GUT-ON-A-CHIP: ACCURATE PREDICTION OF GUT INTERVENTIONS

TNO innovation for life

The Organ-on-a-Chip Early Research Program enables TNO to offer state-of-the-art technologies that help the pharmaceutical industry advance drug development. An accurate, viable alternative to animal testing, on-a-chip technologies model human tissue functioning and accelerate compound development and testing. The Intestinal Epithelial Barrier Chip (Gut-on-a-Chip, [GoaC]) platform allows a deeper understanding of human gut function in health and disease, including permeability, barrier function, mucus adherence, inflammation and host-microbiome interactions.

MODELLING FOR ACCURATE INTERVENTION

Gaining insight into how the human gut responds to interventions is challenging. The complex gut has a protective epithelial barrier consisting of multiple cell types with specialised functions in absorption, transport and metabolism, mucus production, and the secretion of hormones or cytokines in response to food or environmental factors. Each part of the gut also functions differently, and every person has a unique microbiome that plays an essential role in metabolism, absorption and uptake.

GoaC addresses these challenges. The model uses human (or human-like, porcine) intestinal tissue to mimic unique gut functionalities. This includes the different epithelial cell types, an active mucus layer and the lamina propria. GoaC enables accurate prediction of absorption and metabolism, including the effect of microbiome interactions on these processes in a high-throughput setting. This can accelerate drug development and enable the discovery of interventions to improve gut health and reduce dysbiosis.

DISEASE INDUCTION FOR TARGETED INVESTIGATION

GoaC can also aid in the investigation of gut-related conditions, like intestinal barrier dysfunction, inflammatory bowel disease and pathogen-induced pathologies. By introducing bacteria and modelling the mechanisms that trigger these disorders, GoaC enables testing of drug efficacy and helps take the first steps towards treating patients who do not respond to typical interventions, and the development of personalised medicines. For example, a current study is investigating the gut's role in the uptake of drugs in the brain, and how modifications may address non-responsiveness to the drug.

DEVELOPMENT THAT DIGS DEEPER

TNO's revolutionary InTESTine model already provides an effective, static, tissue-based model for testing compound absorption. Now, GoaC provides a microfluidic model in which processes can be studied for up to 48 hours, improving the ability to study the effect of low-permeability drugs, such as Biopharmaceutics Classification System (BCS) 3 and 4 compounds.

The increased viability in GoaC also enables disease induction for immune response or efficacy testing, testing the microbiota's response to different types of intervention and the possibility to run a variety of models using the same tissue. This can accelerate development at nearly every stage. It may also reduce the need for extensive in vivo studies. TNO also offers expertise and advice related to host/microbe interactions and unexpected metabolites that may affect outcomes.

Currently, TNO can run separate models to test both the anaerobic microbiome processes in the lumen, and the aerobic processes at the epithelial layer of the intestinal tract. However, we aim to combine these two models to form a more complete physiological representation of a compound's journey through the entire gut.

ORGANOIDS FOR BROADER APPLICATION

TNO is also investigating the use of tissue- or stem-cell-derived organoids that would be key to studying the responses, appropriate configurations and dosing for a variety of donors, including those from specific populations – whose microbiome may be vastly different from a typical donor microbiome – or in specific age groups, such as in children.

Organoid studies can also explore gut response in human tissue affected by specific conditions, including IBS, IBD, NASH/liver fibrosis and more.

Further study for future progress
Although GoaC technology is available today, TNO will continue to develop and advance the technology, together with interested partners. This includes further investigation of the combination of GoaC technology with other Organ-on-a-Chip innovations to accelerate preclinical investigation of the entire absorption, distribution, metabolism and excretion process. All to help users gain the best understanding of how interventions affect these processes in different populations or age groups.

TNO aims also to develop an even broader translational preclinical platform to improve prediction of compound behaviour. This includes the addition of physiologically based pharmacokinetics (PBPK) modelling to uncover the role of the microbiome in the onset of specific diseases and disorders, and how to intervene in the disease development process. Together with iScreen, InTESTine and GoaC, these PBPK studies will increase understanding of compound kinetics and the gut's role in health and disease processes.

ACCELERATION THROUGH COLLABORATION

GoaC is already available on a fee-for-service basis. But opportunities to bring GoaC technology to clients' in-house laboratories are also possible. TNO is interested in working with partners to further develop accurate gut models and increase the understanding of the gut's role in health and well-being.

TNO is not only seeking partners who are ready to utilise our existing on-a-chip technologies, but also those interested in further research and development.
In pre-competitive partnerships and private collaborations, we will continue the work started in the ERP, and together accelerate, streamline and improve drug and supplement development for effective treatment of disease.

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HEALTHY LIVING

TNO Biomedical Health Research focuses on applying (TNO) technologies that accelerate the drug development process. The Organ-on-a-Chip programme is an example of this targeted application.

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