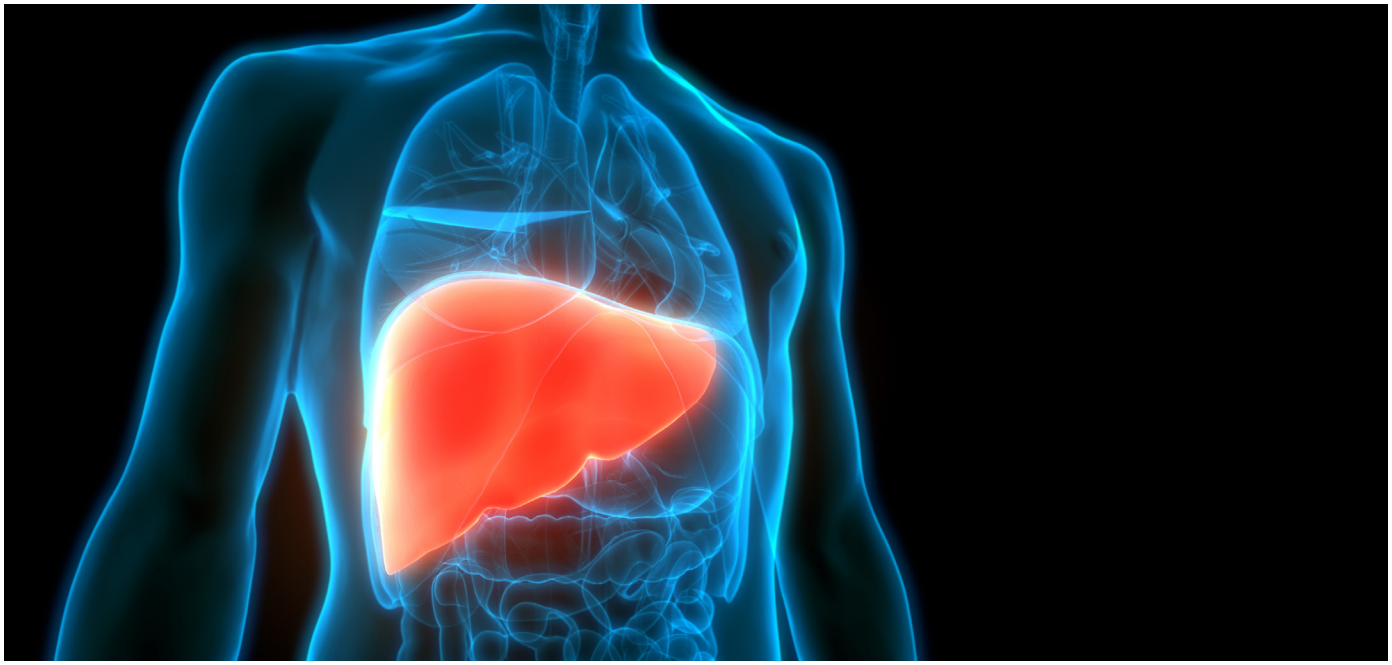
LIVER-ON-A-CHIP: UNDERSTANDING THE COMPLEXITY OF FIBROSIS



TNO innovation for life

The Organ-on-a-Chip Early Research Program (ERP) has enabled TNO to offer a number of state-of-the-art technologies to help pharmaceutical and biotech companies advance and accelerate drug development. An accurate, viable alternative to animal testing, on-a-chip technologies model the workings of human tissue and accelerate compound development and testing.

Liver-on-a-Chip (LoaC) – and subsequent spin-off-technologies – are ready for implementation and use. At the same time, TNO is eager to continue investigating and advancing these innovations for even higher accuracy and further application.

CUTTING-EDGE DISEASE INDUCTION AND EXPLORATION

LoaC offers two revolutionary advancements in the study of the liver's response to drug interventions. First, our multi-step disease induction process accurately mimics disease development in human subjects. Using non-alcoholic fatty liver disease (NAFLD) and, more specifically, non-alcoholic steatohepatitis (NASH) and fibrosis as target conditions, we work with primary liver cells: hepatocytes, Kupffer cells and hepatic stellate cells. In a phased induction process, we initiate lipotoxicity, inflammation, and the specific processes that lead to collagen accumulation and scar tissue development.

Second, LoaC offers advanced measurement techniques for treated liver cells. While many studies mostly rely on microscopic stain imaging to study cell responses after treatment, TNO also observes the entire process at a protein level.

We measure changes at each intermediate step, and monitor inflammation, liver functionality and fat accumulation.

This results in a deeper understanding of how the proposed drug works within the liver. It enables the flexibility to develop protein read-outs that look deeper into liver cell function and monitor secretion of disease markers linked to structural changes in the cells. This cellular-level insight offers deeper understanding of the true workings of a drug intervention and its interaction with the liver.

NASH, LIVER FIBROSIS AND BEYOND

NASH and liver fibrosis are progressive states of NAFLD. TNO has amassed extensive pre-clinical animal models and vast amounts of data about the underlying mechanisms and pathways of these conditions. NASH and liver fibrosis were therefore chosen as the focal point for the ERP. Today, TNO offers a proven, effective method with which to test the efficacy of a drug in the treatment of NASH and liver fibrosis.

TNO also gained extensive insight into other types of tissue fibrosis, and liver fibrosis that occurs in other conditions than NAFLD, making LoaC applicable in a wide range of drug trial scenarios.
If developers wish to understand the liver's response to a particular intervention, LoaC can be utilised. TNO is currently investigating how to apply the model to mimic human diversity, as in clinical trials.

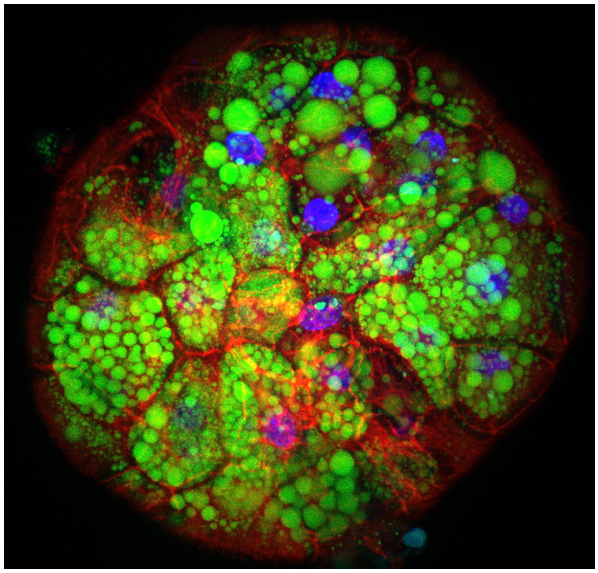
SPIN-OFF TECHNOLOGIES FOR BROADER APPLICATION

With our deeper understanding of liver fibrosis and its underlying disease processes, TNO is also modelling other types of fibrosis and testing the treatments that may combat them. Our extensive portfolio in this field is also available for use in the context of lung, skin and kidney fibrosis. Similar technologies can be applied, for example, to study additional effects of experimental cancer treatment, nutritional interventions on fibrosis and more.

TNO combines insight from LoaC with other cell and animal models to create a robust platform for fibrosis research. But perhaps most importantly, TNO offers its network of clinical research groups and our ability to interpret and analyse all data and results. We do not merely provide a spreadsheet of raw data at the conclusion of our studies. Rather, we offer deeper insight into what the data mean, and how they can be applied.

EXPANDING KNOWLEDGE FOR TRUE HUMAN MODELLING

By combining LoaC with other TNO innovations, companies gain deeper insight into the entire process that is set in motion with the ingestion of a compound. We are currently testing a microfluidic platform that introduces blood circulation and can carry a compound from our Gut-on-a-Chip platform to LoaC and other Organ-on-a-Chip technologies, such as kidney models. In this way, we aim to mimic the transport and pharmacokinetics of drugs through absorption, metabolism, and excretion, and gain an overarching view of a compound's interaction in a human subject.



A micrograph of a liver spheroid (mini liver), with a diameter of approximately 0.2mm. The spheroid is highly saturated with fats (green spheres). In this way, the efficacy of experimental medication against fatty liver can be studied.

TNO is also exploring population-specific or disease-specific models, using diseased cells or disease-mimicking cultures instead of healthy ones, which may result in faster drug development for at-risk patient groups or specific conditions, such as diabetes, dyslipidaemia and more. In addition, we are exploring the possibility of using human stem cell-derived liver cells instead of primary liver cells.

BEST UTILISATION FOR ACCELERATION

To facilitate continuous learning and further development, TNO is making the technology available on a fee-for-service basis. But opportunities to bring LoaC technology to clients' in-house laboratories are also possible. TNO is particularly interested in working with partners to utilise the extensive developments in liver disease research, and applying LoaC to achieve treatments that go beyond diet and lifestyle changes.

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 aim to continue the work started in the ERP, and utilise the most effective technology to 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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