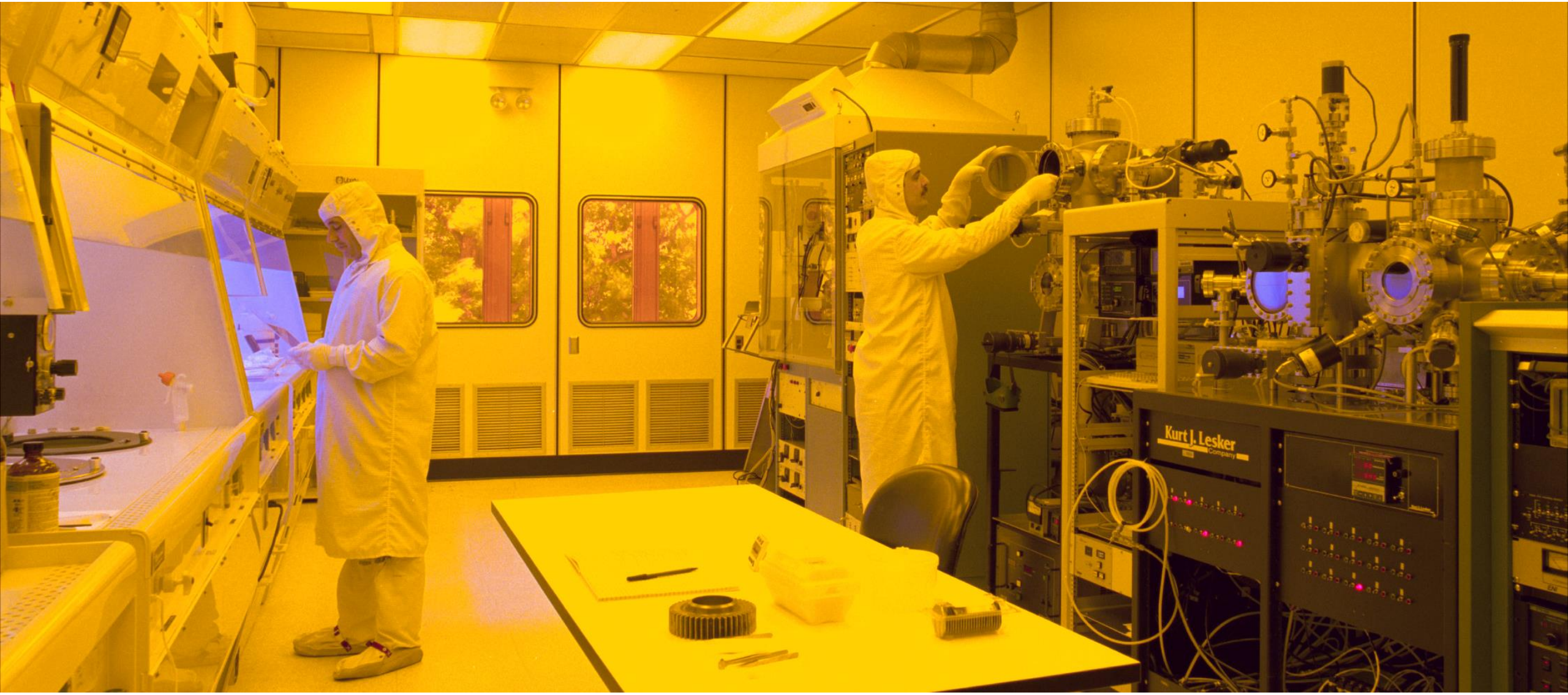
Introduction to polydimethylsiloxane



Polydimethylsiloxane, called PDMS or dimethicone, is a polymer widely used for the fabrication and prototyping of microfluidic chips.

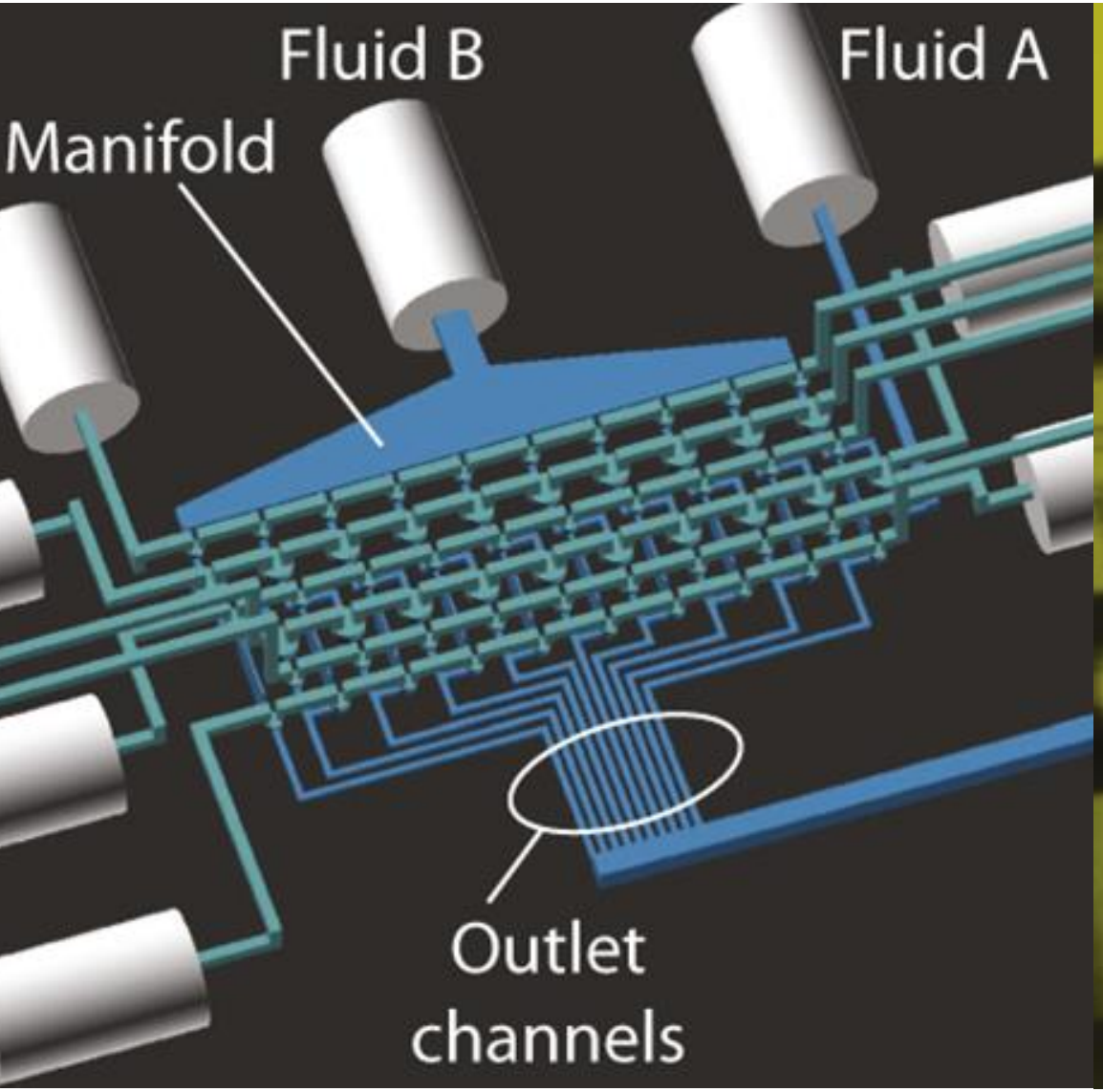
It is a mineral-organic polymer (a structure containing carbon and silicon) of the siloxane family (word derived from silicon, oxygen and alkane). Apart from microfluidics, it is used as a food additive (E900), in shampoos, and as an anti-foaming agent in beverages or in lubricating oils.

For the fabrication of microfluidic devices, Polydimethylsiloxane (liquid) mixed with a cross-linking agent is poured into a microstructured mold and heated to obtain a elastomeric replica of the mold (cross-linked).



https://en.wikipedia.org/wiki/Cleanroom#/media/File:Clean_room.jpg

3-D printing – relatively easy



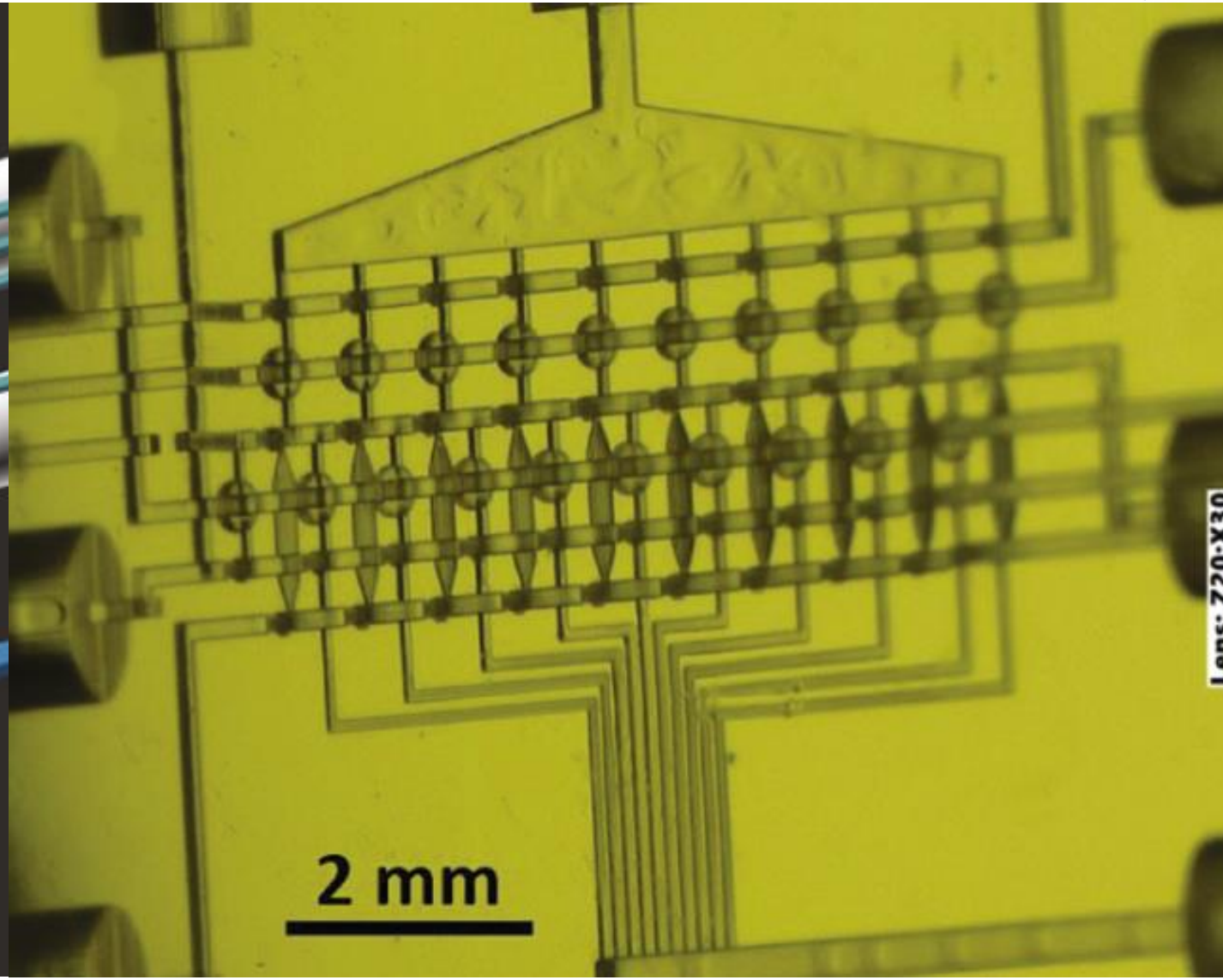


Fig. 6: 10-stage twofold serial diluters. | Nature Communications

Personalized medicine

OPEN ACCESS

EDITED BY
Xiuli Zhang,
Soochow University, China

REVIEWED BY
Gang Li,
Soochow University, China
Wen Shi,
University of Nebraska Medical Center, United States
Ranjith Kumar Kankala,
Huaqiao University, China
Nenad Filipovic,
University of Kragujevac, Serbia

*CORRESPONDENCE
Ramanuj DasGupta,
dasguptar@gis.a-star.edu.sg
Yi-Chin Toh,
yichin.toh@qut.edu.au

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Biomaterials, a section of the journal Frontiers in Bioengineering and Biotechnology

RECEIVED 25 May 2022
ACCEPTED 19 July 2022
PUBLISHED 16 August 2022

CITATION
Ong LJY, Chia S, Wong SQR, Zhang X, Chua H, Loo JM, Chua WY, Chua C, Tan E, Hentze H, Tan IB, DasGupta R and Toh Y-C (2022), A comparative study of tumour-on-chip models with patient-derived xenografts for predicting chemotherapy efficacy in colorectal cancer patients.
Front. Bioeng. Biotechnol. 10:952726.
doi: 10.3389/fbioe.2022.952726

A comparative study of tumour-on-chip models with patient-derived xenografts for predicting chemotherapy efficacy in colorectal cancer patients

Louis Jun Ye Ong[1,2,3,4†], Shumei Chia[5†], Stephen Qi Rong Wong[5,6,7], Xiaoqian Zhang[5], Huiwen Chua[5], Jia Min Loo[5], Wei Yong Chua[5], Clarinda Chua[8], Emile Tan[9], Hannes Hentze[10], Iain Beehuat Tan[5,8,11], Ramanuj DasGupta[5*] and Yi-Chin Toh[1,2,3,4*]

[1]School of Mechanical, Medical and Process Engineering, Queensland University of Technology (QUT), Brisbane, QL, Australia, [2]Centre for Biomedical Technologies, Queensland University of Technology (QUT), Brisbane, QL, Australia, [3]Department of Biomedical Engineering, National University of Singapore, Singapore, Singapore, [4]Institute for Health Innovation and Technology, National University of Singapore, Singapore, Singapore, [5]Laboratory of Precision Oncology and Cancer Evolution, Genome Institute of Singapore, A*STAR, Singapore, Singapore, [6]Biological Resource Centre, Agency for Science, Technology and Research (A*STAR), Singapore, Singapore, [7]Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, United States, [8]National Cancer Centre Singapore, Singapore, Singapore, [9]Singapore General Hospital, Singapore, Singapore, [10]Experimental, Drug Development Centre, A*STAR, Singapore, Singapore, [11]Duke-NUS Graduate Medical School, Singapore, Singapore

Inter-patient and intra-tumour heterogeneity (ITH) have prompted the need for a more personalised approach to cancer therapy. Although patient-derived xenograft (PDX) models can generate drug response specific to patients, they are not sustainable in terms of cost and time and have limited scalability. Tumour Organ-on-Chip (OoC) models are *in vitro* alternatives that can recapitulate some aspects of the 3D tumour microenvironment and can be scaled up for drug screening. While many tumour OoC systems have been developed to date, there have been limited validation studies to ascertain whether drug responses obtained from tumour OoCs are comparable to those predicted from patient-derived xenograft (PDX) models. In this study, we established a multiplexed tumour OoC device, that consists of an 8 × 4 array (32-plex) of culture chamber coupled to a concentration gradient generator. The device enabled perfusion culture of primary PDX-derived tumour spheroids to obtain dose-dependent response of 5 distinct standard-of-care (SOC) chemotherapeutic drugs for 3 colorectal cancer (CRC) patients. The *in vitro* efficacies of the chemotherapeutic drugs were rank-ordered for individual patients and compared to the *in vivo* efficacy obtained from matched PDX models. We show that quantitative correlation analysis between the drug efficacies predicted *via* the microfluidic perfusion culture is predictive of response in animal PDX models. This is a first study showing a comparative

This (the results*) indicated the potential application of in vitro microfluidic platforms in drug screening applications towards personalised cancer treatment

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9488115/ *remark by author of presentation/

Challenge

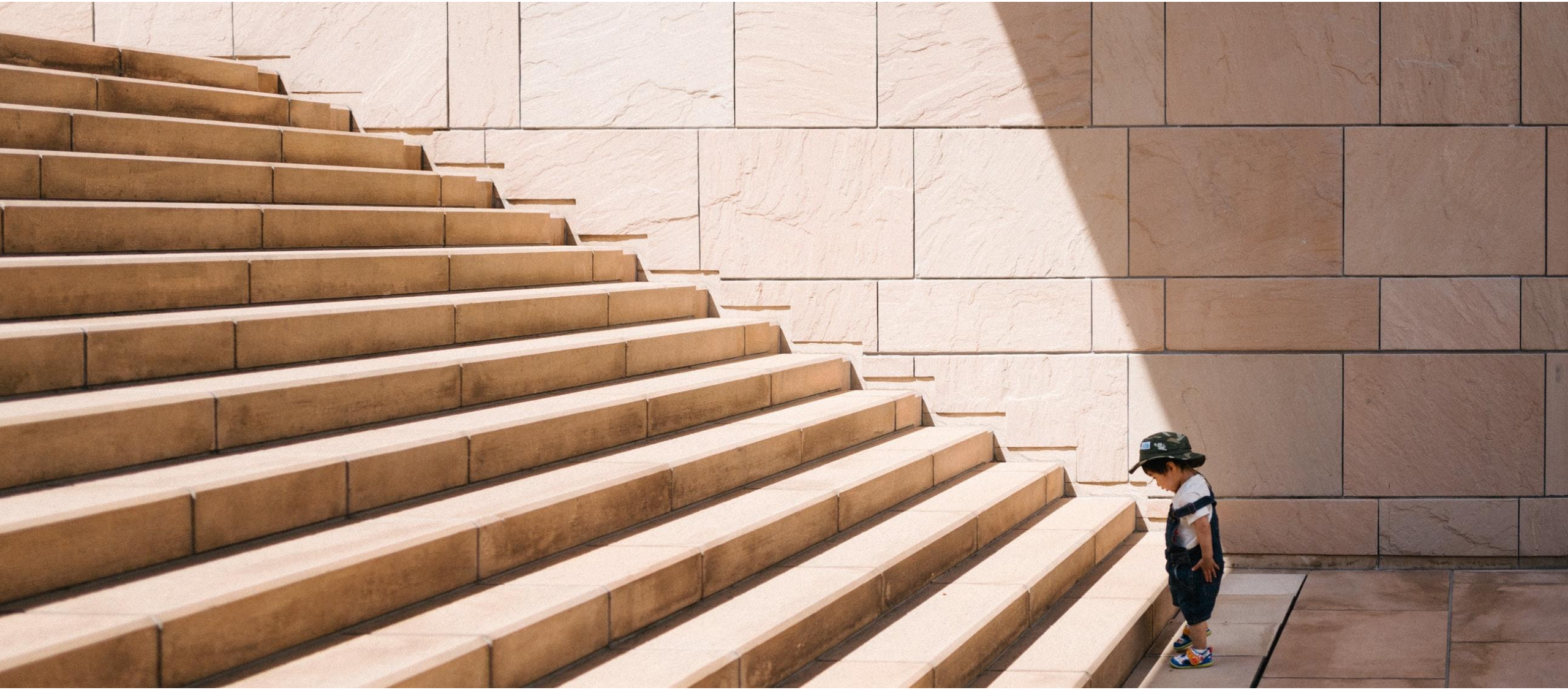


Photo from Jukan Tateisi auf Unsplash

Photo from Apex 360 auf Unsplashn

Transparency

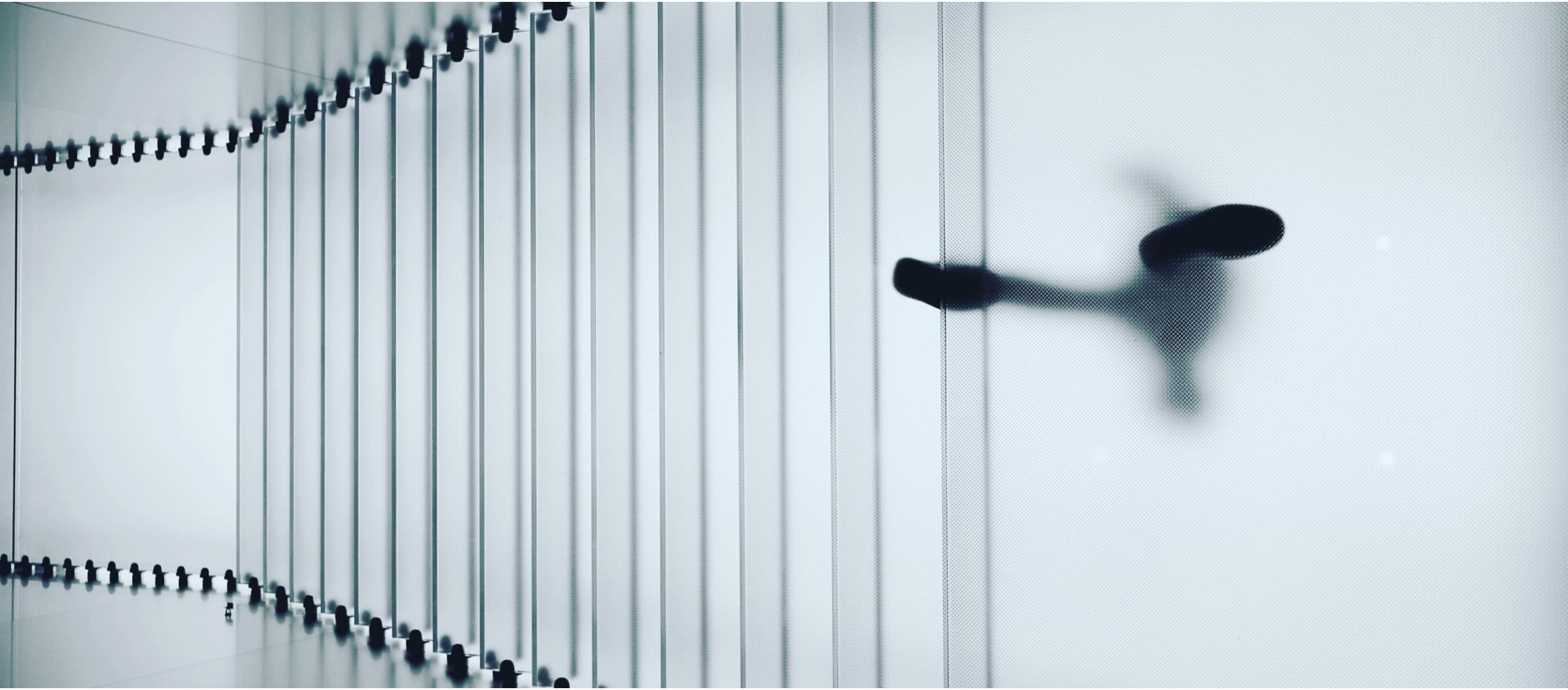
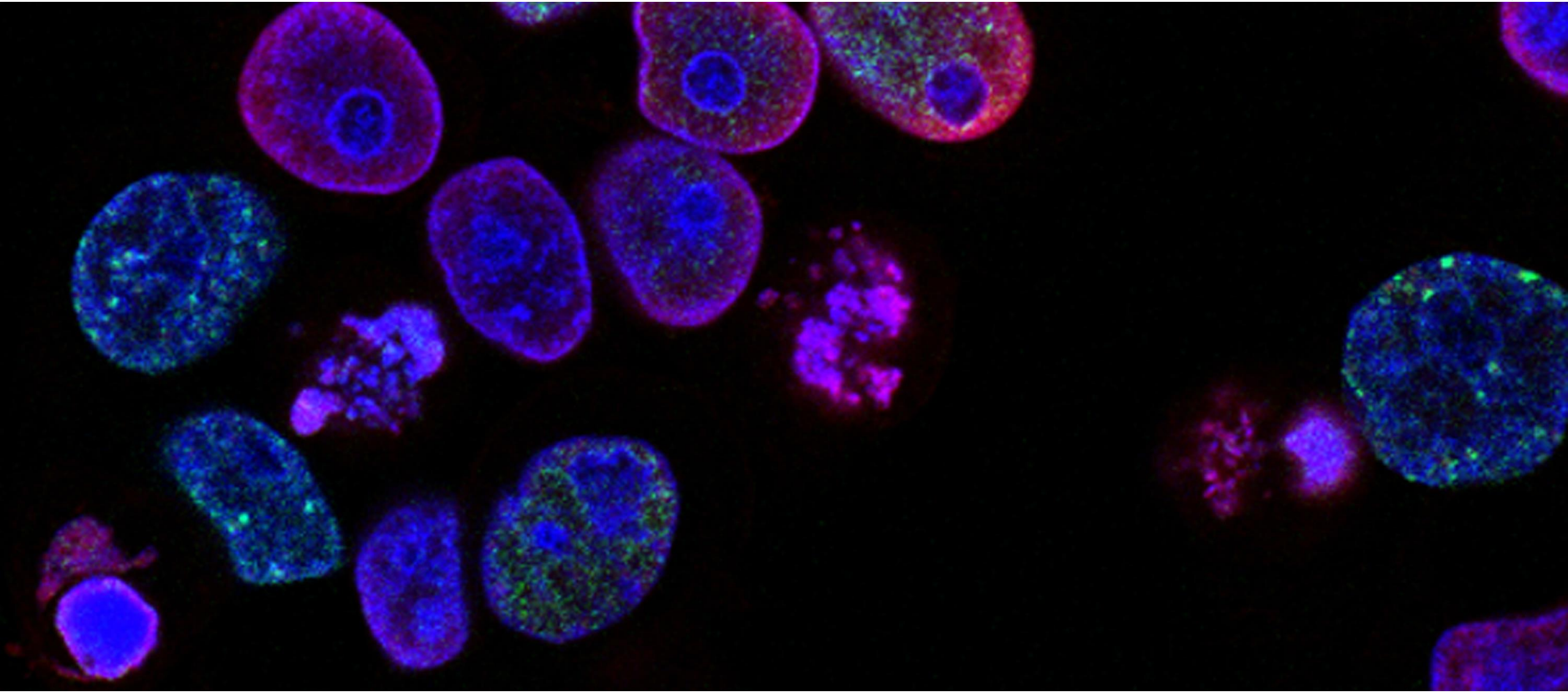


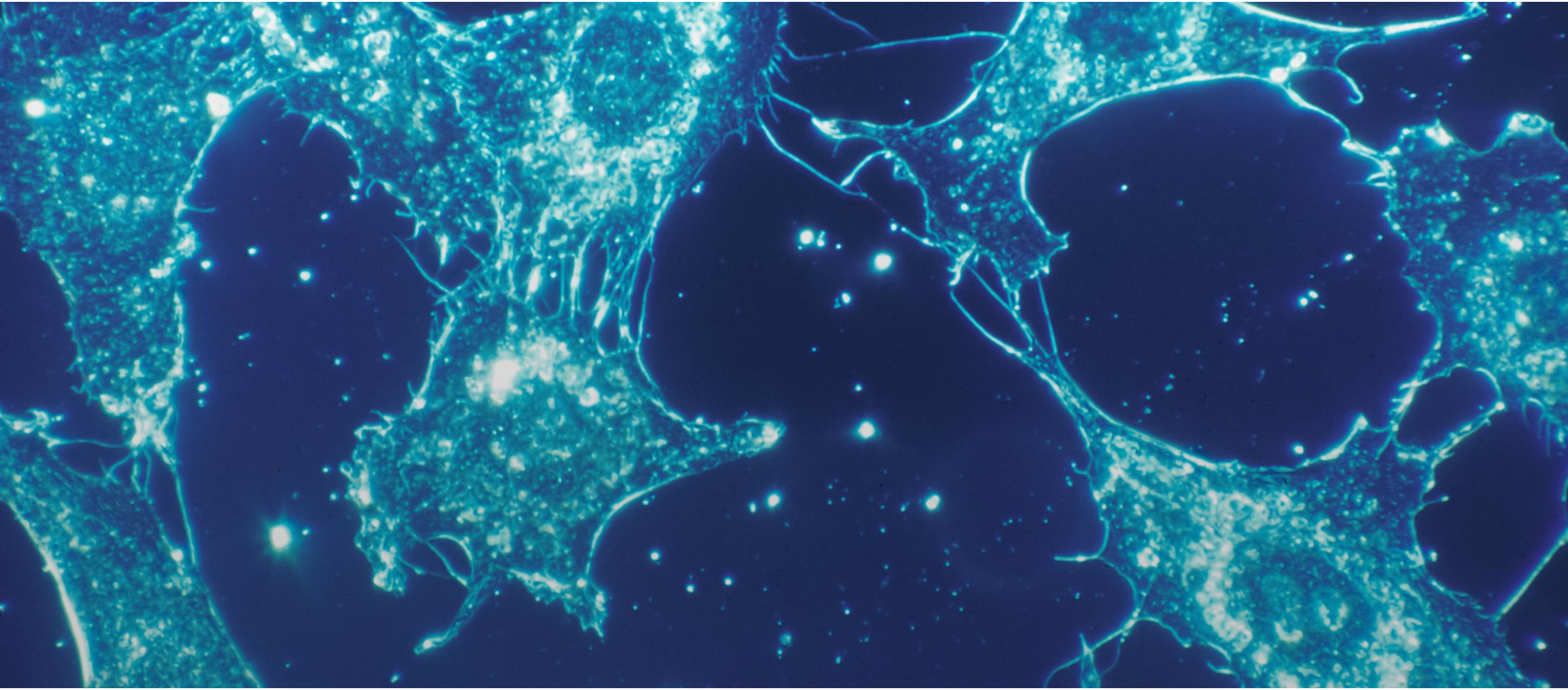
Photo from James Haworth auf Unsplash

Biocompatibility

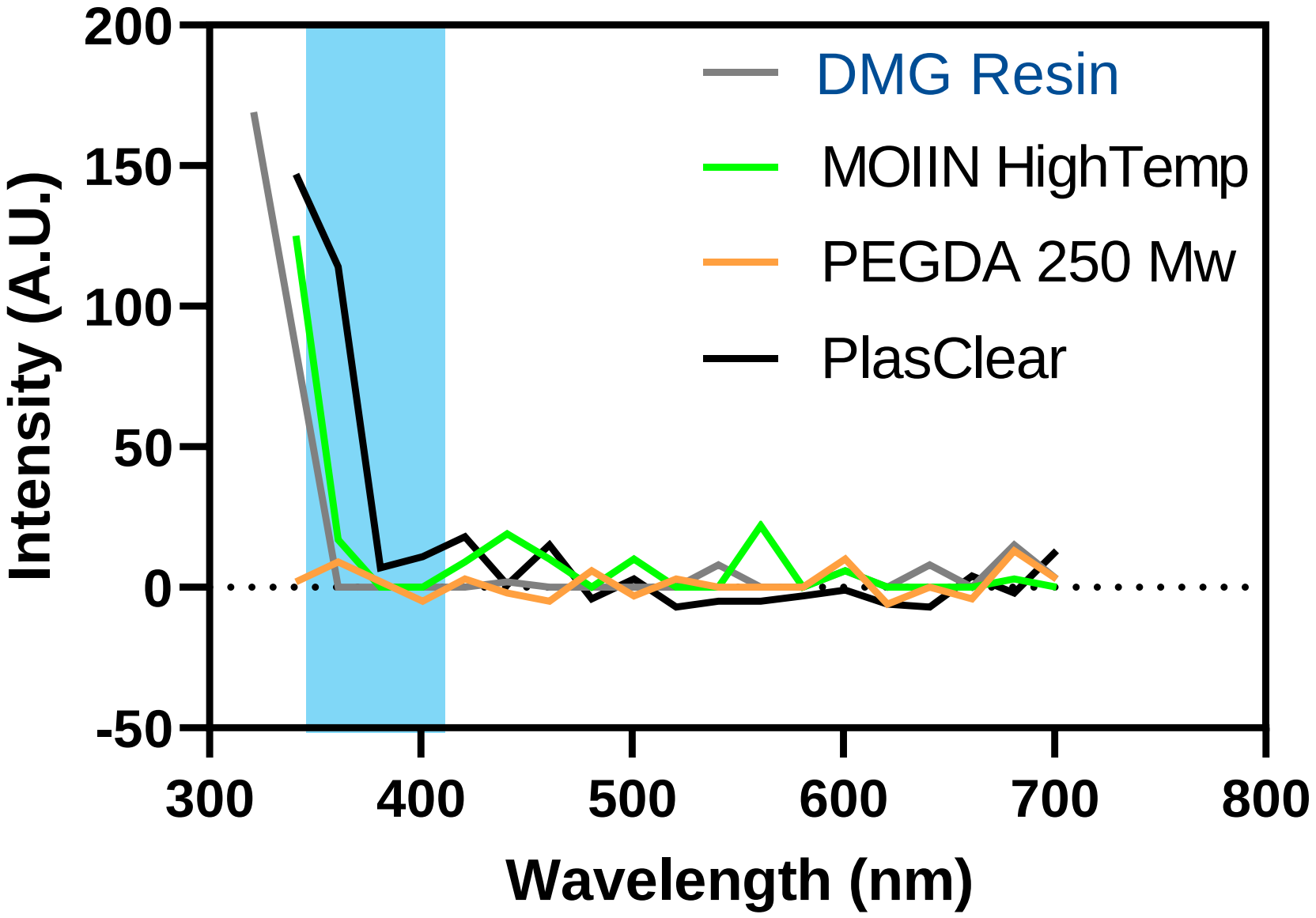


https://unsplash.com/de

Bioinert



https://unsplash.com/de

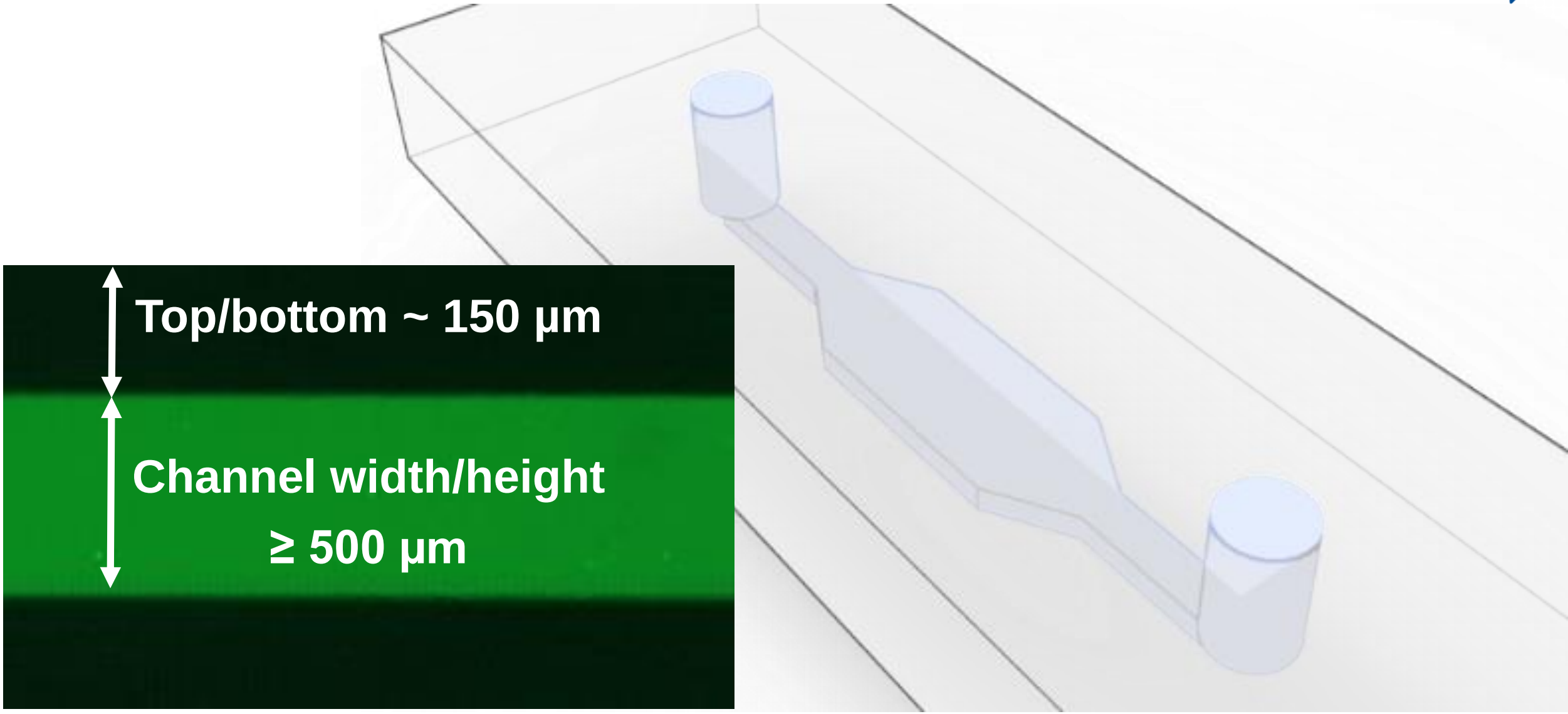


Resin photoinitiators excited at

365 – 405 nm. Fluorescent imaging should exclude UV-range fluorophores

With friendly support from QUT Centre for Biomedical Technologies, Queensland University of Technology, Queensland, Australia

Removal of uncured resin dictates practical approach

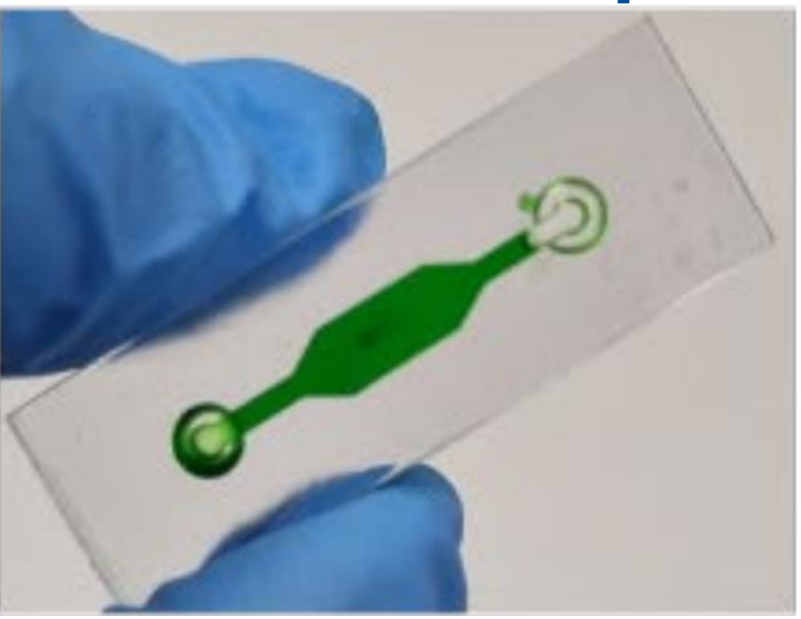


With friendly support from QUT Centre for Biomedical Technologies, Queensland University of Technology, Queensland, Australia

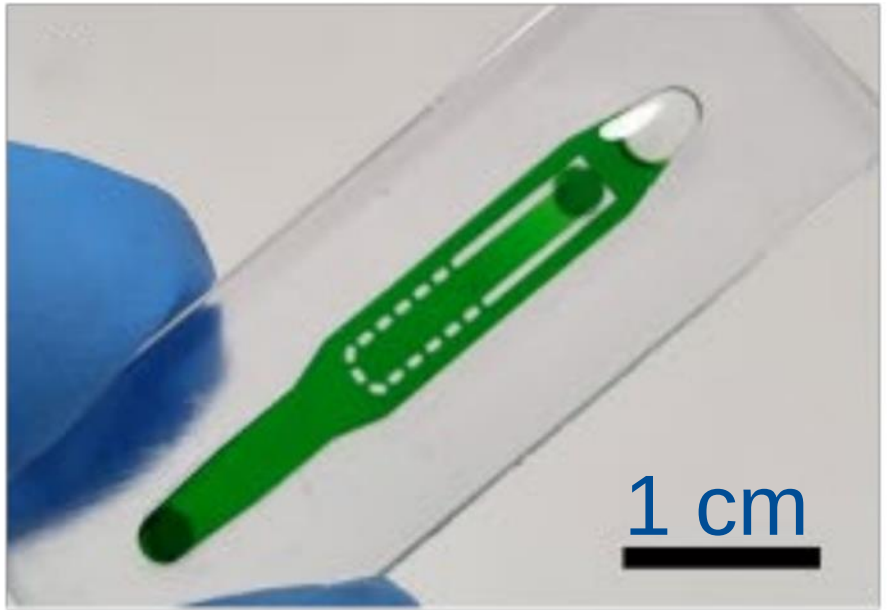
The right viscosity

DMG resin / Asiga printer

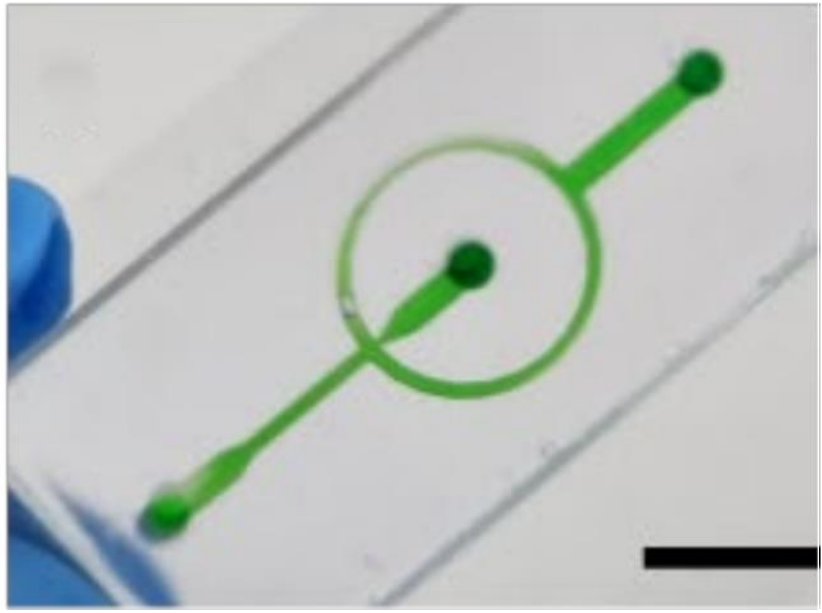
2D culture chip



3D pillar array

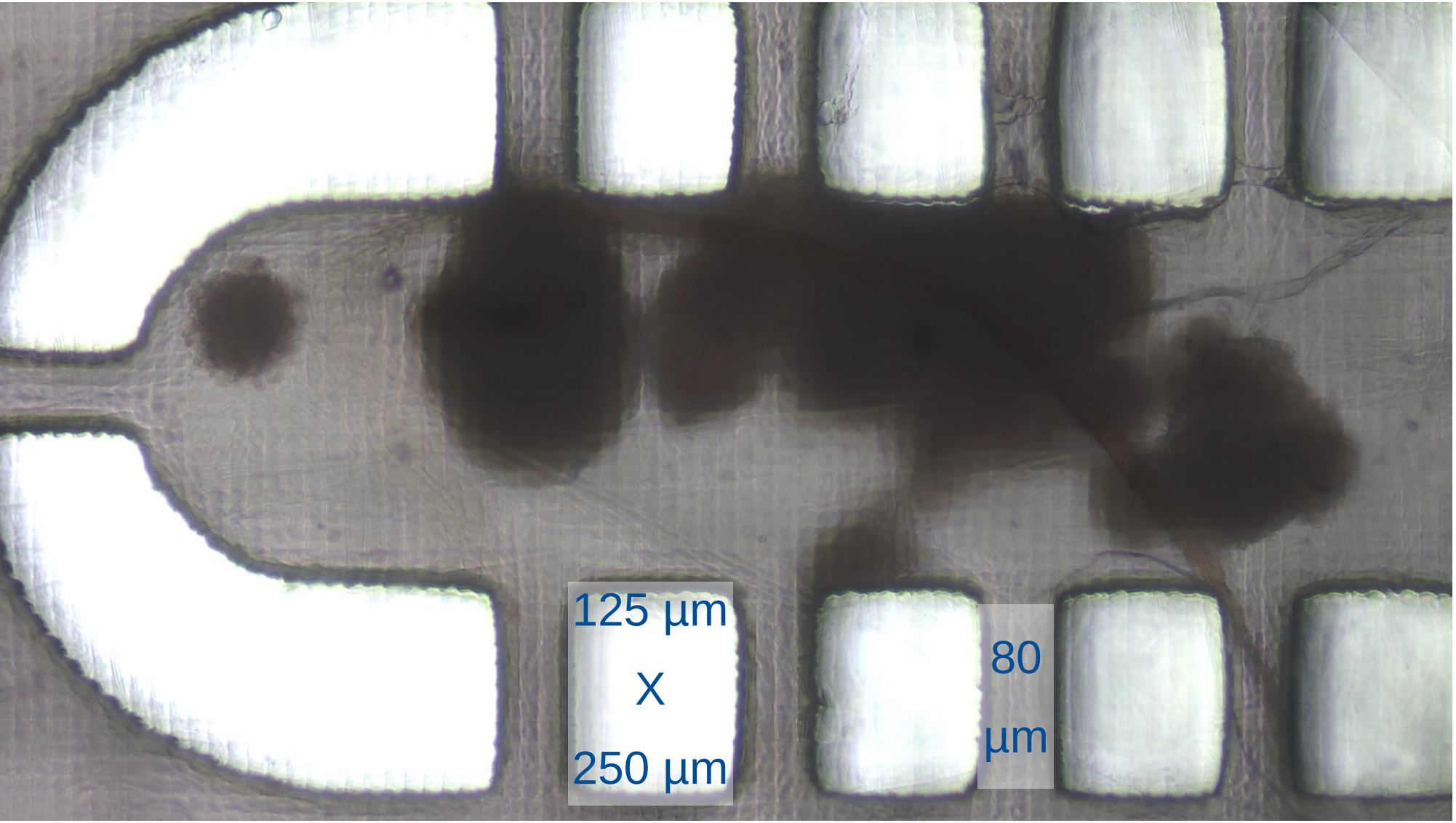


Droplet generator



A case study of MOIIN resins: 3D printed microfluidic devices for cell-based Applications, Louis Ong, Yi-Chin Toh,

DMG resin / Asiga printer



Cells can survive perfusion culture for 3 days

A case study of MOIIN resins: 3D printed microfluidic devices for cell-based Applications, Louis Ong, Yi-Chin Toh,

Improve patient outcomes

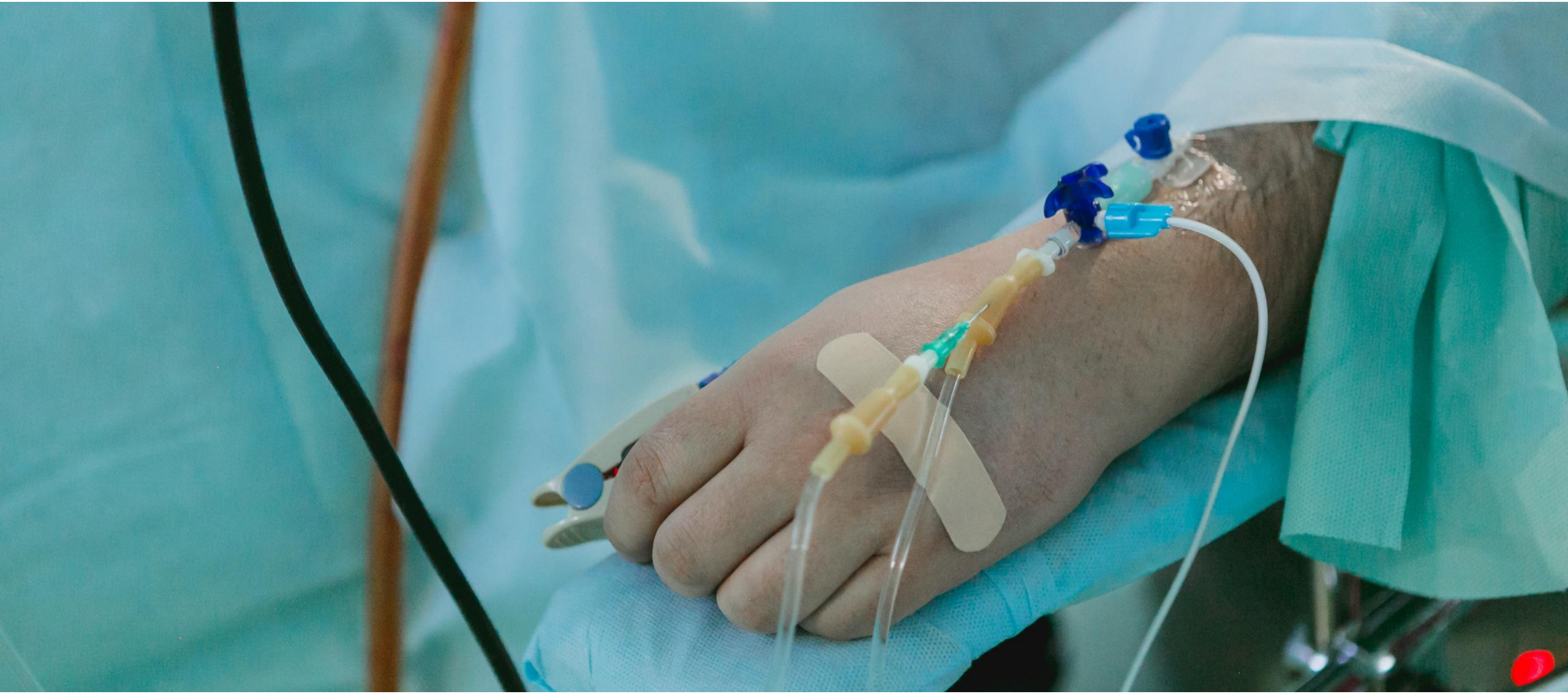
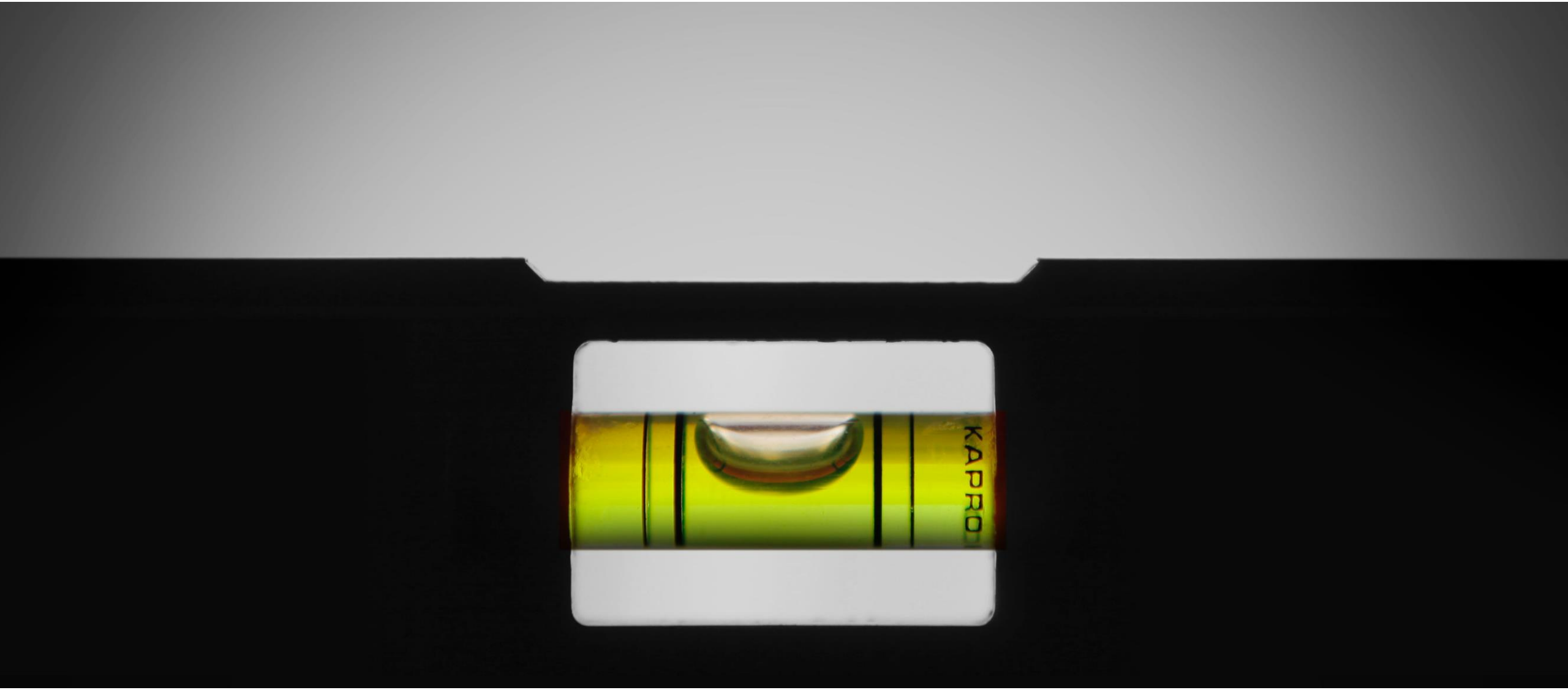


Photo from Olga Kononenko auf Unsplashel

Finding the right balance

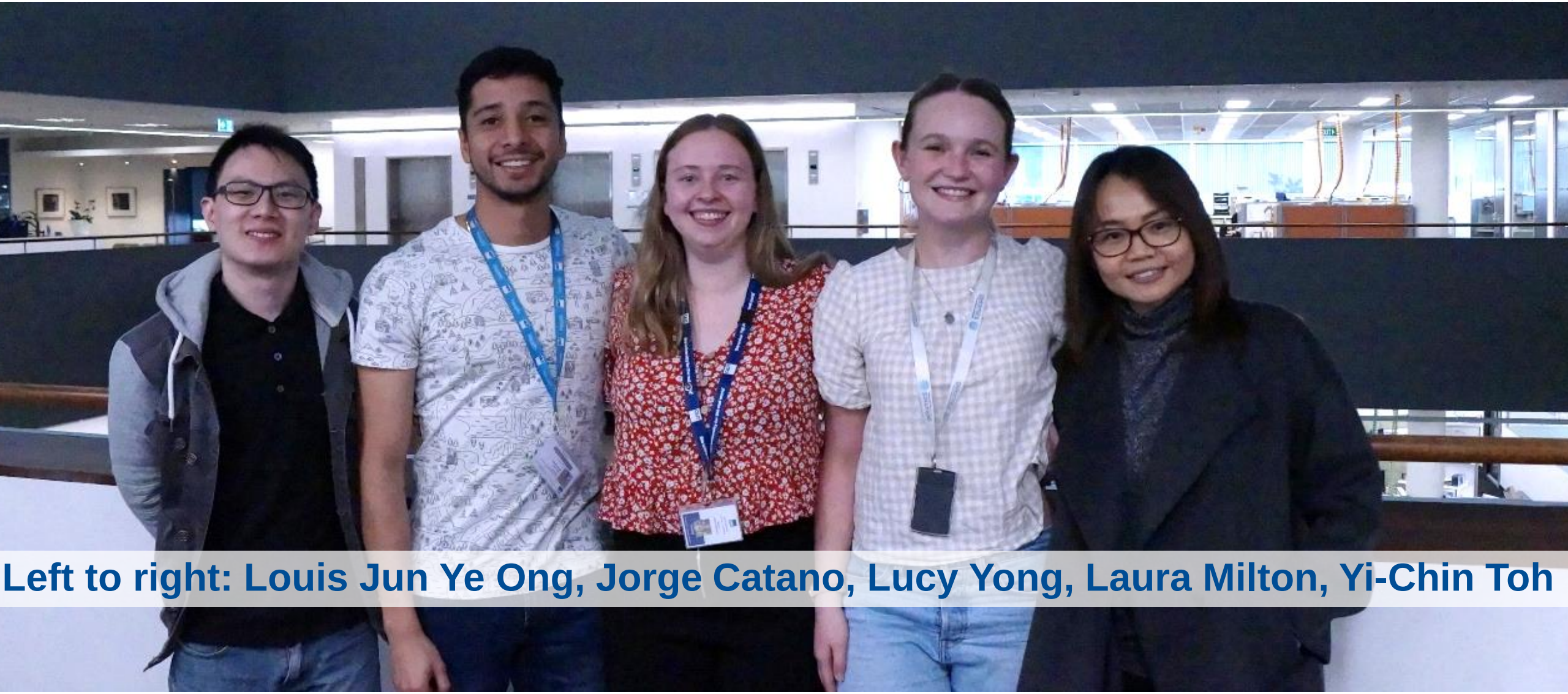


https://unsplash.com/de

When there is some chemistry going on

https://www.pexels.com/photo/colorful-liquids-in-laboratory-glasswares-8326459/

Queensland University of Technology (microte lab)



Left to right: Louis Jun Ye Ong, Jorge Catano, Lucy Yong, Laura Milton, Yi-Chin Toh

https://www.qut.edu.au/about

Are there any