Advancing life sciences through innovation and ergonomics

"Masters of Time" encounter "Masters of Life"

From left to righ: SiMPLIs ready to be used; SiMPLI at work; SiMPLI's future: intelligent membrane for a smart well plate; SiMPLI supplementary design allowing for tissue manipulation free of the clamping plastic gasket.

The context

To better predict the body's response to new drugs, predictive, *in vitro* models of tissues and organs are evolving rapidly as an alternative to *in vivo* animal testing.

In vivo protocols are complex, and the results are not always a reliable prediction of human clinical response. Ethically questionable, animal testing even faces legal challenges, such as the European double ban on the testing/marketing of finished cosmetic products or components that have been tested in vivo (July 2013).

Since standard toxicity certification procedures are mostly, if not exclusively, carried out via animal testing, the dilemma is obvious. The tools to overcome it, though, are simply not yet available.

The market

The global market for in vitro toxicity studies is evolving rapidly, from USD 4.9 billion in 2012 to a projected USD 9.9 billion in 2019.

SiMPLI*next* specifically targets the market for testing for toxicity at an early stage in new material development. The industry's need for early-stage toxicity assessments implies an irreversible shift from in vivo to in vitro (and *in silico*). As the first step in determining the fate of a new formulation in the human body is to observe how it crosses biological barriers (BBs) such as the lungs, kidneys, or blood-brain barrier, predictive, in vitro BB models are required.

The technology

Inserts are basic supports for the development of cellular BB models. They are responsible for all the information collected to date in vitro and are specific to BB models which need a mechanical, non-vascularized structure around which to organize, respecting a precise orientation—a directional architecture that is functional to the definition of the inside, and outside, of the body. Fascinating technologies revolutionizing the in vitro perspective—"scaffold-free" cellular models or even "organ-on-a-chip"—could begin to become reliable tools starting in 2020. But they are disruptive technologies with a "high entry barrier" to both their use and to the evaluation of their information yield.

Today's inserts are permeable, microporous polymer membranes with average pore densities of 5–15%, pore size variation of 0.4–8µm, a fixed thickness of 10µm, and randomly distributed pores.

In SiMPLI—silicon nitride microporous permeable inserts—the current polymer membrane is replaced by an ultrafine ceramic membrane array issuing from state-of-the-art microfabrication, making possible never-before-available design control and robustness features.

SiMPLI*next* proposes producing and marketing these new ultrathin permeable inserts for standard multi-well plates; exactly as for current inserts, but by providing "transparent" mechanical support for in vitro BB modeling. Handling and protocols are very close to those currently used, allowing the introduction of an innovative, "low barrier entry" product consistent with existing data collection and analysis paradigms.

By reducing the mechanical support's thickness, we introduced a biomimetic membrane—a "microfabricated basal lamina". In nature, the basal lamina is the mechanical, non-vascularized support on which epithelial cells lay. The epithelium is typical of all biological barriers. The basal lamina, typically separating the epithelium from the endothelial cells, is the site of the inside-/outside-body interface. Beyond its thinness, a ceramic basal lamina is able to:

- define the contact surface between cell layers and enable cross-talk;
- ensure mechanical support to the tight, impermeable layers of cells;
- allow the passage of nutrients;
- not interfere with the active (biological system energy triggered) crossing mechanism of relatively large molecules, such as particulate matter generated from combustion, or nanoparticles (smart drug carriers or nanomaterials in general). The latter would possibly be actively blocked by the biological barrier function.

This improves the model's relevance to the point of making available information that until now was available only through animal testing.

The product

SiMPLI*next*'s first product is a cell culture insert (SiMPLI) 20 times thinner than currently available inserts. The membranes designed to accommodate cell growth in the SiMPLIs are 500nm thick, ceramic, and have evenly distributed pores, their size and density matching current market requirements. They are transparent both in the optical sense for better viewing, and in the sense of being noninvasive regarding the functioning of the biological model. The ultrathin SiMPLI changes the game in terms of transport, and of model relevance.

The starting product is the simple insert with possible vertical integration such as providing ready-to-use tissues (cell-based assay), and more interesting horizontal integration augmenting the membranes' capacity by adding sensors, actuators, and even embedded data acquisition and processing (smart insert and smart well plate for non-invasive remote control).

SiMPLI and its horizontal integration is protected by two filed patents in the Europe and the US.

This new insert delivers identically reproducible modeling both of an organ and of specific organ function. Its design is inspired by a clear vision that requires the steps that will lead us to the quantum leap to "human testing". Clearly, by the time we get to test on humans, we must have a great awareness and mastery of toxicity, which can only be obtained by further improving the quality of information collected in vitro.

SiMPLI*next* objectives

SiMPLI*next* is a start-up based on the market validation of a CSEM SA spin-off technology.

Product-wise, starting with a large-volume-production/high-reproducibility model, we will later adopt an "expert"/high-customization approach, targeting—as the ultimate goal—the provision of commercial standards for the legal certification of new products/new materials.

SiMPLI*next* opens the treasure of Swiss watchmaking—microfabrication, of which Neuchâtel is the cradle in Switzerland—to the life sciences. It thereby rises to the challenge of demonstrating that biotech and medtech are no longer distinguishable. A new interactive paradigm is needed in order to maintain and increase Swiss competitive advantage, to lead the transition from in vivo to in vitro, and to unlock the market for Swiss in vitro industries. A vision shared with a competent and motivated team both inside and outside the birthplace of the technology concerned—CSEM SA, Neuchâtel, Switzerland.

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