ERP Organ-function on a chip in 2016

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Over the last 2 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 2017. The program has three use cases: gut-, liver- and lung-function on a chip. In addition nano-detection of biochemical (proteins) was explored.

2017

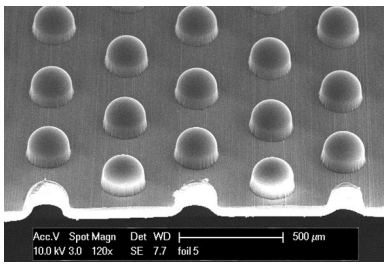
Happy New Year

White paper 'Biology, technology and applications: the 3Dimensions of Organ on a chip' describing our strategy and views in this area was published on October 4th, 2016 and can be downloaded here: https://time.tno.nl/nl/artikelen/organ-on-a-chip-versnelling-in-de-medicijnontwikkeling/

In 2016, TNO became a member of hDMT, *the* national collaboration of institutes, academic groups and companies focusing on state-of-the-art technologies around organ on-a-chip. New collaborations with academia were setup, such as University of Amsterdam on organoids, LACDR on readout technologies. Consortia with small industrial partners Takara and Invitrocue have led to very active collaboration in the development of advanced in-vitro liver models. Negotiations with large industrial partners are also in place.

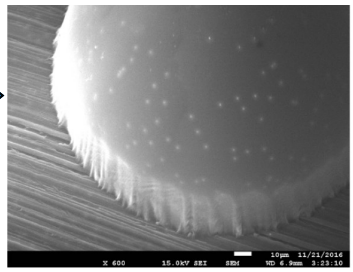
Coupled to the publication of the white paper, a dissemination event for both internal and external stakeholders was organized on 31st of October. The attendance of this event by colleagues, collaborators from academia and industry extended our expectations and showed recognition of TNO as a partner in Organ on a Chip technology, biology knowledge and applications.

Fabrication of a 3D porous gut villi scaffold array



Thermoformed scaffolds in polycarbonate

Ion track etched pores in thermoformed polycarbonate scaffolds



To approach the human intestine epithelium architecture as close as possible, we developed a fabrication process that makes porous 3D villi scaffolds[1]. In a 50 µm thick polycarbonate film, latent tracks are made with high energy ions that are shot through the film and leave tracks of defects in the polymer. These films are then thermally formed in a hole patterned mold with a hot embosser. The polycarbonate is heated above its glass transition temperature and mechanically pushed into the mold. This gives an array of hollow scaffolds, which have currently a diameter of 200 µm and are 200 µm tall (photo 1). The perforations in the polycarbonate film are then made by wet chemical etching of the latent ion tracks that were irradiated in the first step. Here, they have a diameter of about 500 nm and a density of 10^4 pores per mm^2 (photo 2). The scaffolds are inert, biocompatible and will be used to grow intestinal stem-cells on, and to determine the effect of the villi structured scaffold on functionality of the intestinal cells and epithelium. The porosity of the scaffolds enables analysis of transport of drugs, nutrients and metabolites across the intestinal epithelium. Currently we are focusing on improving the aspect ratio of the villi in order to more closely mimic the human gut epithelium.

[1] Truckenmüller *et al.* Flexible fluidic microchips based on thermoformed and locally modified thin polymer films. Lab Chip, 2008 (8)1570-1579

Extended viability of human intestinal tissue in InTESTine

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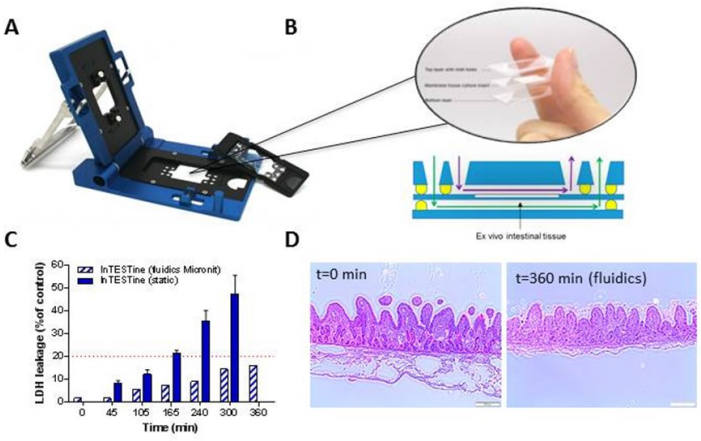

Extended viability of human intestinal tissue in InTESTine by applying luminal and basolateral microfluidic flow. The InTESTine™ model is a platform that applies ex vivo (human) intestinal tissue and has been developed to study processes in the gastrointestinal tract in a physiological 2-compartmental in vitro setting. Under static conditions the intestinal tissue is viable for approximately 3-4 hours after incubation. Here we show that the viability of the tissue is significantly increased by applying luminal and basolateral microfluidic flow using the Micronit chip (**A** and **B**), demonstrated by decreased LDH leakage (marker for cell death) of the epithelium (**C**) and histological examination of the tissue after 6 hours of incubation (**D**). We will further implement this set-up in studying intestinal absorption of pharmaceutical and nutritional compounds over longer time period and studying host-microbe interactions in co-culture with immune cells.

3D liver model for NASH/fibrosis

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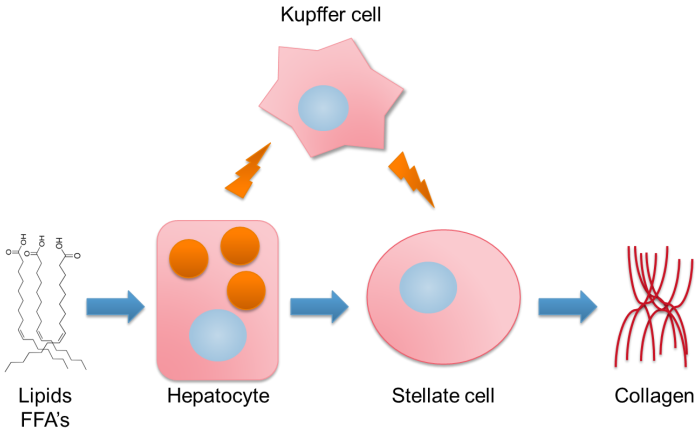
In a recent "call to action" news item in Nature last November it was mentioned that from 2020 it is expected that NASH/fibrosis will be the main cause for liver transplantation. Currently no therapeutic drugs for NASH/fibrosis are available. This is partly due to the fact that we have a lack of knowledge regarding disease mechanisms, availability of biomarkers and predictive models to screen new drug candidates.
For the latter reason a 3D in vitro model is being developed using human hepatocytes and stellate cells. In this system hepatocytes are activated by induction of steatosis using fatty acids in the culture medium (mimicking the dietary high fat intake in patients), and as a read out parameter collagen is used (the main marker of fibrosis). To mimic the human situation as much as possible, in 2017 to the system also an inflammatory component will be introduced, the Kupfer cell (liver specific macrophage-like cells).



http://www.nature.com/nrgastro/journal/v13/n12/full/nrgastro.2016.178.html

Organ function on-a-chip seen from business development perspective

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It is great to see how technology providers promote that their technologies are useful in OoaC applications. Especially (optical) read-out technologies and microfluidic systems focus on this. At partnering events as BioFit in Lille and BioEurope in Köln, we spoke with many of them most of them willing to further explore possibilities of collaboration in TNO's ERP. It also becomes more and more clear that our decision to focus on organ **function**-on-a-chip applications perfectly fits in the thoughts of the big pharma companies with whom we have discussed our program. Next year we will further explore the business opportunities with OoaC within a business innovation boot camp.

For more information about the ERP please contact:

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