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**Title: Progressing a powerful human relevant in *vitro* model of non-alcoholic steatohepatitis (NASH) towards disease modelling and therapeutic development applications**

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide and is characterized by excessive accumulation of lipids in the liver (steatosis). In the presence of hepatic inflammation, steatosis can develop into more severe non-alcoholic steatohepatitis or NASH, that in turn can progress to life-threatening diseases such as liver failure, cirrhosis and cancer. NASH is seen as 'a global epidemic' and is currently a leading cause of liver transplantations. Recent studies indicate that certain genetic polymorphisms are strongly associated with increased susceptibility to NAFLD and progression of the disease. Improving the understanding of the genetic basis of human NASH will allow to facilitate risk stratification of affected patients, permit personalized treatment, and accelerate the development of new therapeutic strategies. The host laboratory has developed a NASH model based on proprietary hepatic differentiation of human postnatal skin stem cell, hSKP-HPC. To date, the hSKP-HPC NASH model has been established as a fit-for-purpose and human-relevant *in vitro* NASH model, which allows the investigation of the molecular mechanisms of potential anti-NASH compounds. A number of promising research questions remain open for investigation and seek to build on this established model.

1) To investigate genetic backgrounds in relation to predisposition towards NASH progression. The hSKP-HPC NASH model is based on donor skin samples and is well suited to the study of genetic polymorphisms and genetic profiles that affect the development of NASH and sensitivity to drug candidates. Potential projects can build on existing knowledge with respect to the effect of PNPLA3 genetic polymorphism on the development and treatment of NASH. However broader population predisposition questions remain.

2) The current NASH model is validated in a 2D monoculture format. While fit for specific research investigations, the addition of physiologically relevant complexity may further enhance the modelling of NASH for therapeutic application including drug discovery. The development of the hSKP-HPC NASH model towards high throughput compatible formats, or towards 3D spheroid/co-culture formats is desirable for drug screening applications.

**Supervisor:** tamara.vanhaecke@vub.be

**Research Group:** https://ivtd.research.vub.be/en/liver-toxicology-disease-models-therapeutics

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