SUCCESS STORY

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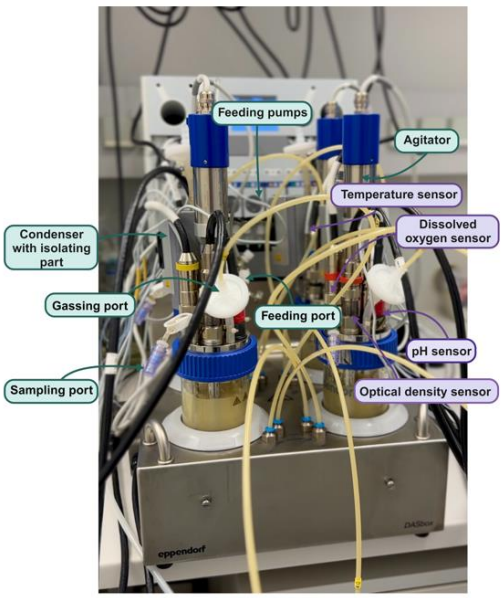

Experimental setup of the DASbox® Mini Bioreactor System (Eppendorf, Germany). Photo: © Kristina Žukauskaitė

"HOW DRUGS MODULATE BUGS" AND "HOW BUGS MODULATE DRUGS"

DEVELOPMENT OF A CUSTOMIZABLE *IN VITRO* MODEL OF THE HUMAN GUT MICROBIOME TO STUDY THE INTERACTION BETWEEN DRUGS, DISEASES, AND MICROBES.

The human gut microbiome is a fascinating and complex ecosystem that has a great impact on our overall health. Food, nutritional supplements, and drugs that are orally ingested at some stage encounter the intestinal microbiome. They interact with the gut microbiome which is capable of metabolizing the drugs and thereby determine the success or failure of the therapy.

Currently, the aspect of the gut microbiome's impact is completely neglected during drug development. Potential interactions are only investigated in post-marketing studies when they become clinically evident.

Thus, the goal of this project was to develop and validate a customizable *in vitro* model of the human gut microbiome to study "how drugs modulate bugs" and "how bugs modulate drugs". In other words – with this microbiome model, we aimed to aid researchers and the industry in understanding the interaction between diseases and the microbiome,

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develop microbiome-modulating therapies, and improve efficacy or reduce side effects of drug therapies. This platform has virtually no limitations to be adapted for all human disease entities and to be expanded to other microbiomes beyond the gut (*e.g.*, urinary, vaginal, skin, lung).

How does *the in vitro* model work?

The developed model is founded on the commercially available DASbox® mini bioreactor system (Eppendorf, Germany), which consists of four glass vessels equipped with a set of sensors. They serve the critical function of monitoring key bioprocess parameters, including temperature, optical density, pH, and the percentage of oxygen in the bioreactors. Bioprocesses are closely monitored in real-time using specialized software.

The bioreactors are inoculated with microbial communities directly extracted from stool samples of healthy volunteers or patients. Within the bioreactors, the extracted microbiomes are cultivated for several days, and treated with a wide array of drugs or other substances of interest. Samples can be taken at any time point, *e.g.,* every 24 hours, to keep track of the changes in the microbiome. These samples undergo a detailed genetic analysis, which allows us to understand the changes in the microbiome when brought in contact with the test substance.

Adaptability and sustainability are the key components

The developed *in vitro* model of the gut microbiome has several advantages over currently available models. Firstly, we only need a short period for the microbiome to stabilize and we use a validated system of stool collection, ensuring that the composition of the microbiome resembles the microbiome of the donor in the best possible way. Secondly, our model is highly adaptable and can be customized at different levels. We can mimic different conditions in the gut by changing the feeding modes and we can model diseases by using the microbiomes from diseased patients. Thirdly, the model is suitable for studying the influence of pharmaceutical or nutritional interventions on healthy and disease microbiomes, making it highly interesting for companies in the field. Lastly, the sustainability of our model is noteworthy as a majority of its components are reusable. The utilization of glass parts also facilitates its application in a project focused on understanding the effects of microplastics on the gut microbiome (COMET Module MicroONE, funded by the FFG).

International recognition of the *in vitro* model

The development and optimization of the *in vitro* model were presented at various national and international congresses in the past years. One of the recent achievements for the development of this model was *the Best Abstract Presentation Prize* during the Moderated Poster Session - *Gut Microbiome: From Mechanisms to Disease* at the UEG Week 2023, the premiere gastroenterology congress in the world, held in Copenhagen, Denmark from October 14-17, 2023.

The recognition and enthusiasm from both the scientific community and industry partners underscore the pressing demand for this *in vitro* model. With optimism, it is anticipated to enrich our understanding of the intricate relationships among drugs, diseases, and the microbiome. This, in turn, holds the potential to pave the way for the development of groundbreaking microbiome-modulating therapies, ultimately elevating the standard of care and treatment methodologies.

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