Maastricht University

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MAASTRICHT CENTRE FOR SYSTEMS BIOLOGY

Describing Critical Transitions in Non-Alcoholic Fatty Liver Disease

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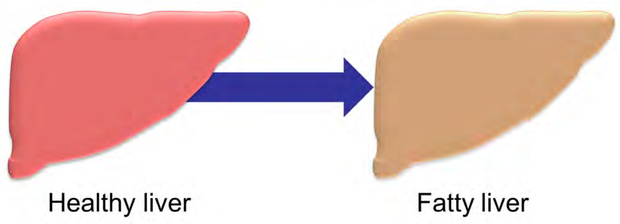
Finding a mechanism for Non-Alcoholic Fatty Liver Disease (NAFLD) development

Imaging *in vitro* disease development to select time points for further analysis

Describing the molecular mechanisms underlying critical transitions using RNA-Seq

BACKGROUND

Non-Alcoholic Fatty Liver Disease

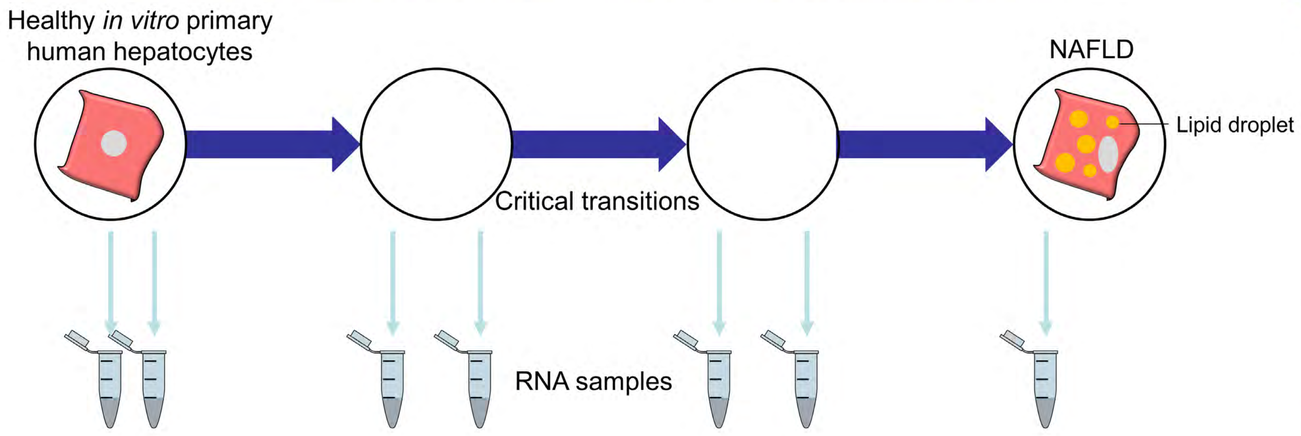


- Prevalent in 24% of worldwide population
- Ranges from simple steatosis to liver fibrosis, cirrhosis and liver failure
- Related to obesity and diabetes
- Important reason for drug withdrawal from the market
- Reversible in the first stages, but therapies are lacking

APPROACH

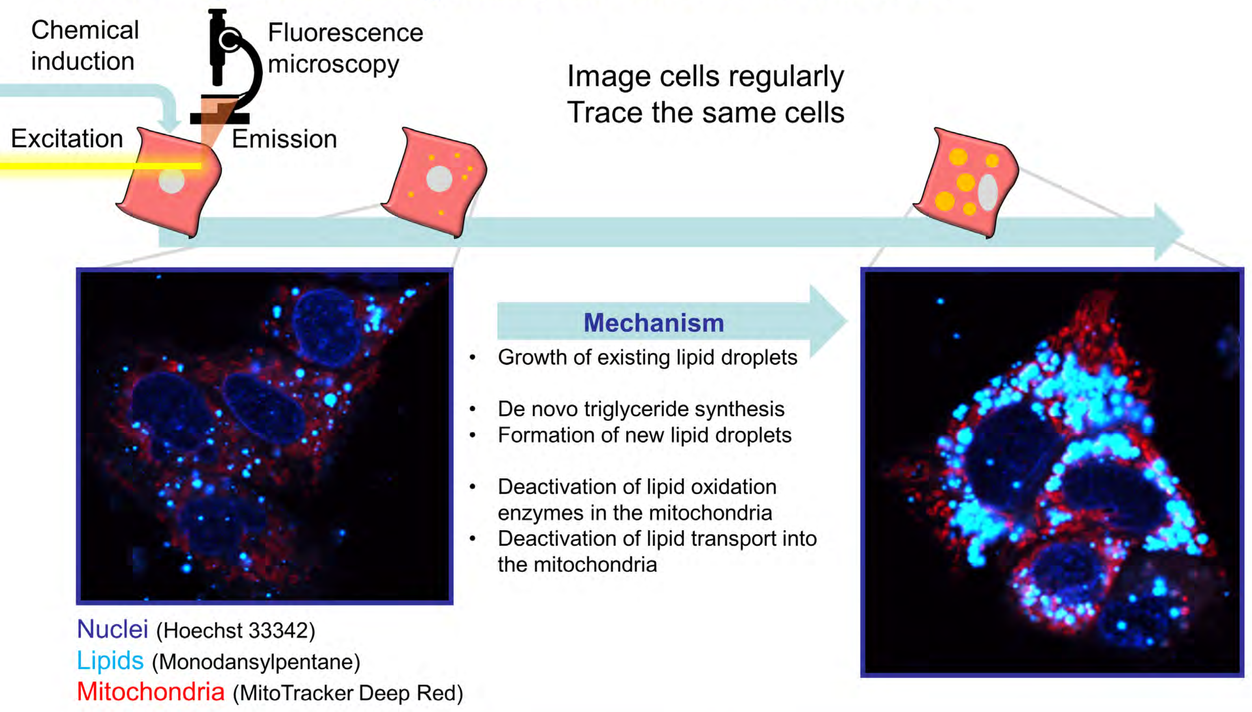
What molecular changes are required for a healthy liver to develop into a fatty liver?

Consider disease development as a process of different phases



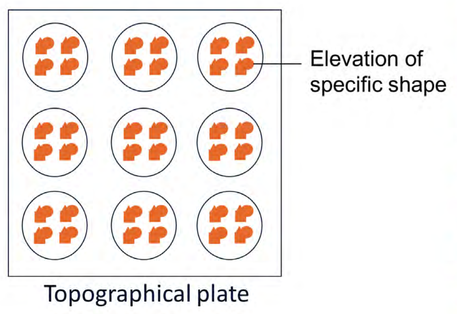
DATA ACQUISITION

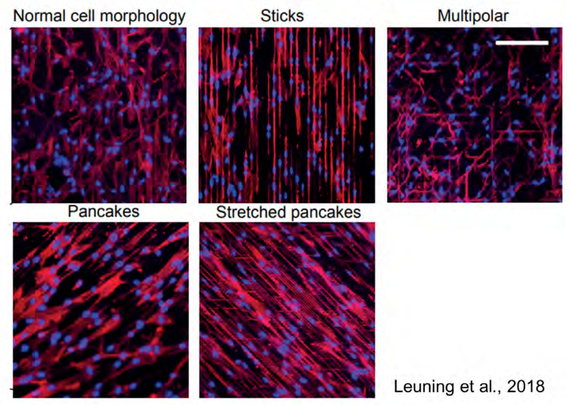
Track single cells using multiplex live cell fluorescence



CELL CULTIVATION METHOD

Extended cultivation is required to find the long-term acting mechanism of NAFLD





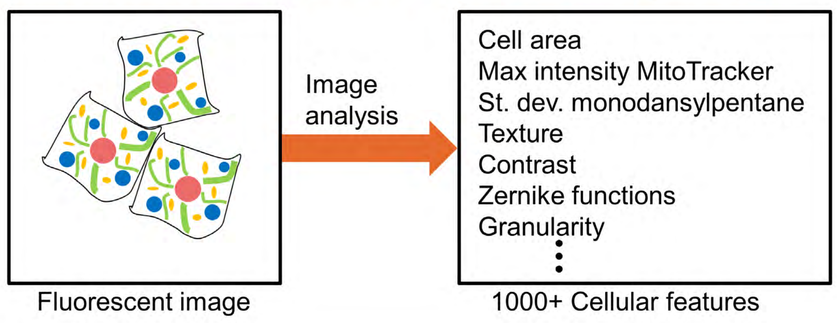
Topographical plates contain cell-specific elevations
The cells change shape due to these elevations

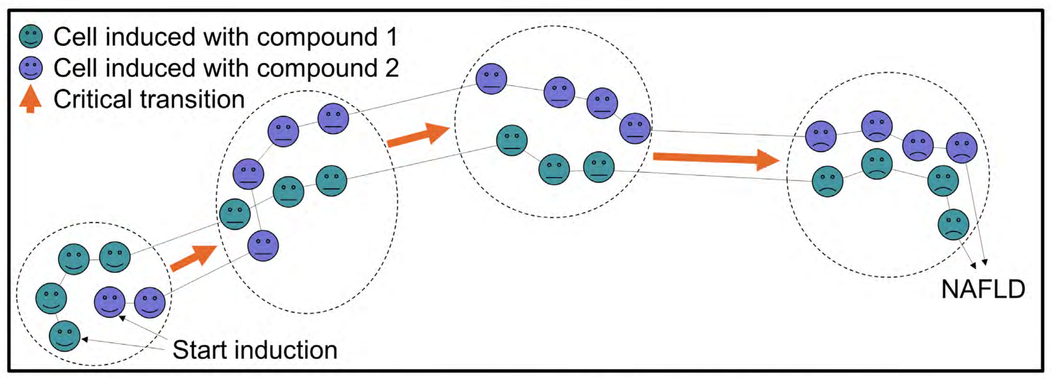
On TopoWellPlates, primary human hepatocytes extend their lifetime from one week to 3+ weeks

Cultivation over a longer period allows for low-dose exposure experiments, activating long-term processes

DATA ANALYSIS

Select critical transitions based on morphology





dimensional space describing morphology (depicted in 2D)

Image many cells per induction

Cluster cells to find phases and critical transitions

RNA-Seq analysis from well-determined time points can reveal molecular effects during critical transitions

Find which molecular processes have a differential activity during the critical transitions

Which therapies can be development to avoid these transitions?

Reference:
Leuning, Daniëlle G., Nick R. M. Beijer, Nadia A. du Fossé, Steven Vermeulen, Ellen Lievers, Cees van Kooten, Ton J. Rabelink, and Jan de Boer. "The Cytokine Secretion Profile of Mesenchymal Stromal Cells Is Determined by Surface Structure of the Microenvironment." *Scientific Reports* 8, no. 1 (December 2018): 7716.

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