

Organ-On-A-Chip: Enabling Technology for Biomedical Engineering Applications



JM Rosser and P Ertl*

Lab-on-a-Chip Systems in Bioscience Technologies, Vienna University of Technology, Austria

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***Corresponding author:** P Ertl, Lab-on-a-Chip Systems in Bioscience Technologies, Vienna University of Technology, Austria,
Tel: +43158801-163605/43 664 605887129; Email: peter.ertl@tuwien.ac.at

Opinion

In 2004, the FDA estimated that 92 percent of drugs which pass preclinical tests, including mandatory animal tests, fail to proceed to the market (Harding 2004) – a situation that has not markedly improved over the last decade. Animal trials are not only controversial due to ethical considerations but also costly to perform, creating the demand for ethically responsible and economic research methods. Furthermore, animal trials inevitably include additional unquantified variables, such as animal health status, reproducible growth, diet, weight, and intrinsic genetic differences [1,2]. Research has conventionally been performed in monolayer cultures, utilizing a 2 dimensional cellular environment in which cells adhere to a plastic surface with no matrix interaction and limited to no possibility for application of relevant chemical and biomechanical cues. In monolayer, many cells lose their function and thus their phenotype, altering cellular proliferation, gene expression and protein transcription. For example, modeling of neurological diseases in traditional, two-dimensional cultures has serious limitations because the human brain is an extremely complex, three-dimensional (3D) structure [3]. At the same time, animal models of certain human diseases such as Parkinson's lack naturally occurring pathology and must be synthetically induced, accounting for the exorbitant failure rate of drugs developed in these models.

In contrast, one new and promising research field which simultaneously addresses the fundamental need to develop alternative methods for animal tests is called organ-on- a-chip technology or tissue microarrays, where the recreation of near native and physiological-relevant culture conditions has shown to promote the formation of tissue-like structures on a microchip platform [4]. Microfluidic principles offer 3D cell culture capabilities, simulating the native cellular environment, lending cells a physiologic atmosphere and bringing protein transcriptomics, secretome analyses, and gene expression to a level more closely resembling in vivo than ever before. The unique combination of microfluidics with 3D cell cultures

systems allows the reproducible re-engineering of the biological niche (e.g. gradients, temperature, pressure profiles, mechanical stimulus), thus establishing micro tissue structures that closely resemble native organs. The premise of any organ-on- a-chip technology is to replicate real organ form and function using a 3D culture of organ specific cell types.

Consequently, five key attributes need to be addressed during the development of an organ-on- a-chip including

- A. Establishment of multicellular architecture that represents characteristics of native tissue,
- B. Functional representation of native tissue,
- C. Reproducible and reliable operation under physiological conditions for a period of 4 weeks,
- D. Representation of in vivo-like phenotypes, and
- E. Exhibiting population diversity.

Similarly, discussion of the niche or cellular microenvironment has saturated tissue related scientific publications in the last 10 years postulating that extracellular matrix, mechanobiology and molecular cell signaling direct the fate of local progenitor cells as well as possibly maintaining the heterogeneous cellular functionality of the tissue itself. This means that altered tissue microenvironments inevitably constrain cellular function, proliferation and progenitor differentiation [5], thus highlighting the need for more relevant tissue models with physiologic cellular behavior. Since age, health status and systemic factors as well as genetic makeup also contributes to in vivo phenotypic behavior such as cell-to-cell and cell-to-matrix interactions, personalized tissue models begin to appear as a realistic goal for the future of clinical diagnoses and pharmaceutical research. It is now largely believed that personalized tissue models with physiologic cellular behavior will offer an immediate avenue for patient customized diagnostics and therapeutic specificity. This concept of personalized medicine has largely come to reality due to the development of induced pluripotent stem cells (iPSCs)

induced from somatic cells [6,7]. With this technology disease-specific human iPSCs and their derived cell types can now be used for in vitro disease modeling [8].

In our laboratory, these advances have led to two novel research platforms: (1) targeting cartilage-on-chip and subsequently pathogenesis of osteoarthritis (OA) as well as (2) iPSC derived midbrain organoids-on-chip recreating naturally occurring Parkinson's disease (Figure 1). Our microfluidic 3D chondrocyte culture microdevice features the main characteristics of cartilage, namely low metabolic activity of primary chondrocytes, expression of matrix-related genes (e.g. Col2, ACAN), longstanding differentiated cellular morphology, physiologic superficial cell alignment and linear cell aggregation as seen in the deep zone of native cartilage [9]. To the author's knowledge, spontaneously cell driven tissue structuring without biomolecular or environmental manipulation has not yet been

described specific to the articular cartilage. Given the similarity of the chondrocyte self-organization in our micro device to that seen in native articular cartilage, it remains likely that our reengineered tissue truly mimics the in vivo situation. Recently, the use of iPSC donor cells for cartilage defect repair and for creating tissue models of cartilage has been proposed based on laboratory differentiation of human synovium-derived iPSCs [2], bringing personalized medicine to the forefront of reality. Our midbrain organoid device is focused at facilitating physiologic neurodevelopment with the capacity to detect aberrations in electrochemistry consistent with onset of disease related symptoms. Not only does this microchip offer previously unfathomed access to neuronal developmental processes but ultimately, this technology will hopefully direct individual clinical care of patients by non-invasive patient derived cell acquisition resulting in therapeutic targeting and associated prognosis [9].

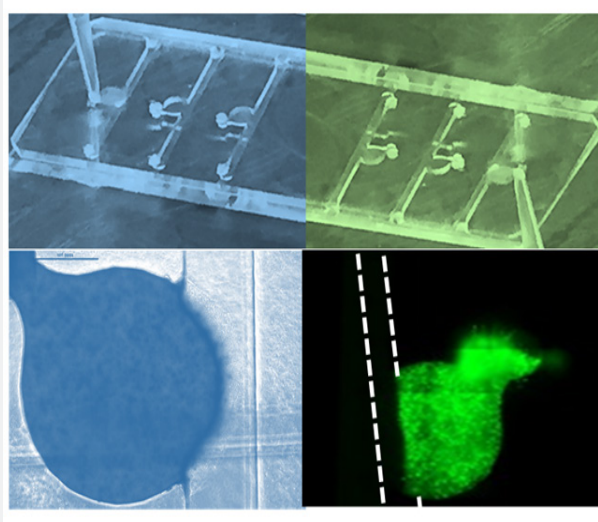


Figure 1: Imag

In conclusion, the integration of complex human biology with microchip technology has led to the development of a variety of advanced organ-on-a-chip systems, which can be used as replacement of animal testing, personalized diagnostic tools and advanced disease models to help improve our understanding of the human body. We expect the application of organ-on-a-chip technology to steadily increase in the next years with the greatest impact in pharmaceutical development [10-12].

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