Cell culturing

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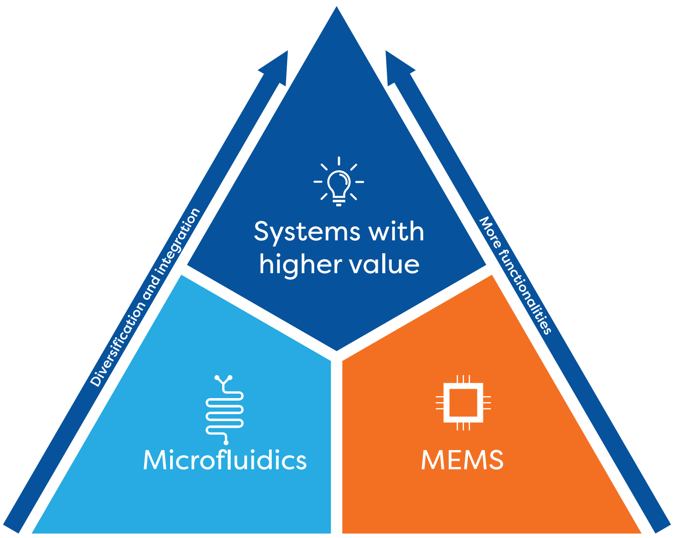
Cell culturing is an emerging market that has great potential for the pharmaceutical industry. The on-chip seeding, feeding and growing of cell material is expected to become a vital part of drug development. The highly controlled conditions under which the cells are cultured, allow very accurate manipulation and testing of these cells. This holds the potential to vastly improve, simplify and speed up the development of new drugs and reduce animal testing.

Organ-on-a-chip

At Micronit, we develop and manufacture devices used for cell culturing. Cooperating with our customers and partners in the biomedical field, we develop cutting edge products that mimic in vitro the in vivo situation as accurately as possible. By combining emerging technologies, we take our devices to a higher level. For example, we bring together MEMS and microfluidics to create autonomously functioning microfluidic systems with a high level of control. Cell culturing allows to recreate the functionalities of an organ in a chip, and this is what organ-on-a-chip (OoC) is all about: taking something large and making it smaller while recapitulating its functionality. For the development of our cell culturing devices we bring biology, microfluidics and microelectronics together on one platform.



By bringing together different fields of technologies, we create systems with a higher value than the sum of the parts.

What's new?

Let's take a look at the most striking new developments in the field at this moment.

Trend 1: Towards sample in, data out in OoC

The first notable development is the hybrid integration of electronics and fluidics. This is done by joining a microfluidic layer and a printed circuit board (PCB), which can contain individual OoC's, sensors and micropumps and realizes the autonomous operation of the platform. The fluidic layer takes care of the distribution of the liquid substances, containing for instance nutrients and reagents.

These 'Smart plates' allow different OoC units to be connected and automatically provide them with the right nutrients and mechanical stimulation by the plate. The plate autonomously monitors the cells and transmits the results to the researchers, thus providing accurate 'sample in, answer out'-data.

Development of the Smart plates requires experts of different fields to work together and find answers to questions like 'which format maximizes the integrability of OoC on a plate?' 'How many fluidic and electrical connections should it have?' 'How can pumps and sensors be included in the fluidic circuits?' 'Are all the different materials and processes needed compatible with each other?'

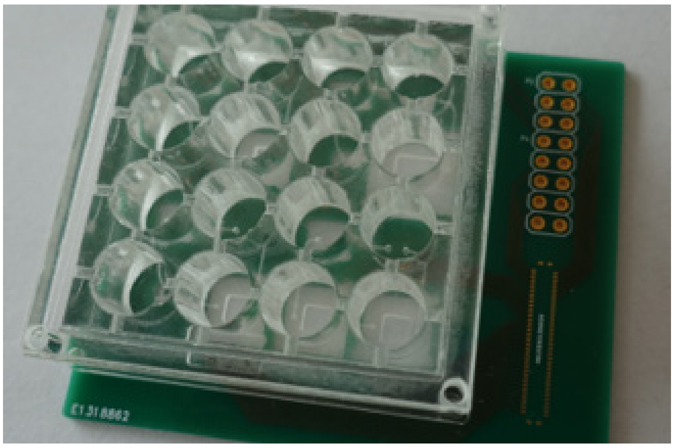
Answering these questions and turning the answers into actions, ensures that these plates can develop into useful products that help OoC gain a larger position in drug development processes. We are proud to be in the hot spot of this development and we and our development partners are looking forward to the validation of these systems.

Trend 2: Customization of the chip, standardization of the interfacing

In vitro biological research has the potential to be used in countless medical fields. To achieve this and make the use of OoC in R&D processes more accessible, it is important to balance two opposing trends: the need for standarization on the one hand versus the diversification of applications on the other hand.

Standardization greatly enhances the accessibility of a device, easing the interfacing or connection with other instruments in the surrounding ecosystem. It makes cross-use of products and technologies possible, thus accelerating and simplifying the adaptation of this technology, in particular for applications where several modules are needed to perform an assay.

Diversification on the other hand is intrinsic in bioengineering. Sometimes we are interested in the electrical signals generated by the cells, while in other cases our readout is purely chemical, some models use cells growing in a well oxygenated environment while others include anaerobic bacteria, some cells need to be mechanically stimulated by forces coming from a strong fluid flow, others need to be periodically stretched, others die if their environment is not nice and calm. As one can imagine, this calls for a high level of customization of the cell culturing platform, and implies that there is hardly going to be a 'one chip fits all' for cell culturing.



Hybrid integration leads to systems that are modular, autonomous and wirelessly powered. They feature wireless data transfer and optical, electrical and biochemical endpoints. Photo courtesy of Moore4Medical consortium.

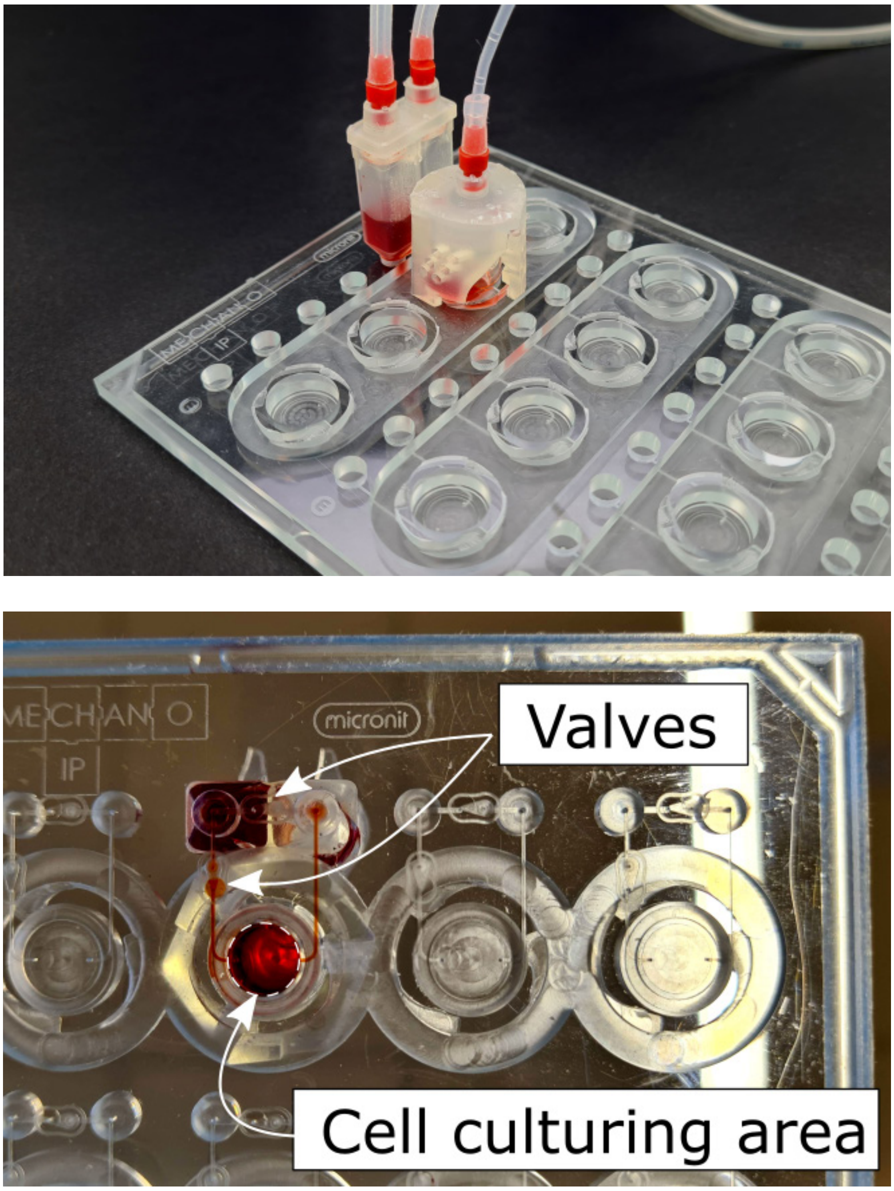
Something that would be of undeniably high value though, is a standardized interface to contain these differently equipped chips. The concept of 'one interface fits all' is a reachable goal that OoC research could greatly benefit from. At Micronit, we choose to work with formats that are compatible with standard formats used by biologists such as multi-well plates (i.e. ANSI/SLAS Microplate Standards), so that our devices can be easily fit on the stage of a microscope in a research laboratory or handled by a high throughput robotic arm in an industrial environment. We adapt our products to the standards in biological workflows, and thus make them compatible with existing research and industrial equipment. Examples of this effort can be found in projects like Moore4Medical and RECardio, and in the collaboration with the University of Twente for the development of the Translational Organ-on-chip Platform (in short, TOP). The TOP platform aims at standardizing the connection between OoC devices, sensors and actuators, and a Fluidic Circuit Board, a wellplate sized device that handles fluidic actuation, creating an easy-to-use interface between the users and the devices.

Trend 3: Stretching the possibilities of conventional biological setups

To make a connection with the current pharma industry, you don't always have to invent something completely new. In fact, it can be very useful to just expand and improve existing tools and techniques.

Over the last decades, biologists have already optimized instruments and protocols to efficiently perform assays in conventional static setups. In cell culturing, Transwell® inserts are very commonly used. Transwell® inserts are small baskets with a porous membrane at their bottom that allow the co-culture of cells on the opposite sides of the membrane, enabling the exchange of liquid (and of nutrients, drugs, etc.) while keeping the cells apart. Being able to add flow to such inserts would allow to expand the toolbox of the biological laboratory, giving control over the dynamic chemical and mechanical stimulation of the cells.

We created a system with fluidic connections compatible with a 96 well plate format that can accept regular Transwell® inserts, and can perform high flow rate perfusion. We integrated reservoirs on the plate to store the liquid, eliminating the need of bulky external tanks, reducing the dead volumes and the risk of passing air bubbles in the system. The reservoirs are pressurized with air, therefore all of the 16 units of the plate can be controlled in parallel using a single pneumatic pump. This grants the plate potential for high throughput processing.



Closed loop circulation. Photos courtesy of MechanoCHIP consortium.

This device is also a nice example of how a technical solution can answer to biological needs. For instance, the culturing of endothelial or bone cells requires strong and sustained liquid flows to better recapitulate the in-vivo conditions. This means that if a syringe was used to perfuse the cells, per chip it would take a very large syringe and a big waste to be able to generate these high flow rates. Since these cells need the high flow rates merely as a mechanical stimulation, the liquid that we pump out of the system can be moved back to the inlet and perfused again. By placing miniaturized one-way valves (i.e. check valves) directly in the microfluidic network of the plate, we managed to create a closed loop recirculation with a very small footprint and minimal control requirements, capable of stimulating and feeding the cells on a standard, resealable Transwell® insert. We believe that CRO's and researchers can easily adopt such a device to lower the barrier from a conventional, static experiment to a simple but biomimetic device.

Micronit as production partner

While our researchers are always excited about developing new solutions and designing new devices, Micronit is also active in the technology transfer of prototypes from collaborators. If the prototype passed a proof of principle, Micronit can help devise processes for production of the item. As a developer of cell culturing platforms, Micronit is always looking for ways to make research and manufacturability meet in the best possible way. When developing a new cell culturing device, the needs and wishes of the researchers are our focal point. But we also have to take into account how we can fabricate the product in large volumes in our factory. Scalability and manufacturability are the magic words here, and Micronit as a production partner will always have eye for these two things from the beginning of every project. Examples of our efforts can be found both among our customers (in the form of microstructured thermoplastic devices suitable for high content bio-assays), and our industrial/academic partners, like the blood-brain barrier (BBB) chip. This chip was developed by the University of Twente and will be industrialized in the newly granted project reMIND. This in vitro model will be used to investigate whether ultrasonic triggering and microbubbles can 'open up' the very selective blood-brain barrier in order to administer drugs into the brain. Medication that could for example treat Alzheimer's or other neurological disorders. Micronit is involved as a production partner in this project, and will be accountable for bringing this valuable tool out of the lab and one step closer to the market, where it could be lifechanging for people suffering from neurological diseases.

What's on the horizon?

If the three pillars of manufacturability, scalability and standardization of the interfacing are properly taken care of, nothing stands in the way for cell culturing to be used on a large scale in biomedical and drug development processes in an increasingly simple way.

But innovations obviously don't stop! There are more exciting developments in the pipeline. Besides hybrid integration and flow control, we are working on engineering the chemistry pre-loaded in our chips, to deliver exactly the surface properties needed for a specific experiment. That is the first step towards the initial integration of not only fluidics and electronics, but also biology, and we look forward to that target! With these developments and others that open up relevant innovations in the biomedical field, we can make a real contribution to a healthier future.

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After studying Biomedical engineering at the University of Pisa, Sandro Meucci held a fellowship at the Italian National Enterprise for nanoScience and nanoTechnology (NEST). In 2015, Sandro joined Micronit as an R&D scientist and was involved in several research projects. Currently, Sandro is part of Micronit's Core Technology Group as a Senior R&D scientist. Based on his knowledge of the needs in research, he develops new technologies in the biomedical field.

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About Micronit

Micronit bv, founded in 1999, with development and manufacturing facilities in the Netherlands and Germany, provides innovative lab-on-a-chip and MEMS solutions using micro- and nanotechnologies. Solutions that help customers improve their products and research, contributing to the quality of life.

Micronit is ISO 9001 and ISO 13485 certified.

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