designed to convert the pathogenic methionine codon (ATG) to a valine codon (GTG), resulting in expression of PNPLA3 148 V wild-type-like variant that functionally mimics native PNPLA3 148I. Unlike gene silencing approaches, RNA editing preserves PNPLA3 protein expression while correcting its pathogenic function, potentially offering superior therapeutic benefit. This study evaluated Axiomer-mediated correction of *PNPLA3* I148M and its impact on hepatic lipid accumulation in a humanized mouse model.
Method: A lead N-Acetylgalactosamine (GalNAc)-conjugated EON was evaluated in FRG mice engrafted with homozygous PNPLA3 I148M PHH. Mice were fed a Western diet 1 month prior to and during treatment. Animals (n = 6 per group) received subcutaneous EON dosing (20 mg/kg, 14 doses over 28 days). Liver tissue was analyzed for RNA editing, steatosis, and macrovesicular lipid droplets (MLD) burden. A clinical-stage PNPLA3 antisense oligonucleotide (ASO) was included as a comparator (0,7 mg/kg, 14 doses over 28 days).
Results: In PHH, the lead 3′ GalNac-conjugated EON induced a dose-dependent correction of *PNPLA3* I148M, achieving 50% RNA editing. In humanized FRG mice, EON treatment resulted in 22% hepatic RNA editing of *PNPLA3* I148M and a marked reduction in MLD, exceeding the effect observed with the clinical-stage PNPLA3 ASO.
Conclusion: Axiomer RNA editing effectively converts the pathogenic *PNPLA3* I148M allele toward a wildtype-like variant, restoring lipid regulatory function and markedly reducing MLD in humanized *in vivo* systems. These findings support further development of *PNPLA3*-targeting EONs as a therapeutic strategy for MASLD/MASH.

SAT-150
Pharmacological inhibition of transforming growth factor-beta-activated kinase 1 (TAK1) in a murine model of metabolic dysfunction-associated steatotic liver disease
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Background and aims: Transforming growth factor-beta-activated kinase 1 (TAK1) is an essential signalling hub regulating hepatic cell death, inflammation, and fibrogenesis via nuclear factor-kappaB and mitogen-activated protein kinases in metabolic dysfunction-associated steatotic liver disease (MASLD). Recently, specific TAK1 inhibitors had been developed and demonstrated efficacy in preclinical models of arthritis, systemic sclerosis, and lung fibrosis. However, we have previously reported severe hepatitis, focal necrosis, and premature death in mice with genetic deletion of TAK1 in liver parenchymal cells. We therefore sought to explore the safety and efficacy of pharmacological TAK1 inhibition in a murine model of MASLD.
Method: Six-week-old male C57BL/6J mice were fed a diet enriched in fat, refined carbohydrates, and cholesterol (Western Diet) for 20 weeks to recapitulate human MASLD. 30 days prior to necropsy, the TAK1 inhibitor HS-276 (25 mg/kg, n = 14) or vehicle (sterile saline, n = 14) were administered intraperitoneally once daily. Serum samples were collected before the start of HS-276 or vehicle and during necropsy two hours after the final injection.
Results: HS-276 treatment led to weight loss during the treatment period (p = 0.034 for interaction). At 30 days, body weight was 5.1% lower in the treatment group (95% confidence interval [CI] 2.0 to –12.3, p = 0.154). No clinical or behavioural changes were observed. HS-276 was detected at an average concentration of 22.5 pmol/mg in liver tissue (95% CI 18.1 to 26.9 pmol/mg) by liquid chromatography-mass spectrometry, confirming hepatic exposition towards the compound. Serum alanine aminotransferase (–42.1 U/l, 95% CI –4.8 to –79.5, p = 0.029) and glutamate dehydrogenase (-45.8 U/l, 95% CI –23.6 to –68.0, p < 0.001) levels decreased comparing HS-276- and vehicle-treated mice before and after treatment. Additionally, perigonadal (epididymal) white adipose tissue was less abundant in mice treated with HS-276 (-0.9 percentage points, 95% CI –0.3 to –1.5, p = 0.005). Weight and histologic appearance of the heart, kidneys, and spleen were unchanged by HS-276 treatment.
Conclusion: TAK1 inhibition by HS-276 was well tolerated in a murine model of MASLD, contrasting our previous findings from genetic models. Our data suggest an attenuation of liver injury and favourable metabolic effects, highlighting the potential of TAK1 inhibition for the treatment of MASLD.

SAT-151-YI
Intramuscular fat in steatotic liver disease is linked to muscle function impairment, insulin resistance and specific inflammatory pathways in the liver
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Background and aims: A muscle-liver axis, described on the basis of muscle density, appears to operate in cases of metabolic steatohepatitis. Here, we want to investigate the muscle phenotype (surface and intramuscular fat) by magnetic resonance imaging (MRI) in relation to muscle function and liver disease.
Method: Patients with SLD with an increased liver stiffness on transient elastography (≥7.8 kPa) were prospectively recruited. They underwent liver/skeletal muscles MRI and liver biopsy on the same day. Controls underwent the same MRI protocol. Mean liver and muscles (abdominal and paravertebral muscles) fat were measured by proton density fat fraction (PDFF). Muscle mass was assessed at the third lumbar vertebrae using the skeletal muscle index (SMI). Intramyocellular (IMCL) and extramyocellular lipids (EMCL) of right soleus and tibialis anterior were quantified using proton magnetic resonance spectroscopy. Muscle strength was assessed by the Liver Frailty Index (LFI). Liver biopsies were used for both histology and bulk mRNA sequencing.
Results: Patients with SLD (n = 92, 54 MASLD, 38 ALD) and controls (n = 10) were comparable for age. Ballooning was identified in 50% and fibrosis was graded as ≥ 2 in 63% of the SLD cohort. Median liver PDFF (19% vs. 3%, p < 0.001), mean muscle PDFF (22% vs. 9%, p < 0.001) and mean SMI (54 cm^2/m^2 vs. 36 cm^2/m^2, p < 0.001) were higher in the SLD group compared to controls. Despite significant metabolic differences such as BMI or presence of type 2 diabetes, muscle PDFF, LFI and SMI were similar in MASLD and ALD groups. Participants with

SLD and high muscle PDFF (>30%) showed decreased muscle strength compared to participants with low PDFF (<30%) but comparable age and BMI in both sexes. No correlation was found however between EMCL, IMCL and the liver frailty index while insulin resistance specifically correlated to soleus EMCL in MASLD ($r = 0.72$, $p = 0.005$) but not in ALD. Finally, transcriptomic analysis reveals that muscle fat is associated with an upregulation of hepatic inflammatory pathways and a downregulation of bile acid synthesis and fatty acid degradation.
Conclusion: Muscle fat assessed by MRI is increased in the presence of SLD and is associated with decreased muscle strength. EMCL are linked to insulin resistance in MASLD. Mechanistically, this disruption of the muscle-liver axis is associated with hepatic transcriptional changes including upregulated inflammatory pathways and downregulated bile acid biosynthesis and fatty acid degradation.

SAT-152
Dissecting paraoxonase 1 genotype combinations modulating paraoxonase activity and risk of dysglycemia and liver fibrosis
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Background and aims: Metabolic disorders such as dyslipidemia, metabolic dysfunction–associated steatotic liver disease (MASLD), and diabetes are promoted by chronic pro-inflammatory and pro-oxidative states. Paraoxonase 1 (PON1), a liver-derived enzyme associated with high-density lipoproteins (HDL), plays an important antioxidant role by hydrolyzing oxidized lipids and protecting against oxidative stress–induced damage. Genetic variation in PON1, particularly in promoter and coding regions, modulates enzyme expression and activity, thereby influencing susceptibility to metabolic and cardiovascular diseases. This study investigated the genetic determinants of serum paraoxonase (PONase) activity and their relationship with dysmetabolic phenotypes.
Method: A genome-wide association study was conducted in 922 Portuguese individuals from the PREVADIAB2 cohort. Genetic variants and haplotypes related to PONase activity were analyzed, and associations with dysglycemia and liver fibrosis were evaluated in individuals aged over 55 years.
Results: We identified two key PON1 variants as determinants of PONase activity: rs2057681 (in strong linkage disequilibrium with the non-synonymous Q192R variant) and rs854572 (located in the promoter region). Analysis of rs854572–rs2057681 haplotypes revealed that specific combinations differentially modulate PONase activity and confer risk or protection for dysglycemia and liver fibrosis, depending on the rs2057681 genotype context. Notably, although PONase activity was strongly associated with PON1 variants, it did not directly correlate with dysmetabolic phenotypes, suggesting that genetic context and haplotype structure, rather than enzyme activity alone, shape disease susceptibility.
Conclusion: These findings highlight the complex genetic architecture of PON1 and its role in metabolic disease risk, supporting the use of PON1 genetic information to uncover predisposition to dysmetabolic conditions. Our results provide insights into the interplay between PON1 genetics, enzyme function, and dysmetabolism, with implications for risk stratification in metabolic liver disease.

SAT-153
Combined exposure to alcohol and the PNPLA3 I148M variant drives hepatocytes toward pro-inflammatory, oncogenic, and profibrotic states in a western diet model
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Background and aims: The genetic variant PNPLA3 I148M and alcohol consumption are distinct risk factors for the progression of steatotic liver disease, yet the mechanisms by which they interact to accelerate pathology remain incompletely defined. This study aimed to resolve how the combination of a Western diet, alcohol, and the PNPLA3 I148M genotype reshapes hepatocyte identity, pathway activity, and intercellular signaling networks.
Method: We used single-nucleus RNA sequencing (snRNA-seq) to profile liver tissue from mice exposed to a Western diet and alcohol, comparing controls with those carrying the PNPLA3 I148M variant. Prior to sequencing, injury was verified via histology. We identified hepatocyte subpopulations and constructed cell fate trajectories to assess state transitions. Pathway activities were quantified using Gene Set Variation Analysis (GSVA), and intercellular communication was inferred using CellPhoneDB. Findings were validated through protein quantification of inflammatory, metabolic, and fibrogenic markers.
Results: The combined exposure to Western diet, alcohol, and PNPLA3 I148M drove a coordinated shift in hepatocyte composition, yielding the highest abundance of stress-responsive subpopulations, including interferon-stimulated and injury-response hepatocytes. Trajectory analysis indicated that the combined treatment drove hepatocytes from quiescent states into phenotypes characterized by upregulated glycolysis (adj. $p < 0.001$) and oxidative phosphorylation (adj. $p < 0.001$). This was accompanied by a reciprocal downregulation of core functions, such as bile acid metabolism (adj. $p < 0.001$). Joint exposure enhanced profibrotic signaling interactions (adj. $p < 0.05$), specifically collagen-integrin, PDGF, and TGF-β interactions. Protein analysis corroborated these findings, showing significant elevation of inflammatory markers IL-1β ($p < 0.01$) and NLRP3 ($p < 0.01$), apoptotic cleaved Caspase-3 ($p < 0.05$), and fibrogenic markers COL1A1 ($p < 0.01$) and α-SMA ($p < 0.01$) in the combined treatment group relative to controls.
Conclusion: The interaction between alcohol and PNPLA3 I148M synergistically rewires the hepatic transcriptomic landscape, driving hepatocytes away from metabolic homeostasis toward inflammatory and apoptotic programs. This joint exposure promotes an energetically demanding injury response consistent with oncogenic priming and creates a signaling niche that actively drives fibrogenesis.

SAT-154
Kupffer cell-specific deletion of Sirt6 ameliorates diet-induced metabolic liver disease via macrophage reprogramming
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) progression involves hepatic macrophage activation. Preliminary analysis of published single-nucleus RNA sequencing (snRNA-seq) data indicated decreased *Sirt6* expression in liver macrophages from MASLD patients and high-fat diet (HFD)-fed mice. We aimed to investigate the functional role of *Sirt6* specifically in Kupffer cells (KCs) during diet-induced steatohepatitis (MASH).
Method: SIRT6 downregulation was validated in multiple murine models (PA-treated primary KCs, MCD/HFD-fed mice, *db/db* mice) via