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Commentary

A Commentary on Complex *in vitro* Cell Culture Stressing the Importance of Fluid Flow and Illustrated by Organ on a Chip Liver Models

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About the Study

The translation of new technology from development into widespread commercial use is a complex and time-consuming process that requires significant investment. The above article looks at some important market needs for more complex *in vitro* models, the technical difficulties that must be overcome, particularly those connected with introducing fluid flow using microfluidics, and illustrates the economic benefits of more accurate models for drug toxicity. Beyond the strong ethical arguments for replacing the use of animals in drug safety testing and medical research, the author believes that financial benefits of adopting the new *in vitro* technology are becoming clear and will drive the adoption by industry.

There is a trend towards increasing the complexity of *in vitro* cell culture which is driven by a need to improve the accuracy of toxicology screening in drug development, as well as economic and ethical factors for replacing the use of animals in medical research and drug development. Despite the intense efforts to develop organ on chip models there has been limited success because of the technical challenges as well as the complexity compared to existing *in vitro* methods.

Complex *in vitro* cell culture, particularly in the context of Organ-on-a-chip (OOAC) models, relies heavily on the introduction of fluid flow to mimic physiological conditions. This is crucial for maintaining cell health, function and interaction, especially in models like liver-on-a-chip, where nutrient and oxygen transport, as well as waste removal, are essential for accurate drug testing and disease modelling.

Both micro and milli-scale flow technology have been employed to fabricate OOAC devices, but the technical problems are challenging. One key design requirement is the need to sample conditioned media or take cellular material for end point analysis. Fluid flow in microfluidic channels is difficult to optimize. Narrow microscale tubes, air bubbles or blockages can restrict medium flow and limit oxygen delivered to the cells, but this can be solved by increasing the radius of the flow channels Several successful designs have used computer fluid flow modelling to ensure flow stress, nutrient supply and partial oxygen pressure are achieved during operation. Some commercial developers have increased the pressure to overcome the restrictions on flow but it increases the capital cost and complexity of the control system for the OOAC device. It is important to limit the pressures experienced by the cells under culture to those found in the human body and certainly below those found in large Arteries (systolic 120mm of Hg to diastolic 80mm of Hg). This article describes the merits and disadvantages of syringe, peristaltic and pneumatic pumps.

Although *in vivo* relevance is a desirable criterion, it is the commercial benefit that will drive acceptance of these more complex models by industry. The goal for pharmaceutical companies is a significant improvement in the success rate of new drug candidates in clinical trials. These companies will require the OOAC technology to be validated by testing a portfolio of compounds with known positives and negatives. The new technologies must also be more accurate and cost effective than predictions from animal models. References to the relevant economic data are provided in the paper.

The paper illustrates the criteria for physiological relevance by looking in detail at liver models. Drug toxicity assessment depends on accurate assessment of IC50 values for a candidate drug compound. The cells should express the correct CYP P450 enzymes over three or more days and this is now routine in many OOAC devices

For drug toxicity studies, a single organ model can be beneficial. However, for disease research a systemic (multi-organ) *in vitro* model is an important step on the way to replacing the use of animals. Models of metabolic crosstalk and the interactions between metabolically active organs, such as skeletal muscle, the liver, adipose tissue, the pancreas and the gut, will be needed to study diseases such as type 2 diabetes and non-alcoholic fatty liver disease. Flow can improve the viability and functionality of a single organ model, but it is essential for a multi-organ model.

The commercial availability of OOAC devices is increasing but there are important differences influencing the take up by industry and academia. Industry is less sensitive to cost and requires validated protocols. The academic research community

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requires more flexible and affordable OOAC tools. The business models and market focus of the companies developing OOAC are now evolving to meet these differing requirements. The technical difficulties associated with the development of more complex models, especially in use of microfluidics, are better understood and being solved. The first evidence for the economic advantages available from the adoption of the new technology by industry and academia is now emerging and signposted in the references in the paper.