Method: Various endocrine FGF analogs have been profiled using 2D and 3D ex vivo human liver and adipose models, under conditions which mimic fasted and fed states by varying media glucose, insulin, and glucagon concentrations. The biological activity of different endocrine FGF analogs was characterized using transcriptomics and candidate protein expression analysis. We used a functional coculture 3D liver model to understand direct hepatic effects of FGF21 activity on steatotic, inflammatory, and fibrotic readouts.

Results: FGF21 and AKR-001 suppress TGF-b-induced fibrogenic gene expression in a human hepatic stellate cell line. In 3D liver microtissues consisting of primary hepatocytes and various nonparenchymal cells, FGF21 and AKR-001, but not FGF19, suppress DNL and triglyceride accumulation. In this 3D human liver cell co-culture model, FGF21 and AKR-001 also suppress inflammatory activation by LPS to a greater extent than FGF19, while also suppressing fibrogenesis. Unbiased transcriptome profiling of these 3D liver microtissues, and of human adipocytes differentiated in vitro, demonstrated that AKR-001 recapitulates FGF21's regulation of key metabolic pathways supporting its potential for use as a therapeutic in NASH patients.

Conclusion: FGF21 and AKR-001 exert direct actions in human adipocytes, hepatocytes, and liver non-parenchymal cells consistent with suppression of steatosis, inflammatory activation, and fibrogenesis. These actions appear to be mediated by FGF21's canonical receptors FGRF1c/2c/3c, since agonism of FGFR4 does not seem to contribute additional efficacy in these tissues. This supports the appealing pharmacology of AKR-001, which has been reported to have favorable effects on markers of glycemic control and lipid metabolism and to be well-tolerated in humans.

SAT017
Propionate intervention attenuates NASH while negatively affecting cognition

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Background and Aims: There is an increasing interest to elucidate the health effects of short-chain fatty acids (SCFAs) on metabolism, obesity, and brain function. Obesity is often associated with the development of non-alcoholic steatohepatitis (NASH) and cognitive impairment. We herein investigated potential health effects of the SCFA propionic acid (PA) on NASH development and brain function including cognition and behaviour readouts.

Method: During 17 weeks of run-in, LDR−/−/−Leiden mice received either high-fat diet (HFD) to establish obesity or chow as control. Obese mice were matched into groups (n = 15/group) and treated with propionic acid (PA+HFD), or a reference fatty acid (caproic acid; CA+HFD), or HFD without supplements (HFD). Cognitive and behavioral effects, as well as metabolic and inflammatory risk factors, were assessed prior to and after 12 weeks of treatment. At endpoint, liver, adipose and brain tissue were histologically and biochemically analyzed.

Results: PA, but not reference CA, reduced body weight and this effect was independent of food intake. PA also reduced fasting insulin levels and plasma cholesterol levels relative to the start of intervention. In addition, PA reduced total and subcutaneous fat mass, but did not affect VAT inflammation. Histopathological analysis of the liver demonstrated that PA reduced macrovesicular steatosis, hypertrophy and inflammation. Consistent herewith, PA reduced the inflammatory marker serum amyloid A and lowered the hepatic collagen content. PA treatment did not affect behavior in the open field test but mice showed impaired spatial memory, i.e. the latency to find the platform in the Morris water maze was increased. In line with these findings, we observed alterations in tissue integrity and gene expression in the hippocampus, a brain region important in memory consolidation. The reference fatty acid CA exerted no effects on the above readouts.

Conclusion: PA treatment during obesity had favorable metabolic effects, reducing body weight gain, improving metabolic risk factors and reducing the development of NASH and associated fibrosis. Simultaneously, PA had detrimental effects on the brain, reducing synaptogenesis signaling and affecting spatial memory. Altogether, the results from this study indicate that while the beneficial metabolic effects of PA treatment seem promising, it can also have negative effects on brain functioning and cognition, and should therefore be treated with caution.

SAT018
A shortcut from non-alcoholic fatty liver disease to HCC: c-Myc, a promising theranostic target

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Background and Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) has rapidly risen as one of the leading etiologies for HCC and represents a large societal and health problem. Many factors are responsible for the high risk of NAFLD-related HCC development. Lately, oncogenes have been suggested to be determinant; however, their role still remains unknown.

Here we analysed the impact of the proto-oncogene c-Myc in the development of murine NAFLD and NAFLD-associated HCC.

Method: Transgenic mice bearing overexpression of c-Myc in hepatocytes (alb-MYC+) were studied at baseline conditions (36 weeks, 1 year) as well as after application of Western diet (WD).

Fig.1 Proto-oncogene c-Myc in the development of murine NAFLD and NAFLD-associated HCC. (A-C) alb-MYC+ mice exhibited profound spontaneous changes at 36 weeks: (A) hypertrophy of eWAT cells; (B) macrovesicular steatosis and (C) significant collagen accumulation in liver; (B) Multiple tumour nodules in alb-MYC+ mice livers after 10 months of WD feeding.

Results: Mild obesity (Fig.1A), spontaneous hyperlipidaemia, glucose intolerance and insulin resistance were characteristic of 36 week-old...
alb-MYC<sup>tg</sup>. Moreover, alb-MYC<sup>tg</sup> mice exhibited profound hepatic changes at baseline, characterized by significant macrovesicular steatosis (Fig.1B), hepatocellular ballooning and increased triglyceride content, compared to WT littermates. Liver injury and inflammation associated with elevated serum transaminases, marked infiltration of CD45 and F4/80 positive cells, increased caspase-3 activity, up-regulation of the ER-stress response and ROS production, significant collagen accumulation (Fig.1C) and compensatory proliferation were apparent in transgenic animals at 36 weeks. In agreement with earlier studies, 20% of alb-MYC<sup>tg</sup> mice developed HCC at 1 year of age. Importantly, the application of WD exacerbated metabolic abnormalities, steatohepatitis, fibrogenesis and substantially enhanced the tumor incidence and tumor growth resulting in the formation of multiple tumour nodules after only 10 months of feeding in 100% of alb-MYC<sup>tg</sup> mice (Fig.1D).

**Conclusion:** In the present study, we identified a novel function of c-MYC for the progression from NAFLD to HCC. It can be speculated that targeting of c-MYC in patients with NAFLD could reduce the risk of HCC development. However, further analysis is needed to uncover the underlying mechanisms and risk factors.

**SAT019**

Sex differences of adipose tissue dynamic changes in NASH progression of morbid obese patients: a preliminary study

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**Figure:** (abstract: SAT019)