# A case-study for Diversity & Inclusion for standardization: Large-Area Manufacturing of Integrated Microfluidics

Auke Jisk Kronemeijer

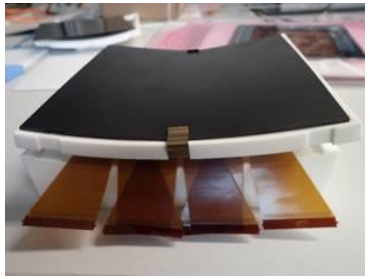
Holst Centre
powered by imec & TNO

# Holst Centre

- ✓ Started in 2006 on initiation from Philips Research, named after Gilles Holst, first director of Philips Research
- ✓ Located at the High Tech Campus in the heart of Brainport area, home of Dutch high tech industry
- ✓ Aimed at fostering and orchestrating innovation with and between companies

# TNO at Holst Centre

- Located at the High Tech Campus in the heart of Brainport area, home of Dutch high tech industry
- Aimed at fostering and orchestrating innovation with and between companies
- R&D on all aspects of technology: design, novel fabrication processes, systems and integration, measurements and characterization
- Application domains ranging from energy, health, semicon to CE.

# Holst Centre Fundamentals

- Managed and run by 2 reputed R&D institutes: TNO and imec
  - TNO: biggest Dutch R&D organisation focused on applied research aimed at improving societal welfare coupled to economic growth
  - imec: famous Belgian R&D institute aimed at advancing chip technology

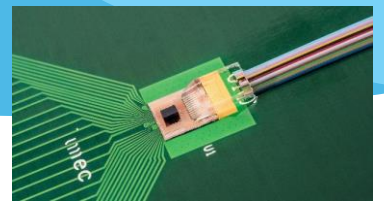
TNO innovation for life

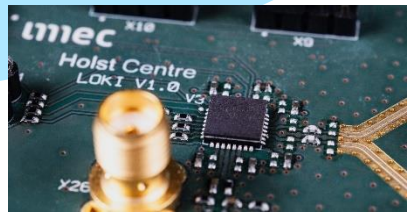
- Thin film and flexible electronics
- Energy storage

imec

- Health care technology
- Integrated photonics
- Low-power wireless communication
- Edge AI





# Holst Centre Profile

Holst Centre

**250 own staff**
**30 nationalities**

**>60 partners**

Universities

Knowledge institutes


**~10 PhD Students**
**~40 MSc Students**

**15 industrial residents**

Industry

- Substrates
- Materials
- Equipment
- Components
- End products

# R&D orchestrator

- One-stop shop approach
- From application requirements to full system design and material and equipment development
- Organizing and executing complex and disruptive innovations with and along the value chain

| Technology | Components | Systems | Applications & Data analytics |
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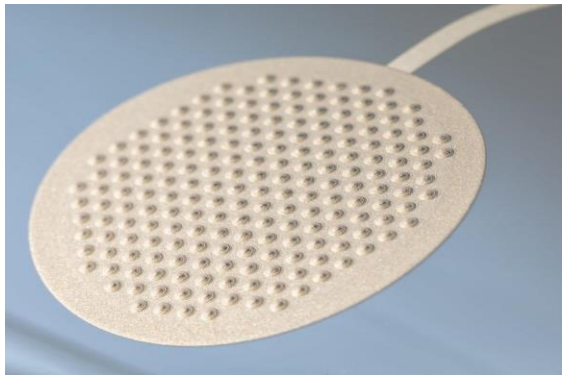
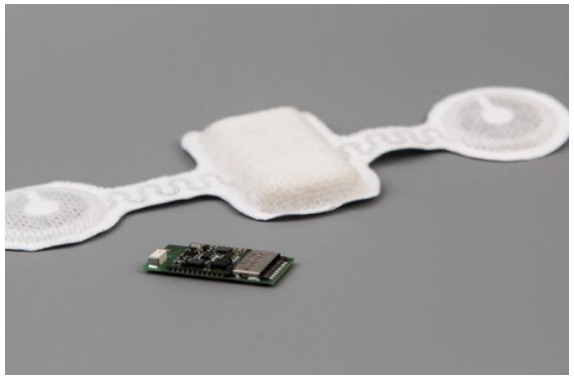
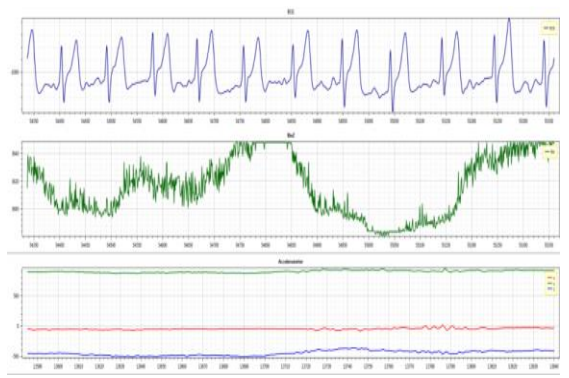
|  |  |  |  |
| Materials, equipment, processes => pilot line | Electrodes, sensors, electronic components | Health patch, IoT devices, optical switch | (Clinical) trials, data analysis, algorithms |

# Industrial partners

Holst Centre
powered by imec & TNO


powered by
TNO

# Start-ups / spin-offs

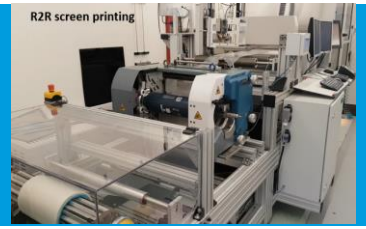
Holst Centre

# Overview Holst Centre Roadmaps

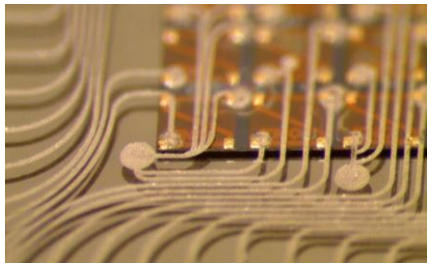
Holst Centre

Strong competences in
- Thin film electronics
- Hybrid printed electronics



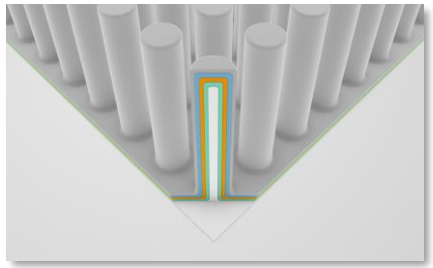


New manufacturing technologies
- High resolution printed electronics technologies
- High-throughput assembly
- Sustainable electronics



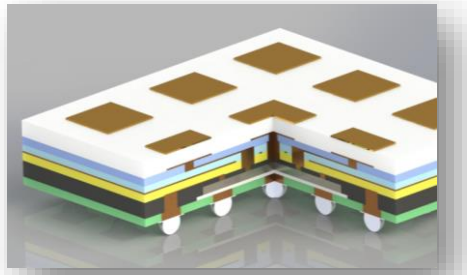
Healthcare devices
- Medical wearables
- Large area sensors
- Ultrasound wearables
- Organ-on-chip

Energy storage
- Next-gen batteries
- Next-gen electrolyzers



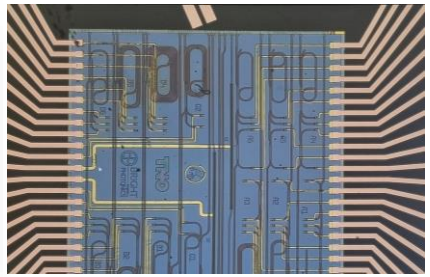
Advanced packaging
- Power chip packaging
- RF chip packaging
- Photonic chip packaging

CITC Chip Integration Technology Center

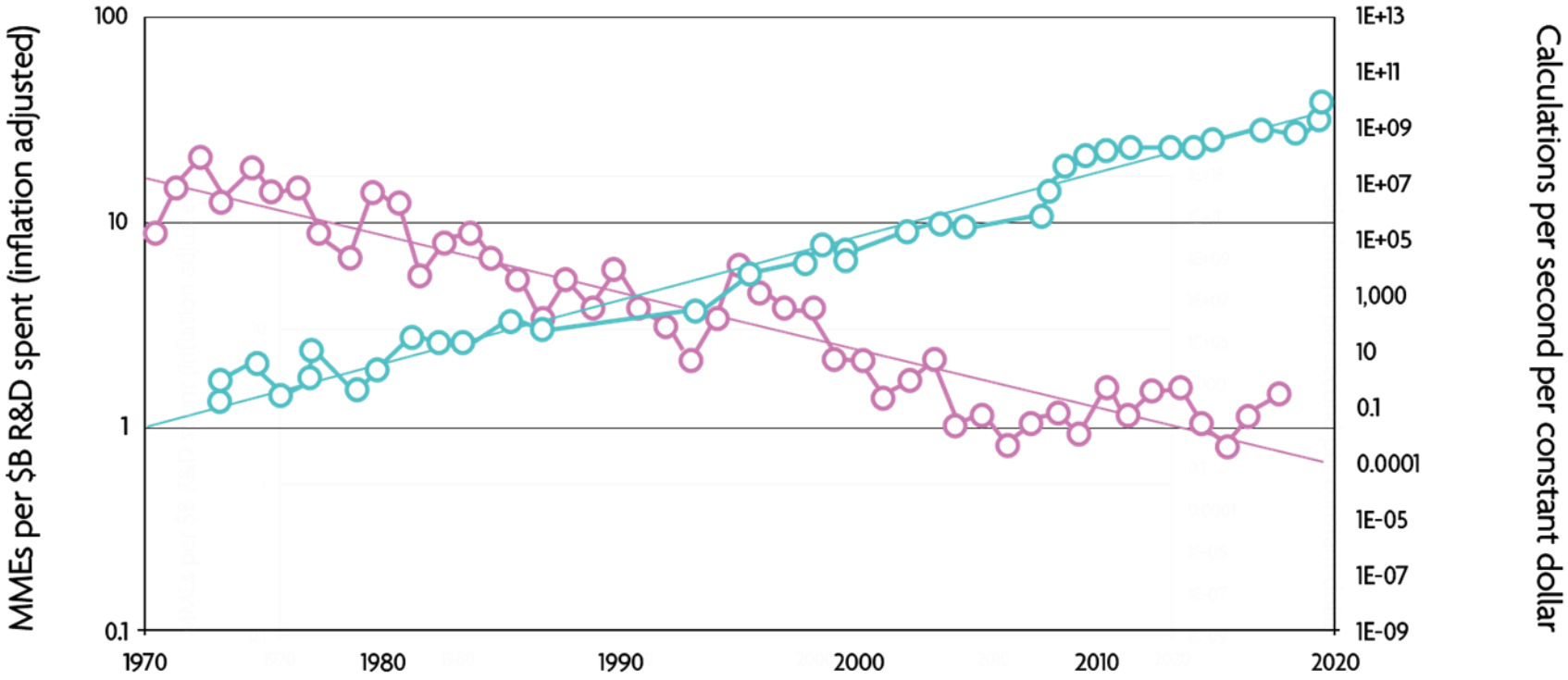


Integrated Photonics
- Metrology
- SiN
- InP
- Heterogeneous integration

PITC Photonic Integration Technology Center



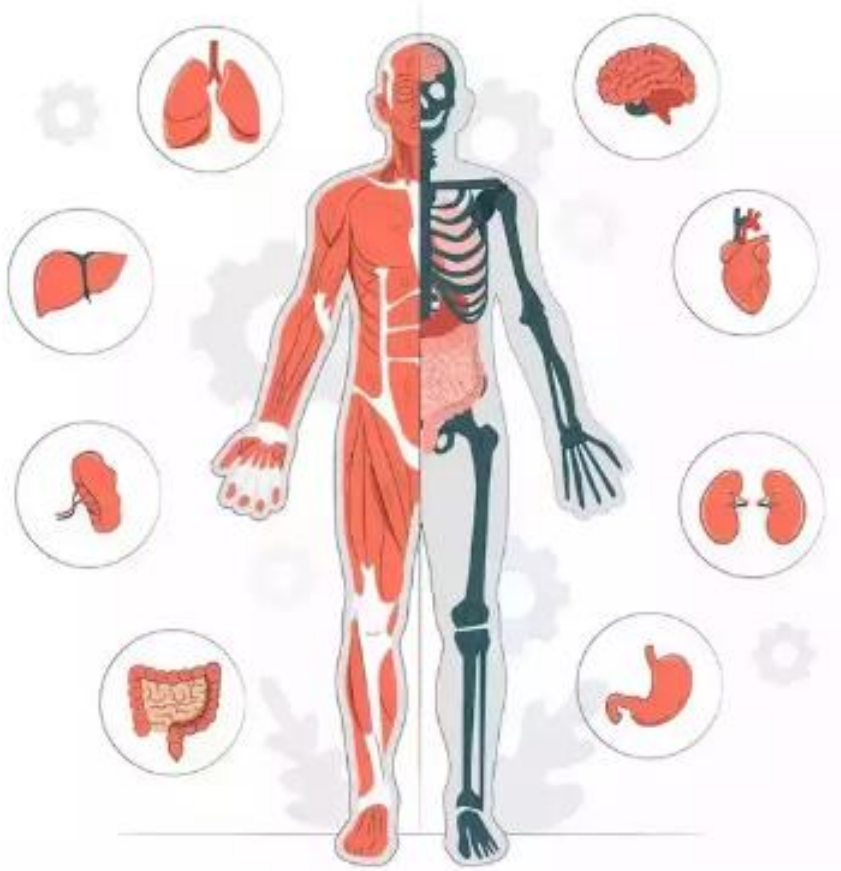
# Organ-on-Chip: Rationale




Between 60-90% of the drugs that pass animal test **fail** in clinical trials

# Microphysiological systems (MPS) - definition

- *“MPS technologies refer to microfluidic cell culture device* ***replicate*** *the structure, function, and (patho)physiology of* *and organs in in-vitro laboratory settings”*



# Key modules in a MPS

## MICROFLUIDICS

Used among other things for culture fluid input, waste fluid output, cell seeding, and to mimic shear stress and gradients.

## BIOLOGY

Human derived (stem)cells positioned within a 2D or 3D structure. Different cell types can be combined.

## ACTUATION

To actuate the physiological micro-environment either physical, electrical or chemical actuation can be used.

## MONITORING

To measure parameters real-time and to gather reliable data.

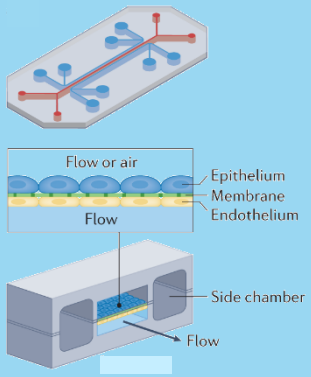
# Example of a state of the art MPS



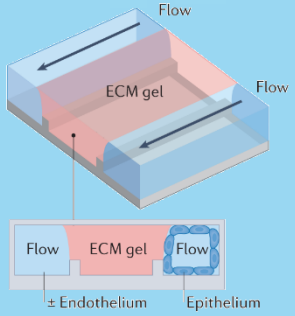
Source: TissUse

# MPS are not widely adopted!

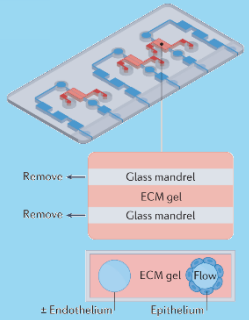
- Academia embraces MPS
- Pharma requests more automatization, higher throughput, high content data gathering & analysis
  - Current platforms not scalable, manual operation
  - Lot's of different geometries; no standardization
  - Cost-effective (Mass) Manufacturing typically not taken into account
  - Integration of Electronics & Sensors only starting



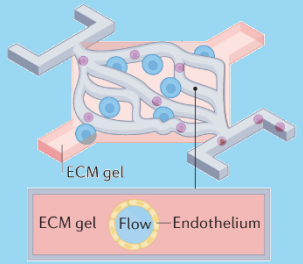

Emulate



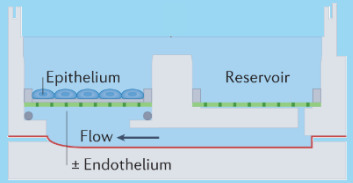

Mimetas



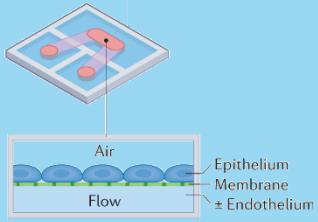

Nortis




Aracari Biosciences




CN Bio Innovations




Draper

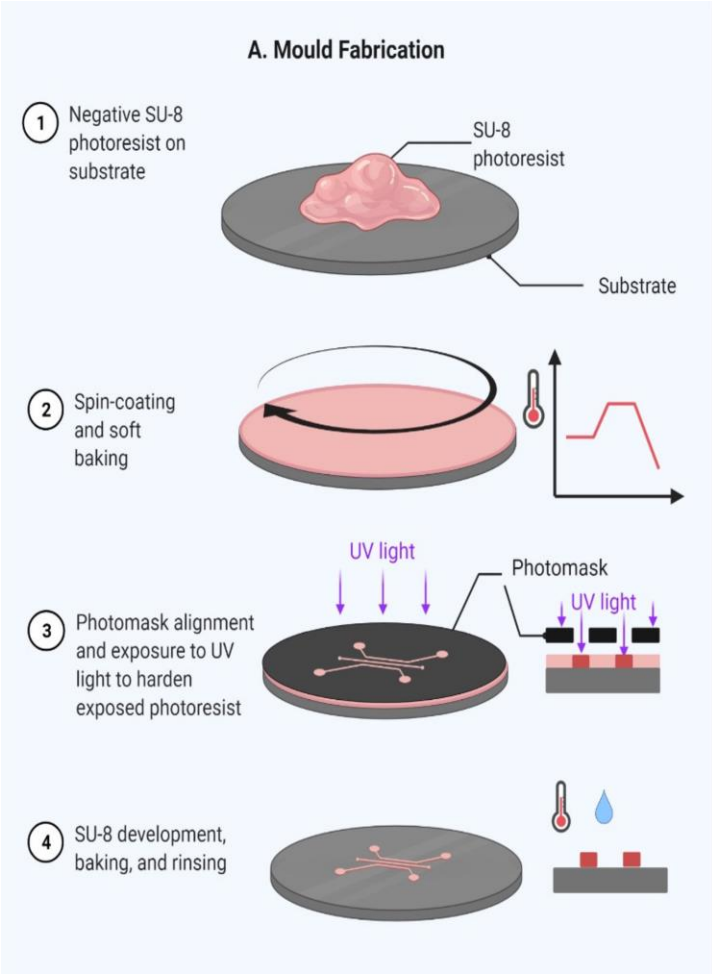


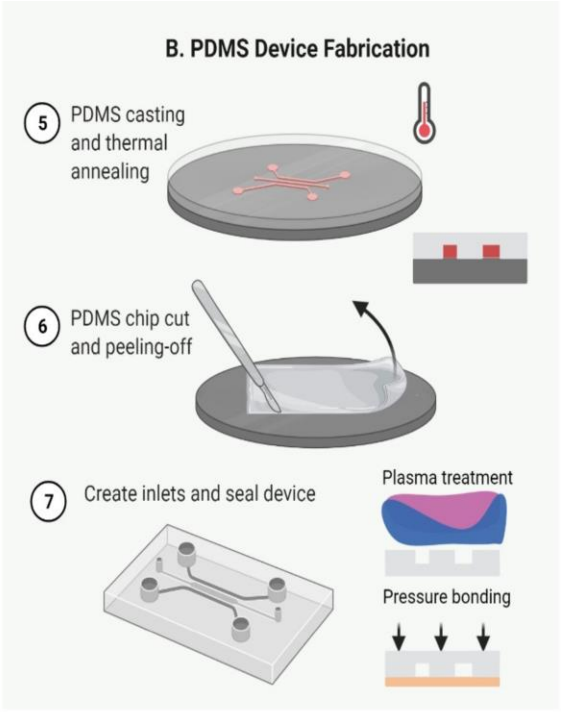
Human organs-on-chips for disease modelling, drug development and personalized medicine. Nat Rev Genet 23, 467–491 (2022). https://doi.org/10.1038/s41576-022-00466-9
Piergiovanni, M., Leite, S. B., Corvi, R., & Whelan, M. (2021). Standardisation needs for organ on chip devices. Lab on a Chip, 21(15), 2857-2868.

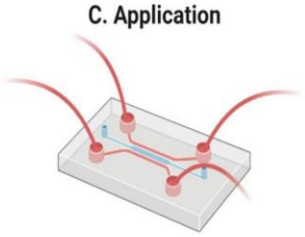
# Fabrication of microfluidics

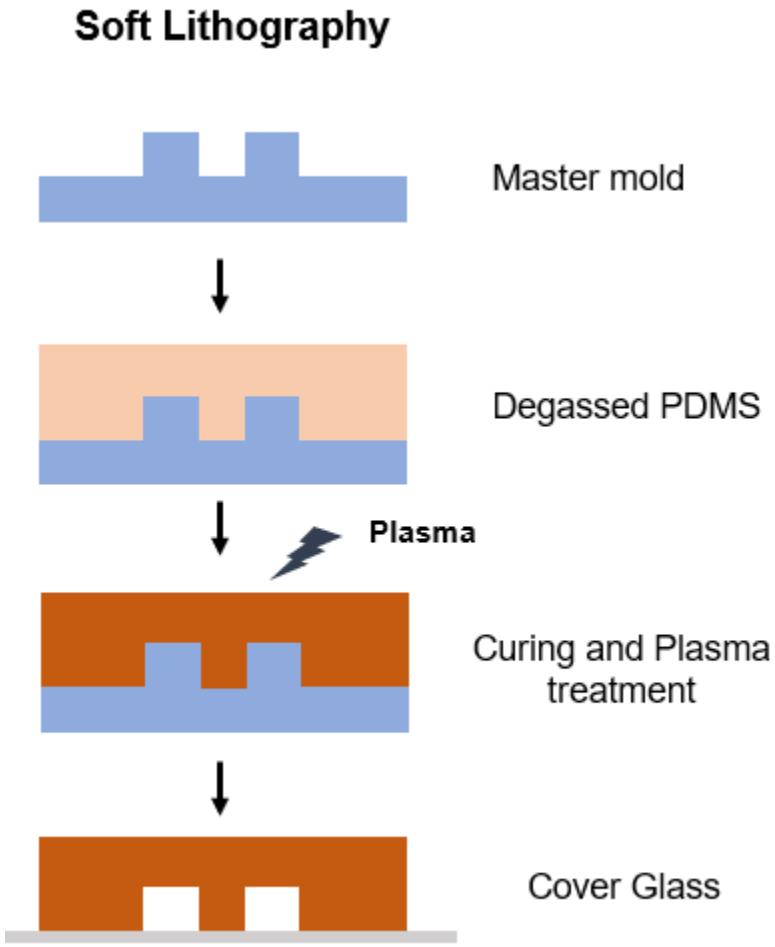
- **Low volume fabrication**
  - Soft lithography (PDMS)
  - Milling
  - Laser fabrication
  - 3D-printing
- **High volume fabrication**
  - Hot embossing
  - Injection molding
  - Imprinting
  - Dry-film resist lamination & patterning

# Soft lithography



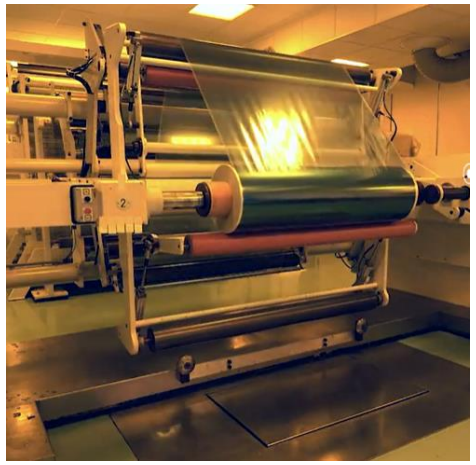



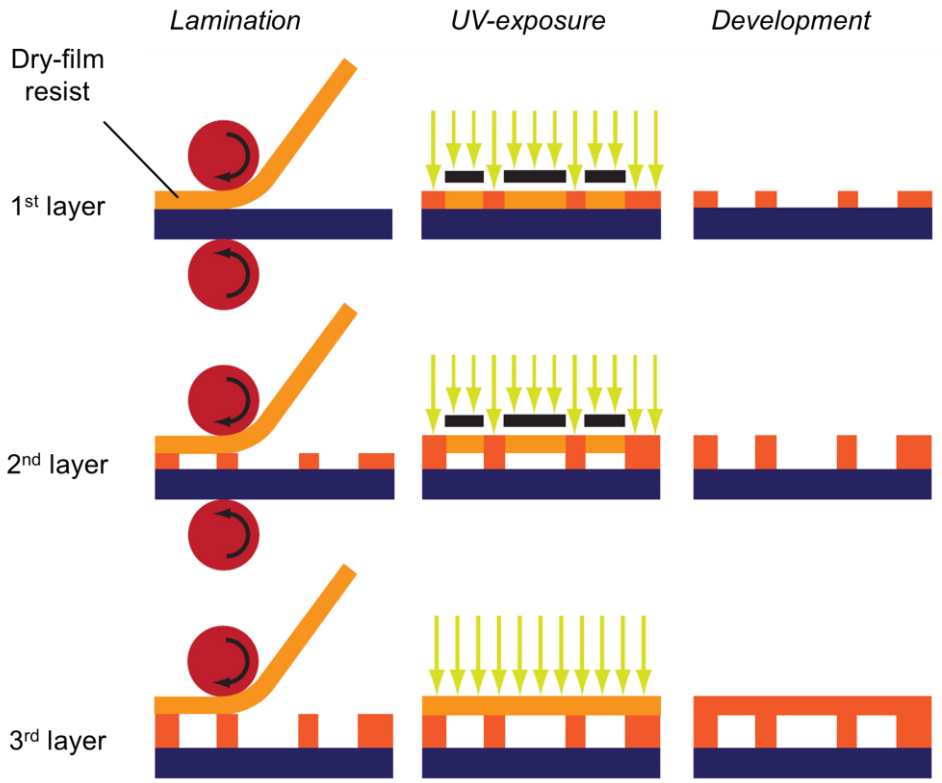



# DFR lamination & patterning

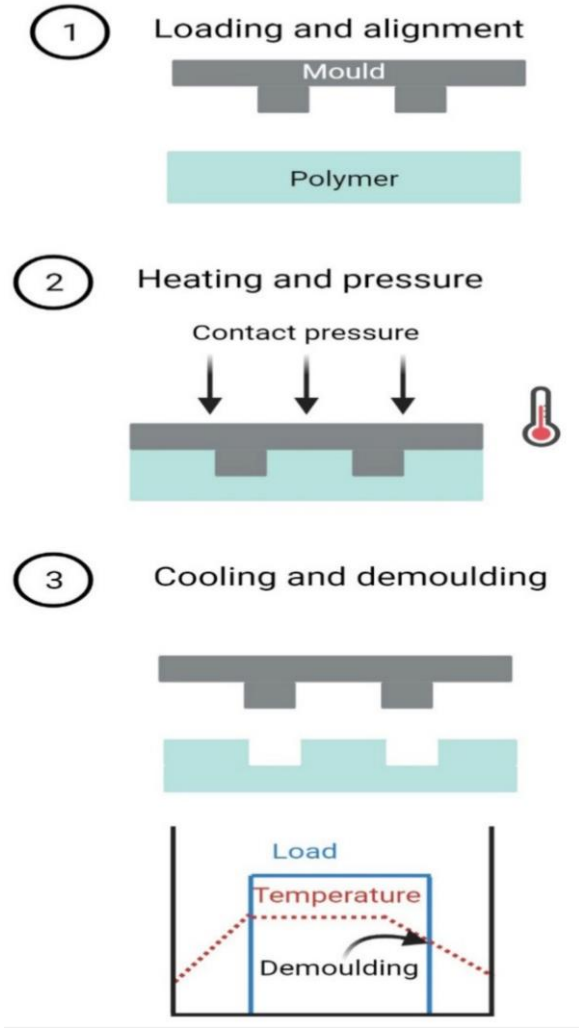
Dry-film resists:

- Thickness: 10-500 µm
- Width: upto 75 cm
- Length: tens/hundreds of meters
- Biocompatibility proven

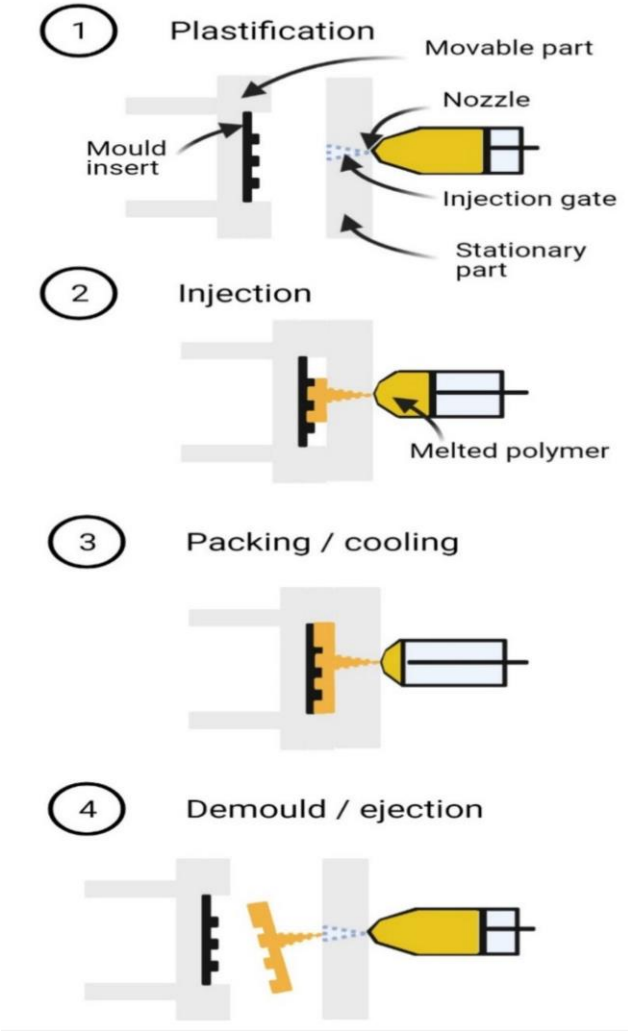




# Hot embossing

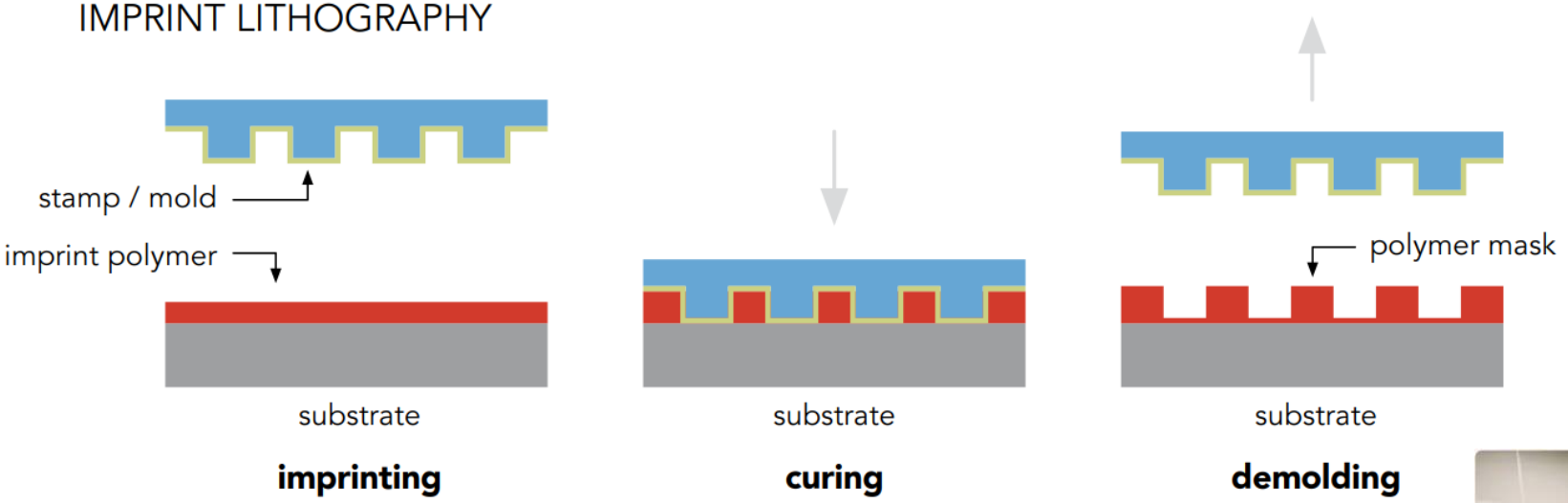


# Injection molding



# Imprinting

IMPRINT LITHOGRAPHY




# Comparison technologies

| | Injection molding | Hot embossing | (R2R) Imprinting | Litho dry-film resist |
|---|---|---|---|---|
| Mold cost | High | Low | Low | Not necessary |
| Unit cost | Low | Low | Low | Depending on substrate size |
| Cycle time | ~30s | Tens of minutes | Seconds | Depending on substrate size |
| Complexity of part geometry | 3D | 2.5D | Limited to thin films | 2D |
| Aspect ratio | Low | High | Low | Moderate |
| Suitable for low quantity | No | Yes | Yes | Yes |
| Commonly used for | Low-cost scale-up & 3D complex geometry | High precision & high quality microstructures | Large area nano/micro patterns | Large area nano/micro patterns *in combination with other functional layers* |

# Comparison of materials

| Material | | Silicon | Glass | PDMS | PS | PC | PMMA | COC/COP | DFR | Paper |
|---|---|---|---|---|---|---|---|---|---|---|
| Property | Optical transparency | N/A | High | High | High | High | High | High | High | Low |
| | Solvent resistance | High | High | Low | Low | High | High | Excellent | High | High |
| | Gas permeability | Low | Low | High | Low | Low | Low | Low | Low | High |
| | Hydrophobicity | Hydrophylic | Hydrophylic | Hydrophobic | Hydrophobic | Hydrophobic | Hydrophobic | Hydrophobic | Hydrophobic | Amphyphilic |
| Fabrication methods | | Wet etching, dry etching | Wet etching, RIE | Replica molding | Injection molding, hot embossing | Hot embossing | Injection molding. Hot embossing, Micro machining, Laser ablation | Injection molding | Lithography | Lithography, printing, cutting |
| Mass manufacturing capability | | Low | Low | Low | High | High | High | High | High | High |
| Material cost | | ~7$/4” wafer | 0.15$/microscope slide | ~150$/kg | <35$/kg | <35$/kg | 2-4$/kg | 11-35$/kg | ~500$/kg[1] | NA |

[1] Low volume price

# Roadmap = Microfluidics + Electronics

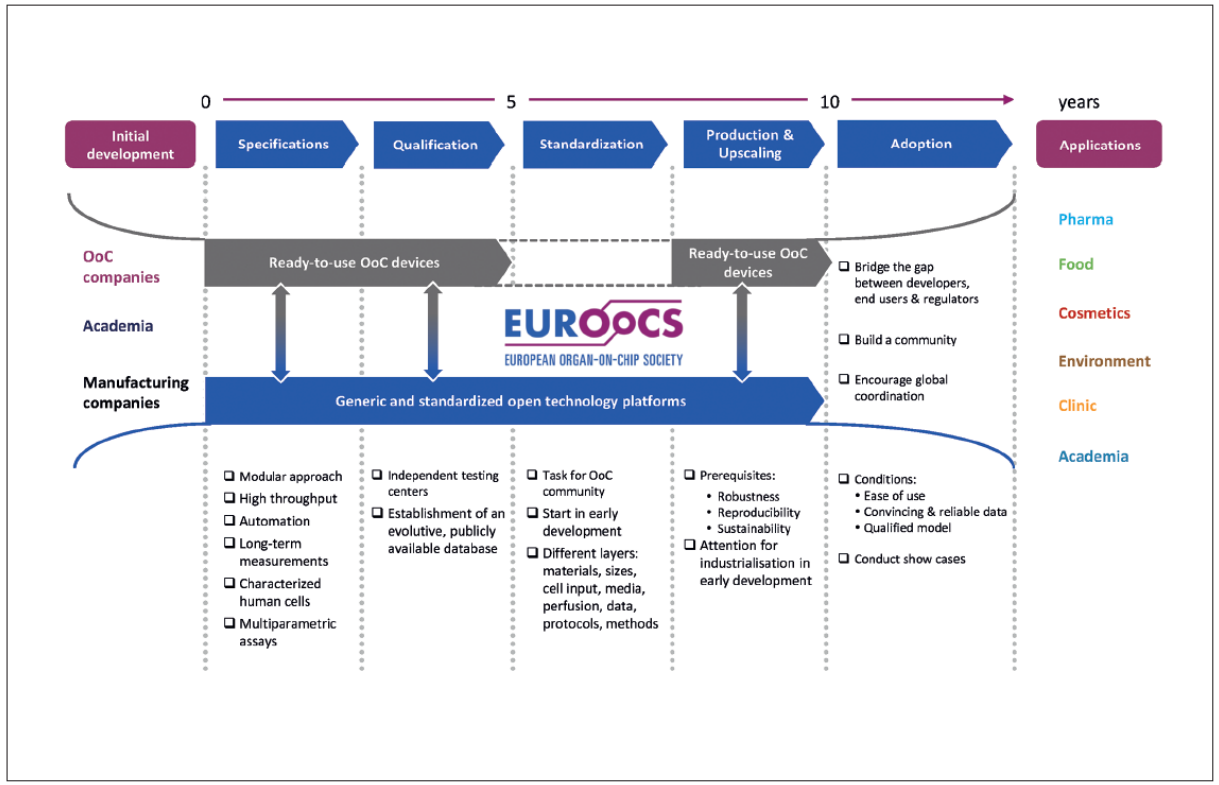



Fig. 6: The ORCHID roadmap for OoC development

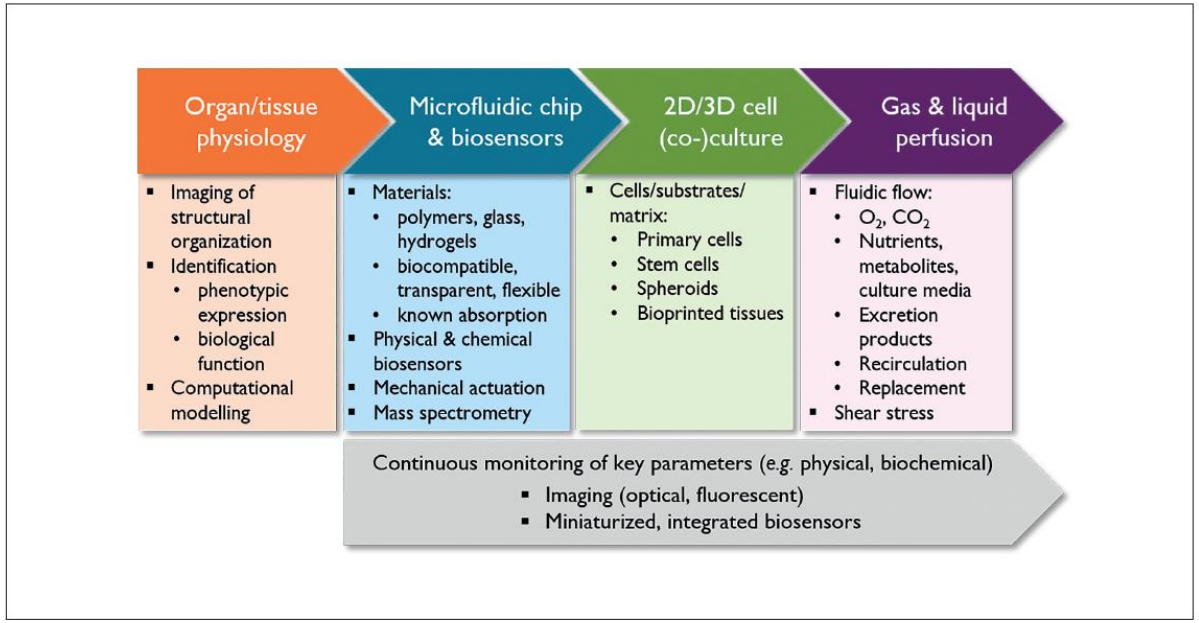
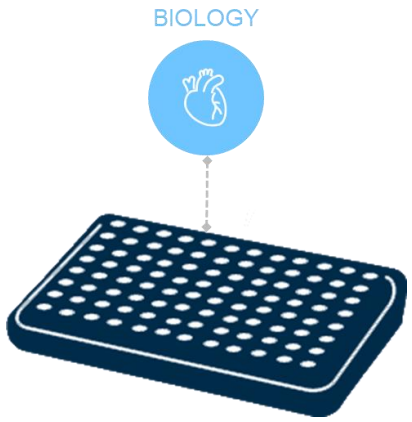


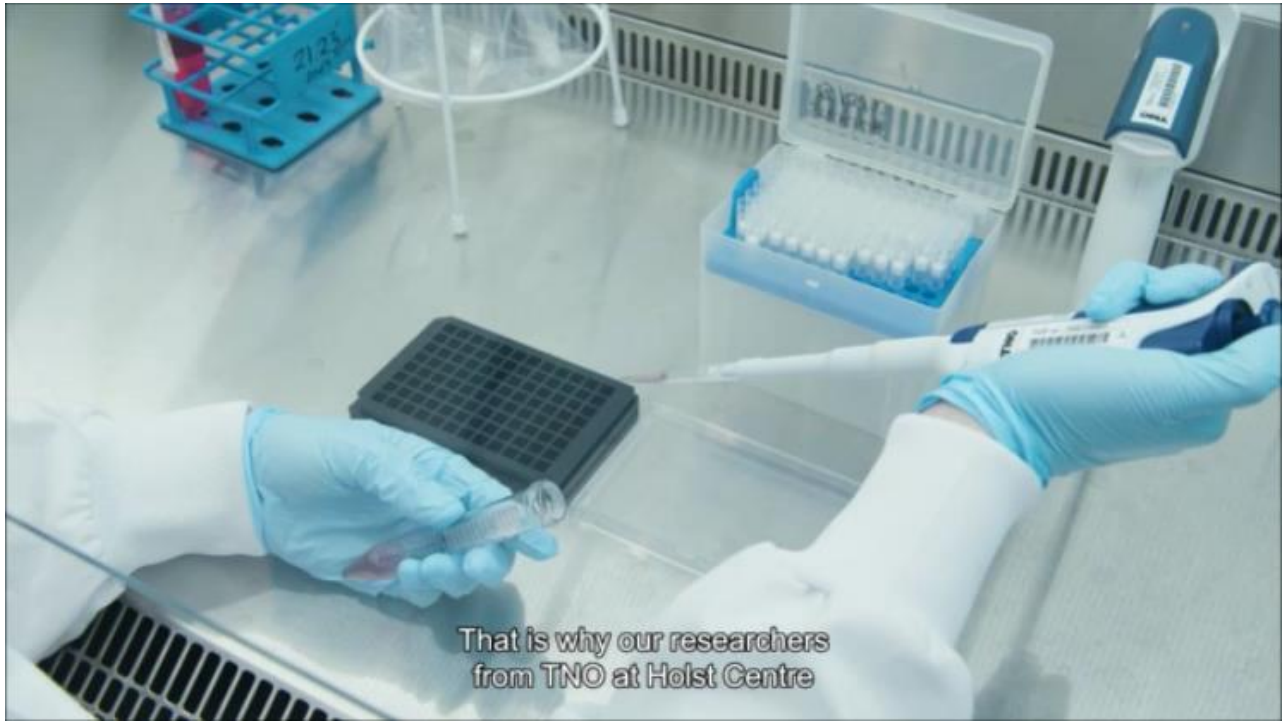

Fig. 1: Simplified synopsis of the OoC value chain, according to the ORCHID analyses

# Use of the standardized multiwell plate for OoC

- Standardized[1] multiwell plate is the default format used in clinical diagnostic laboratories




*Standardized multiwell plate*

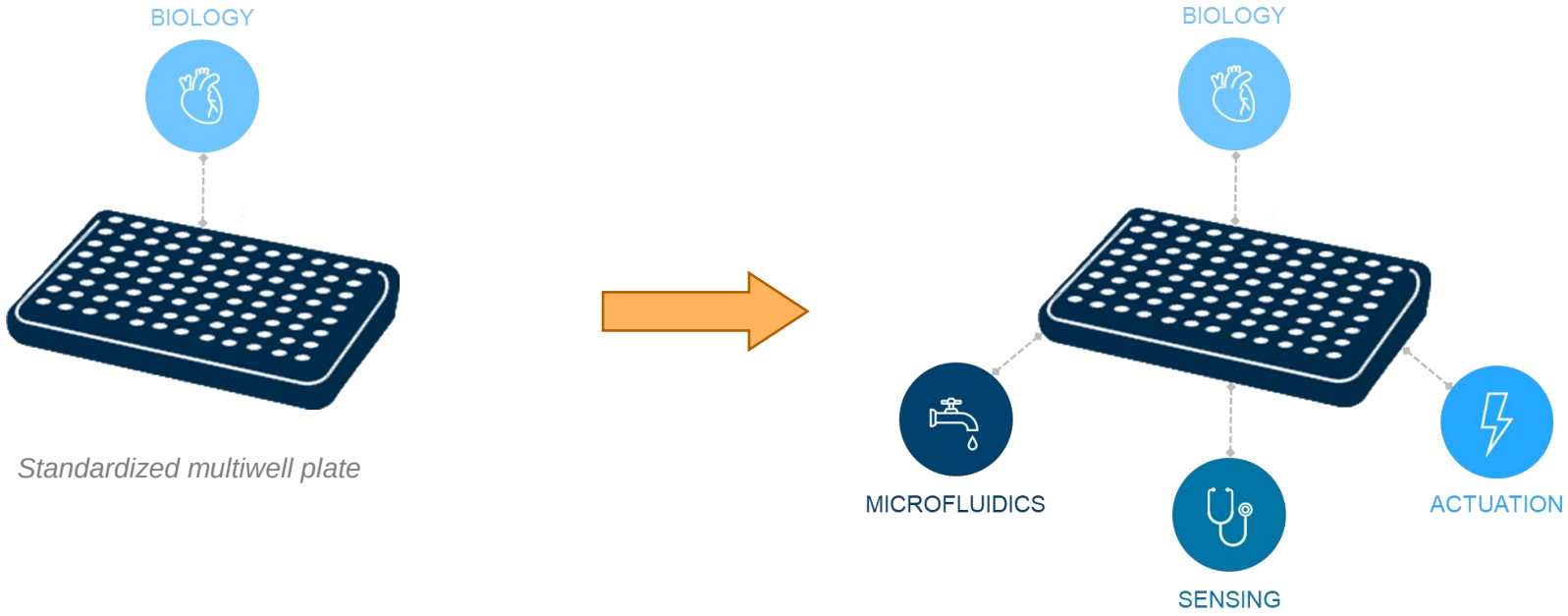





1. ANSI SLAS 1-2004 - Footprint Dimensions for Microplates".

# Making the standardized multiwell plate SMART

- Standardized[1] multiwell plate is the default format in clinical diagnostic laboratories
- By adding functionality to the multiwell plate we can make it **SMART**
- Combination is key in mimicking the physiological environment of the human body




*Standardized multiwell plate*

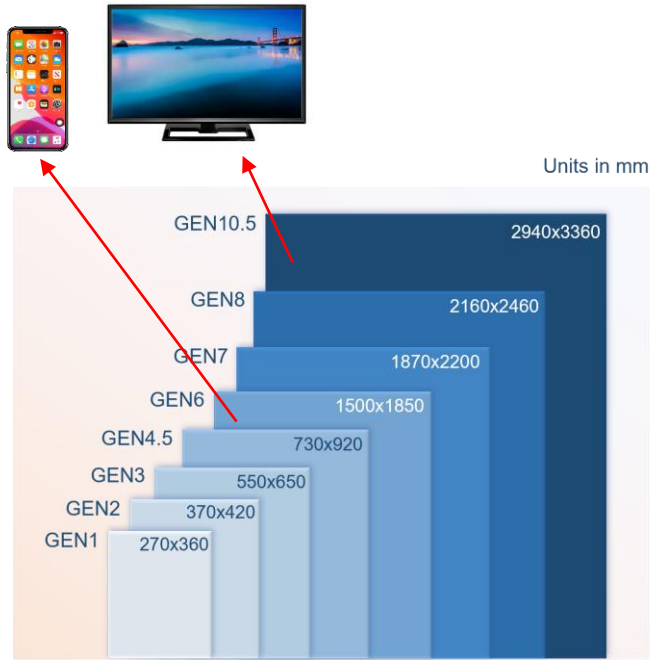
*SMART multiwell plate*



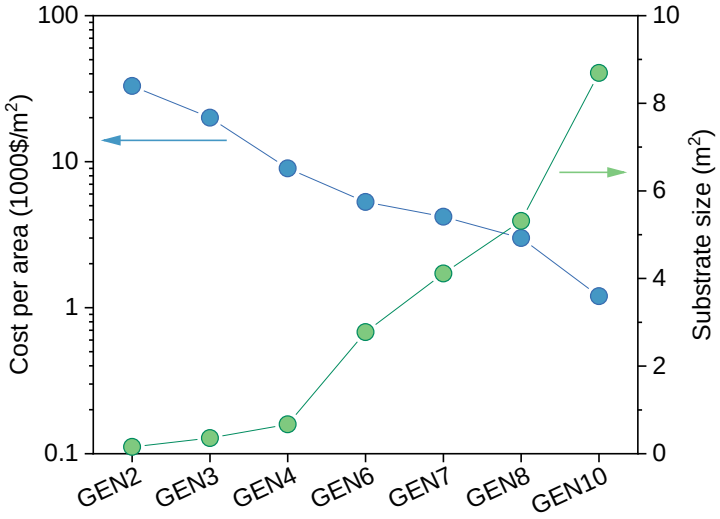
1. ANSI SLAS 1-2004 - Footprint Dimensions for Microplates".

# Diversity: Flat panel display (FPD) technology

- Cost reduction by upscaling substrate size




*Different generations of mother glass substrates*




*Cost per area / substrate size vs. generation scaling*[1]

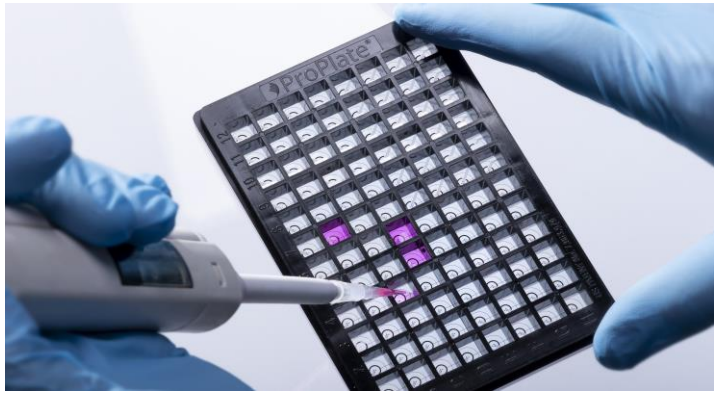
*Flat Panel Display (FPD) fab*

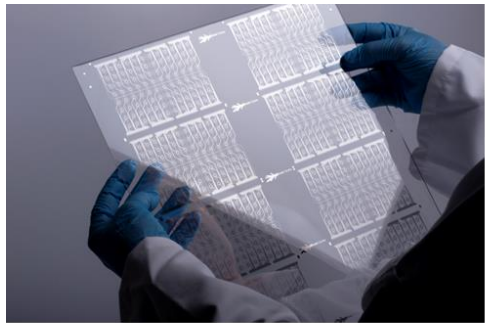
Excerpt from: *Organ-on-Chip technology at TNO at Holst Centre*



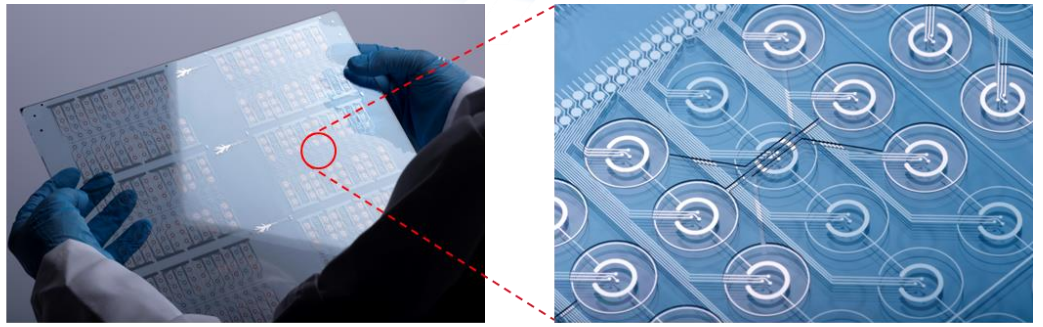
[1] From Novelty to Ubiquity: Challenges & Strategies of Scaling the LCD Platform

# Building Blocks



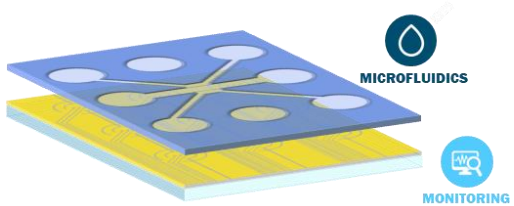


Micro-electrode arrays on
32x35 cm² glass substrate

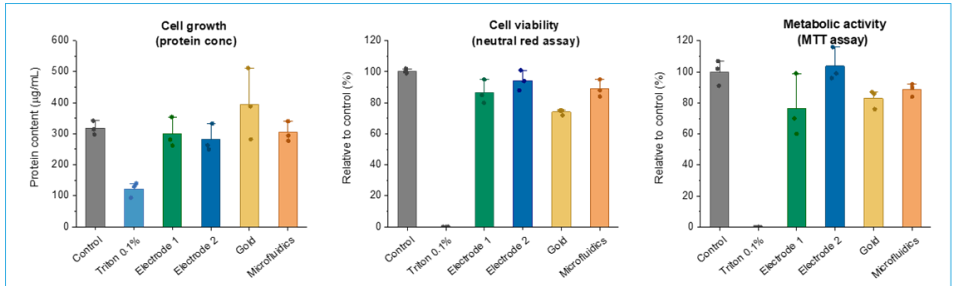


Micro-electrode arrays + microfluidics on
32x35 cm² glass substrate

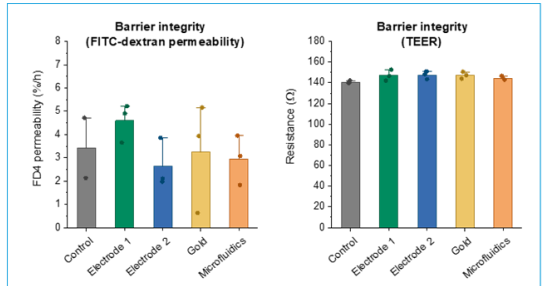
Bridging Manufacturing Technology to Biology





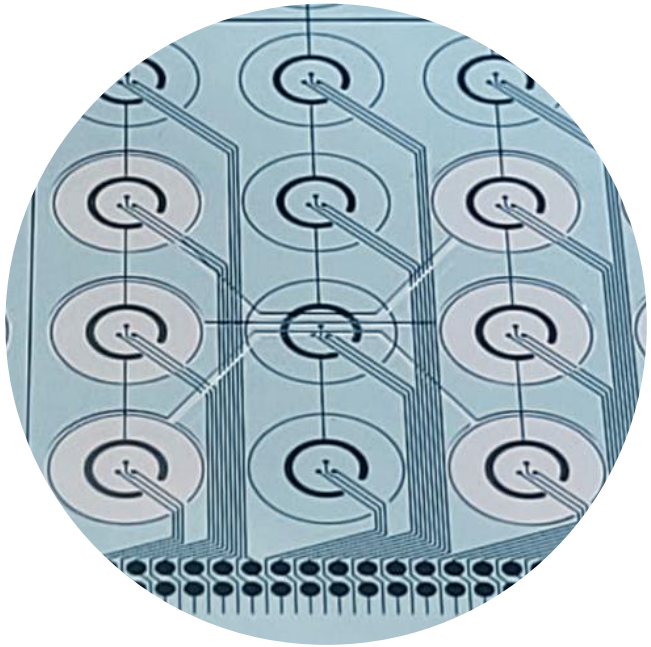

Direct effects on the tested materials



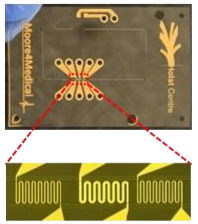

Indirect effects on the tested materials

Youtube: TNO - Holst Centre and Heathy Living & Work - Smart Multiwell Plates

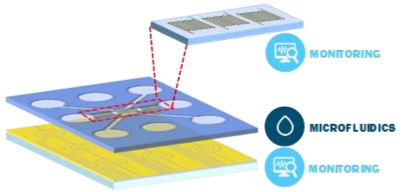
# Inclusion: Sensor Integration

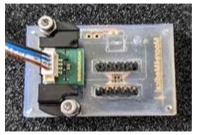


## New Organ-on-Chip Modules: Integrated Flow Sensor & Optical pH Sensor

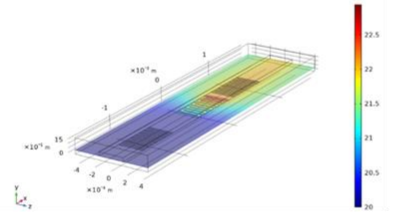


*Foil-based Flow Sensor*

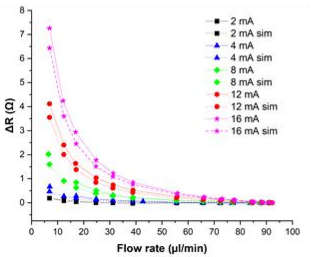


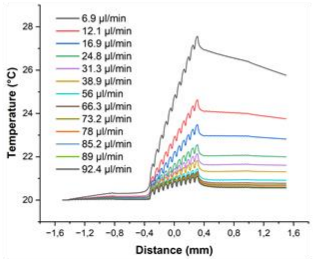
*Integrated Flow Sensor*



*COMSOL 3D Model of Flow Sensor*

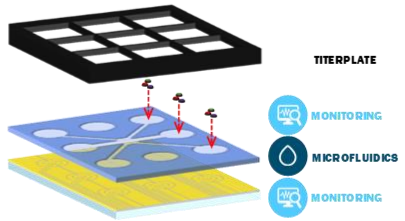


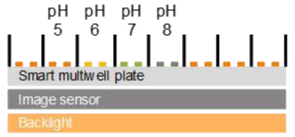

*Experimental & Simulated Resistance Change of the Downstream Electrode*




*Simulation of the Fluid Temperature*

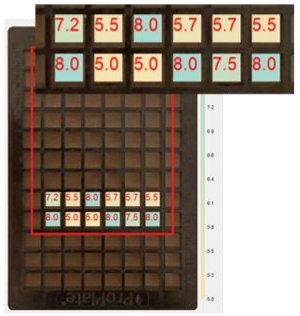
*pH Sensitive Coating Printed in Multiwell Plate*




*Optical pH Sensing in Multiwell Plate*

*Image Sensor with pH Sensitive Multiwell Plate*




*Optical Read-out of pH*

# Roadmap

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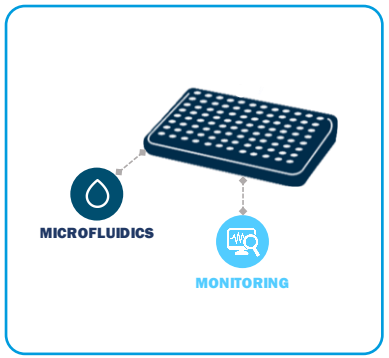
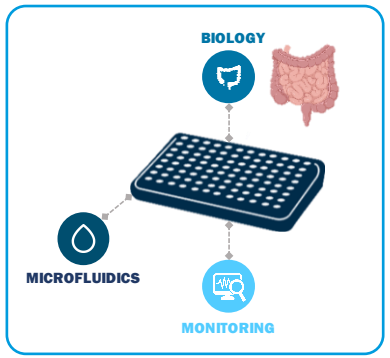
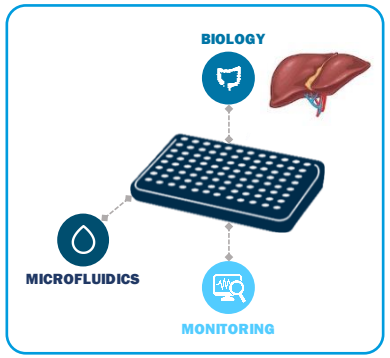
### Integrated Barrier Model

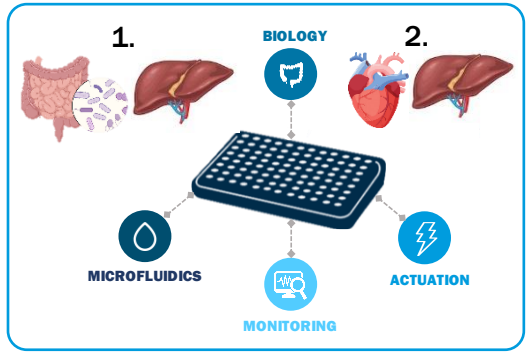



### Single-Organ Multiwell Plate

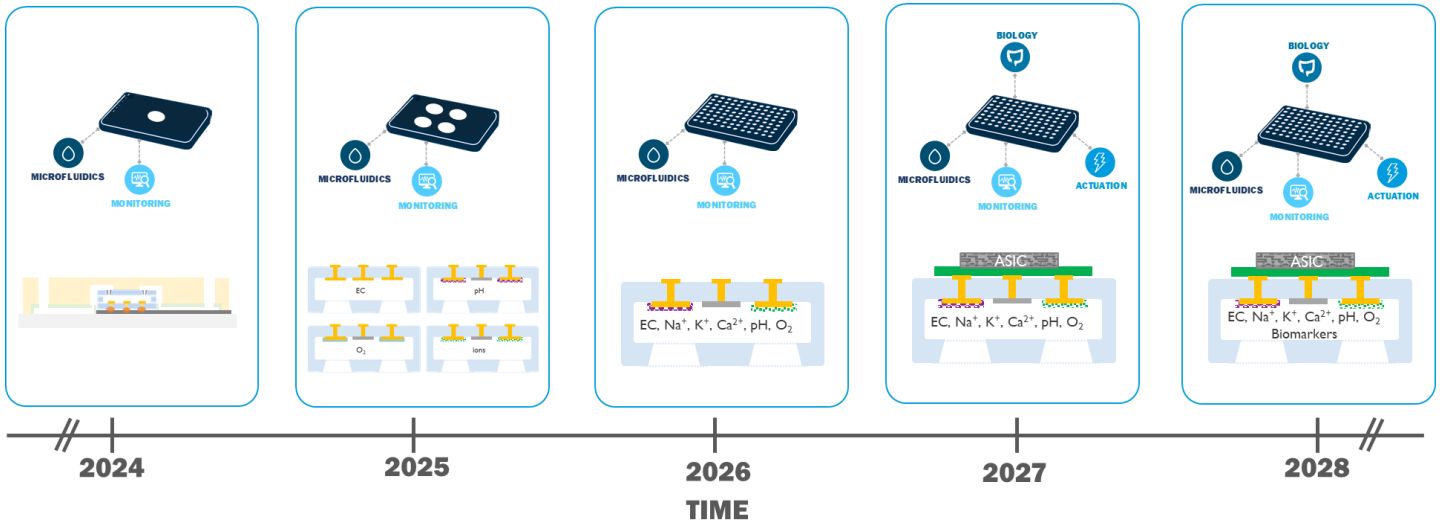



### Multi-Organ Multiwell Plate




### Discrete Sensor Integration

# Diversity & Inclusion in Standardization of Testing Protocols

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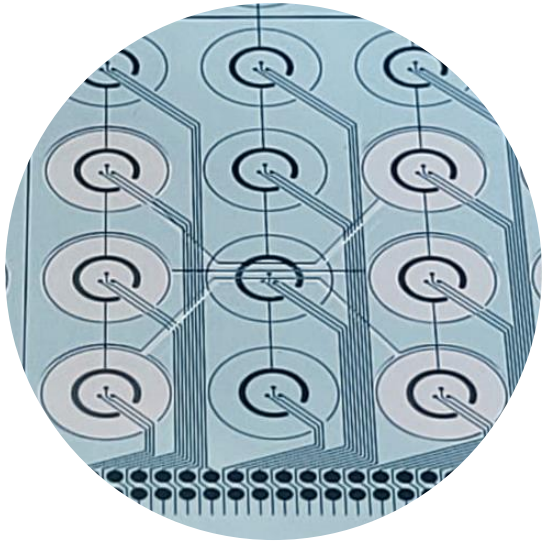
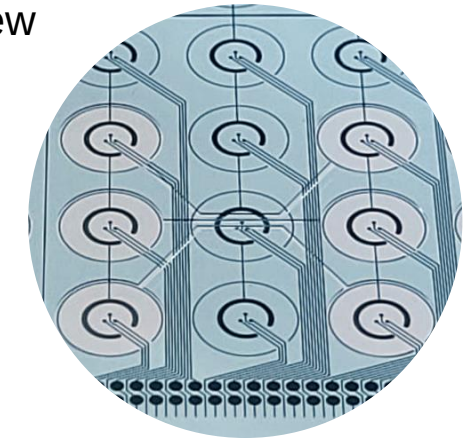
- The case for **Diversity**: Testing of microfluidics needed when new manufacturing technologies are entering the field with need for benchmarking
  - Measurements standards need to be compatible with different manufacturing technologies / manufacturing workflows



- The case for **Inclusion**: New domains opening up where single manufacturing technologies are able to realize integrated microfluidics and electronics components.
  - Call to action to not consider them separately and provide standards for measurements in both sub-domains, but advocate for an **integrated approach**

# Call to Action: Integrated Test Methods

- Topics to consider
  - Standard needed for layouts, connections & thus testing of leak tightness – between microfluidics as well as microfluidics/electronics components & materials
  - Maximum pressures channels, connections, but moreover, integrated components in channels can handle, *e.g.* before component delaminates / disconnects fluidically but also electronically
  - Testing of Active Integrated Components *in operation*, *e.g.* electronic valve operation
  - Materials specifications, e.g. from the microfluidic but also electronic functionality point of view
  - Testing protocols compatible with online/inline manufacturing based on the different platform technologies



# Thank you!

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