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Automation of Multi-Organ-Chip Assays

Hendrik Erfurth[1], Florian W. Huber[1], Ann-Kristin Muhsmann[2], Ricky Bayer[2], Leopold König[1], Juliane Hübner[1], Flora Kiss[2], Christian Hoyer[1], Roland Lauster[2] and Uwe Marx[1,2]

[1] TissUse GmbH, Berlin, Germany [2] Department of Medical Biotechnology, Technische Universität Berlin, Berlin, Germany

1 INTRODUCTION

With the approval of the FDA Modernization Act 2.0 the requirement to use animal testing for drug development has finally been eliminated – paving the way for innovative animal-free technologies like Multi-Organ-Chips (MOC). However, there are still major challenges ahead. Currently, the full potential of MPS cannot yet be fully exploited.

The high complexity of MOC-based assays leads to a high amount of manual work in the execution and analysis of these assays. Handling and analyzing these complex organ models requires advanced methods. Therefore, finding effective solutions to address these challenges becomes crucial.

Automation of assays on Multi-Organ-Chips has emerged as a promising solution. By integrating a robotic system, numerous benefits are achieved. Firstly, automation reduces manual effort and enables more efficient assay performance.

Secondly, automation enhances assay accuracy and reproducibility. Robots execute precise manipulations and measurements, minimizing human errors and variations. This improves result quality and promotes comparability across experiments and laboratories.

Thirdly, automation facilitates scalability by enabling larger experiments with Multi-Organ-Chips. This opens up opportunities to study complex organ interactions and investigate disease models at a systemic level.

The automation of Multi-Organ Chip Assays holds immense potential in biomedical research. In collaboration with the Technical University of Berlin, a robot for the automated handling of Multi-Organ Chips has been developed as part of a funding project by the German Federal Ministry of Education and Research (Grant No. FKZ031L0099). This poster aims to present the design and functionality of this new robotic system.

2 THE HUMIMIC AUTOLAB

The HUMIMIC AutoLab is a newly developed robot that can operate up to 24 multi-organ chips fully automatically. The system is compatible with the HUMIMIC Chip2, Chip3 and Chip4. The robot consists of several functional units: Platform (Fig. 1b & c), Handling, Cold Storage (Fig. 1 a bottom) and Microscope (Fig. 1 d).

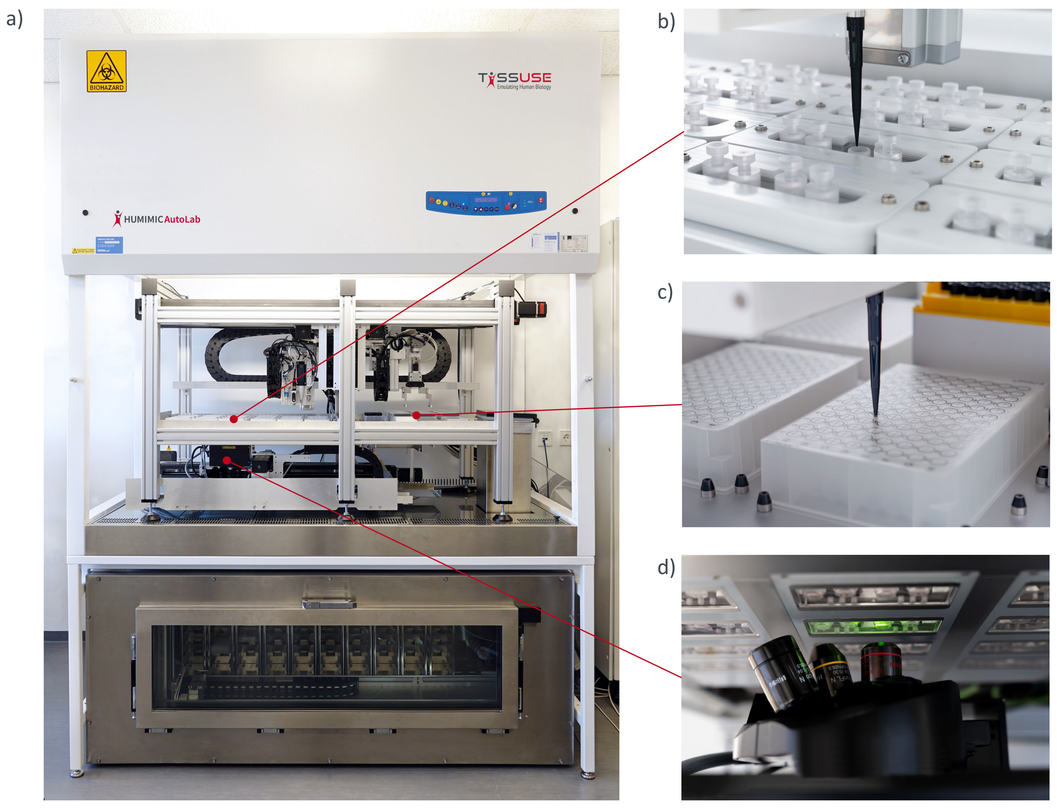

Fig. 1 HUMIMIC AutoLab a) Front View b) Chip-Platform c) Well-Plate-Platform d) Microscope

In the platform, up to 24 Multi-Organ-Chips can be cultured simultaneously. An incubation system is integrated in the platform, which regulates the temperature of the chips. The microfluidic pump of the chips is controlled by an integrated pump controller. This enables pulsatile and systemic media circulation inside the chips. The platform also has an area for storing multi-well plates and pipette tips. In this area, media and substances can be premixed. A heating plate allows the media to be preheated before being pipetted into the chips.

The handling system consists of two independent gantries on which several tools are mounted. Two integrated grippers are used to open the chip lids and to transport the multi-well plates. The dispenser can be used to exchange media, to apply substances and to take samples. This combination of chip platform with integrated incubator and chip handling ensures culture conditions are kept constant even during media changes.

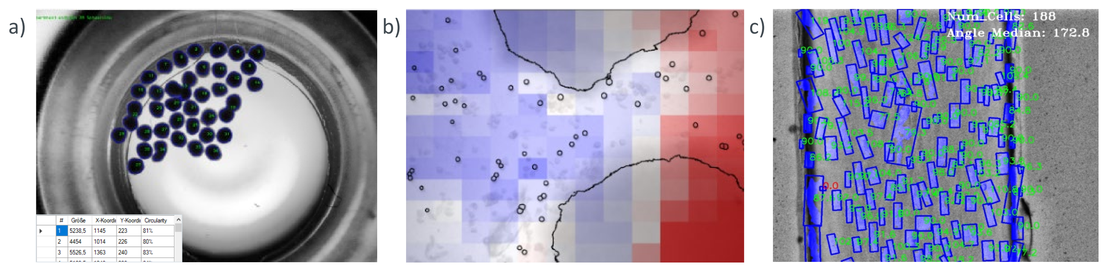

Fig. 2 Automated microscope analysis a) Spheroid Tracking b) pH heat map with spheroids c) AI based endothelial cell detection

The fresh media and substances and the samples can be stored in the cold storage at 4°C. The cold storage has its own handling system for multi-well plates and can automatically store or provision them.

To ensure sterility and operator protection, the robot is housed in a class II safety cabinet.

A movable brightfield and fluorescence microscope is installed under the chip platform (Fig. 1d) With the use of the microscope, the experiment can be easily observed over the entire experiment duration. Quality control or image-based analysis can be routinely performed. For example, the number, size and morphology of spheroids (Fig. 2a) or CO_2 or pH-value distributions can be measured (Fig. 2b). In addition, deep learning techniques can be used to detect cells (Fig. 2c) and perform virtual staining.

The robot is controlled by the specially developed HUMIMIC LabOS. The LabOS allows to plan and execute a complete test and to document all necessary process parameters and measurements.

3 EXEMPLARY BIOLOGICAL ASSAYS

Based on several experiments, it was shown that a variety of different multi-organ chip assays can be performed using the robot. The most important examples are listed in Table 1.

Tab. 1 Examples of assays that were successfully performed on the robot

Organs		Objective	Duration
	Intestine & Liver	Industry assay on liver toxicity	14 days
	Gastric Cancer & Liver	Biotransformation of chemotherapeutic prodrugs	5 days
	Bone marrow	Industry assay on hematotoxicity	35 days
	Neurospheres & Liver	Biotransformation of neurite growth inhibitors	7 days

The feasibility of assays with different types of organ models was demonstrated by the listed assays. Spheroid models, barrier models, scaffold based models and fluctuating cells could be successfully cultured.

The main advantage of automated assay execution is the possibility of particularly elaborate or complex assays. As an example, the results of an 24h PB/PK assay with sampling and dilution every 1-4h is shown in Fig. 3.

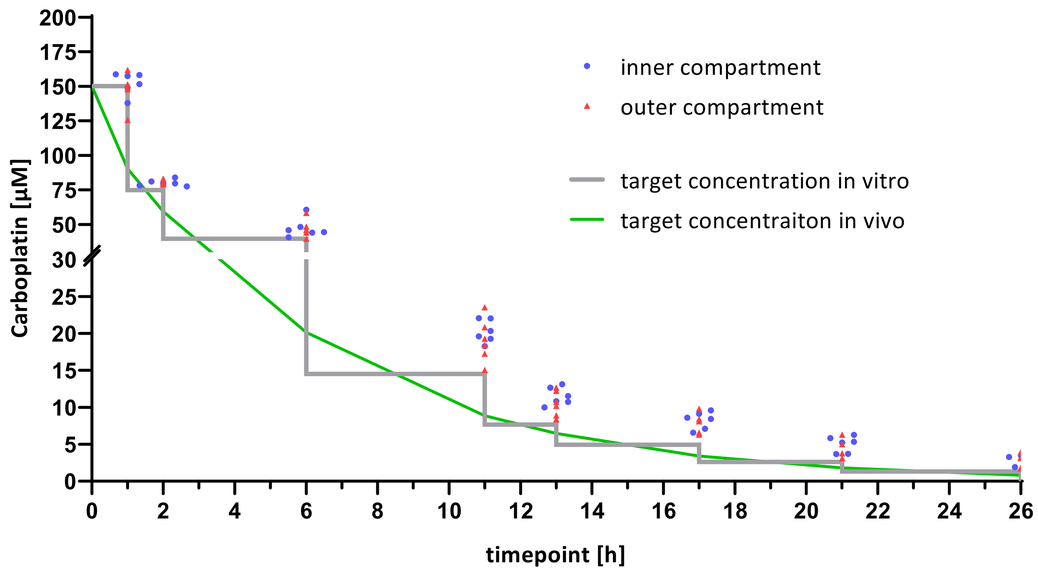

Fig. 3 Concentration of Carboplatin over time during assay execution

Using this exemplary assay, it was shown that the robot can replicate a PB/PK-like profile due to its high pipetting speed, which would not be possible in the conventional way without automation. This allows ADME-like profiles to be modeled in the chips.

4 CONCLUSION

Based on the HUMIMIC AutoLab, it can be shown that in the future MPS based assays can be performed with a higher throughput and with less manual effort. MPS-Assays performed with automated systems lead to a higher standardization and reproducibility, high-content data and the possibility for AI-based analysis. Together, these are important factors in advancing regulatory acceptance and industry adoption of MPS-based assays.

TissUse GmbH
Oudenarder Straße 16
13347 Berlin, Germany

www.tissuse.com
+49(0)-30-5130264-37
hendrik.erfurth@tissuse.com

Institute of Biotechnology
Berlin Institute of Technology
Medical Biotechnology

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