

ERP ORGAN-FUNCTION ON A CHIP IN 2017

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Over the last 4 years, the ERP Organ function on-a-chip evolved from a seed ERP (2015) into a full ERP (in 2016) and is still further growing towards 2018. The program has three use cases: gut-, liver- and lung-function on a chip. In addition nano-detection of biochemical (proteins) was explored.

The results achieved were disseminated in oral presentations and posters at scientific events. Two scientific manuscripts are in preparation. A dissemination event 'Organ on a chip: from dream to implementation' for both internal and external stakeholders was organized in November 2017. The attendance of this event by colleagues,

collaborators from academia and industry was even better than at our event in 2016, indicating a growth of interest in TNO as an established partner in this area. In 2018, our Organ on a chip program will be presented at the Organ on a chip & Tissue on a chip conference in Rotterdam by no less than 2 oral presentations!



TOWARDS A PERSONALISED IN VITRO TEST SYSTEM FOR NASH INTERVENTIONS

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Non-Alcoholic SteatoHepatitis (NASH) is a form of fatty liver disease, which mainly affects people with diabetes and obesity and is seen as one of the major societal and economic problems in healthcare. NASH can further progress to life-threatening liver fibrosis, liver cirrhosis, and ultimately to liver cancer. Based on the continuing epidemic of obesity through much of the world, it is expected that the prevalence of NASH will increase further during the next decade. Since currently no accepted drug exist, there is an urgent need for

innovative treatments preventing NASH/ fibrosis development or cure of the disease. For this accepted biomarkers and translational test models are a prerequisite. In 2017, within the Early Research Program (ERP) "Liver function on a chip" of TNO, we have established an in vitro 3D coculture platform with human induced pluripotent

stem cell derived hepatocytes (HiPS-Heps) and human hepatic stellate cells (HSC). For a better prediction of efficacy of medicines in individual patients, in 2018 we will investigate whether a personalised stem cell based in vitro system could give relevant information on individual therapeutic interventions



IN-VITRO MONITORING ORGAN ON A CHIP SYSTEMS USING NANO MECHANICAL BEHAVIOR

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bioNOMI is the cross-over between two early research programs of TNO; Organ on a Chip and 3D nano manufacturing. ioNOMI is the cross-over between two early research programs of TNO; Organ on Chip and 3D nano manufacturing. We focus on the potential of monitoring organoid structures based on their nano-mechanical behavior. The first aim is to demonstrate the capability of this properties. The second aim is to develop and integrate dedicated nanomechanical instrumentation for invitro organ on a systems to characterize and monitor the cell functionality and viability. AFM (Atomic Force Microscopy) has proven to be a mature research tool for measuring

the nanomechanical properties of tissue and cells. Recent advances in AFM allow measuring the local stiffness of bio-logical samples. The local stiffness shows good correlation with the functional behavior of the cells. Monitoring of the local stiffness responses of cells when exposed to stimuli in-vitro could be a gamechanger for organ on chip concepts, where tissue or (stem)cell derived organoid structures in microfluidic systems are used for organ mimicking systems. The bioNOMI team is exploring the cause and quantifying the changes in nano-mechanical properties of tissue and cells when exposed to drugs. We focus on intestinal epithelial monolayers and extra cellular matrices. The monitored nano-

mechanical dose response curves through AFM will be compared by standard cell viability and permeability readout techniques.

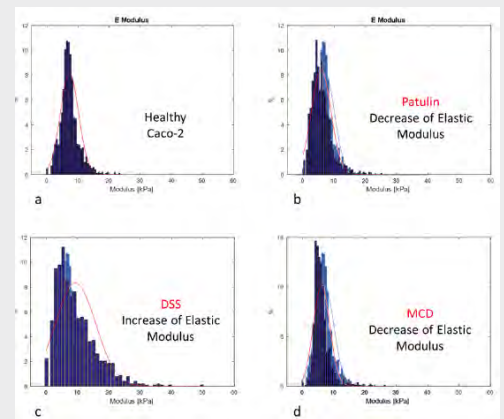


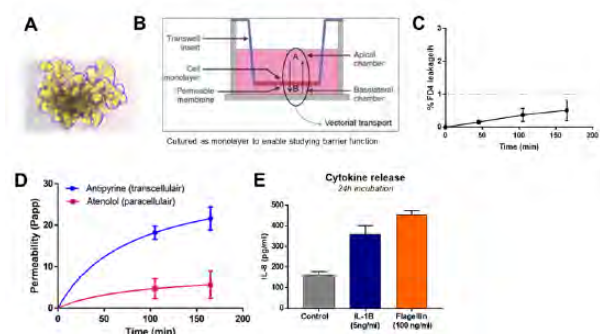
Figure: Histogram of the distribution of the local elasticity of caco-2 cells mimicking the intestine epithelial membrane. a: Reference of healthy cell, b: elasticity when exposed to Patulin (10 uM, 4hours), c: elasticity when exposed to DSS (10% w/v, 4hours) and d: elasticity when exposed to MCD (10 mM, 4 hours).

HUMAN INTESTINAL ORGANOIDS CULTURED AS PHYSIOLOGICAL BARRIER MODEL

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Human intestinal LGR5+ stem cell derived organoids possess many features of the human intestinal tract, including self-renewal and expression of the various cell types of the intestinal epithelium (i.e. enterocytes, Goblet cells, endocrine cells and Paneth cells).

Standard 3D culture in Matrigel results in a closed organoid structure with an internal luminal volume (Fig a), whereas culturing the intestinal organoids as an attached monolayer on a permeable membrane provides better opportunities to study barrier functionalities. By culturing human intestinal stem cell derived organoids as a barrier model integrity (Fig b-c; Transwell set-up and vectorial leakage of FD4), transport properties (Fig d; paracellular transport of atenolol and transcellular transport of atenolol) and pro-inflammatory epithelial responses (Fig e). Future opportunities include studying interindividual and populational variation in absorption and inflammatory responses, also by co-culturing with human intestinal (personalised) microbiota in a microfluidic device.



NEWS FROM BUSINESS DEVELOPMENT

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TNO's approach in organ-on-a-chip is now seen by technology providers as well as potential end-users of this technology; the pharma and food industry. TNO organized a Symposium "Organ on a Chip: from dream to implementation", 30 Nov 2017, where more than 60 representatives of industry and academia were present and shared their view on how to implement the promising technology of organ on a chip into practice. Lianne Stevens presented TNO's gut-on-a-chip at the MicroNano-Conference in Amsterdam; a joint presentation with the WUR and Micronit. Via Social Media (TNOtime, LinkedIn) we published about a planned Public-Private Partnership Organ on a Chip as well as on how Organ-on-a-chip technology will make drug development more efficient.

Ongoing activities:

- *We are exploring the possibilities of using the gut on a chip model for application in testing water quality as a follow up on Evita's talk at the "Lab Analyse 2017" in Rotterdam on the 19th of September last year.
- *Via hDMT we have received a request for validation of an organ-on-a-chip device.

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