Unraveling the individual contributions of the PPAR isotypes to the pan-PPAR agonist lanifibranor-induced improvements of the vascular alterations and liver histology in a rat model of early NAFLD

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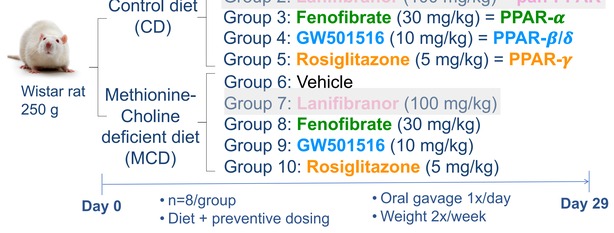
Background & aim

The **pan-peroxisome proliferator-activated receptor** (pan-PPAR) agonist **lanifibranor** completely **normalised** altered intrahepatic vascular dysfunction and **improved** liver histology in **a rat model** of **early NAFLD** (EASL *abstract 3547*).

The **underlying mechanism** was explored through the mono-PPAR agonists: **PPAR-α, PPAR-β/δ, PPAR-γ** in a rat model of early NAFLD.

Methods



- ***In vivo*** portal venous pressure **(PVP)** assessment.
- ***In situ ex vivo* liver perfusion** in the same animal to assess baseline transhepatic pressure gradient **(THPG)** at different flows.
- **Histological staining** on liver tissue: **SAF**-score and **% steatosis quantification**.
- **Dose-response curves** with methoxamine (Mx) and acetylcholine (ACh).

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1 Results

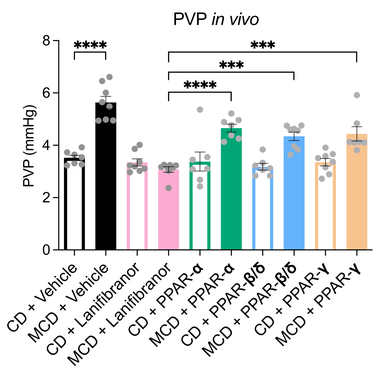
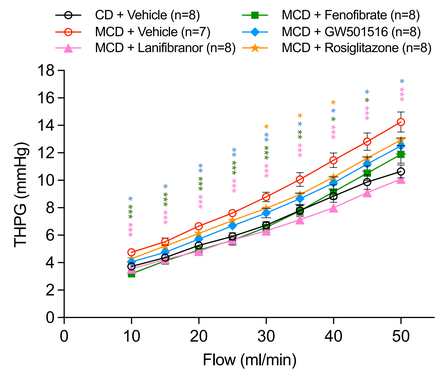


Figure 1: *In vivo* PVP

Strong elevation of PVP in vehicle-treated MCD rats vs. controls (5.64 ± 0.63 vs. 3.52 ± 0.24 mmHg, p < 0.0001). **Lanifibranor** normalised increased PVP in MCD rats. The **mono-PPARs** in contrast caused partial improvement of PVP.

Figure 2: *In situ ex vivo* THPG

The THPG is increased at all flows in MCD rats vs. CD rats (e.g., at 30 ml/min: from 8.78 ± 0.35 to 6.73 ± 0.28 mmHg, p < 0.001). **Lanifibranor** normalised the elevated THPG in MCD rats at all flows. The **PPAR-α**, **PPAR-β/δ** and the **PPAR-γ** agonists caused partial improvement.



Conclusions

In early NAFLD mono-PPAR agonists:

- Improve the increased portal pressure (for all 3 PPAR agonists).
- Improve liver histology (mainly PPAR-α).
- Normalise intrahepatic vascular dysfunction (mainly PPAR-β/δ and PPAR-γ)

However, lanifibranor exhibits more pronounced improvements, indicating that its beneficial effects results from an additive effect of combined mono-PPAR agonism, as opposed to mono-agonism.

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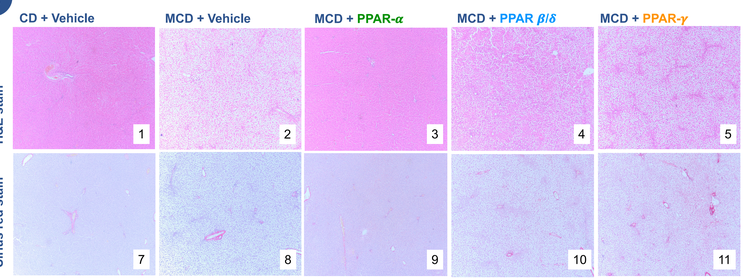

Figure 3: Liver histology

Lanifibranor improved steatosis with a reduction of 19.7 ± 4.8 %. **H&E stain:** no inflammation. **1)** Healthy control liver (all CD livers treated with mono-PPAR agonists were similar). **2)** Severe steatotic liver. **3)** Full inhibition of steatosis by **PPAR-α** agonist. **4)** Weak decrease of steatosis by **PPAR-β/δ** agonist (11.72 ± 5.28 %). **5)** Minimal improvement of steatosis by **PPAR-γ** agonist (decrease of 7.15 ± 6.73 %). **Sirius red stain: 7-11)** No fibrotic tissue present.

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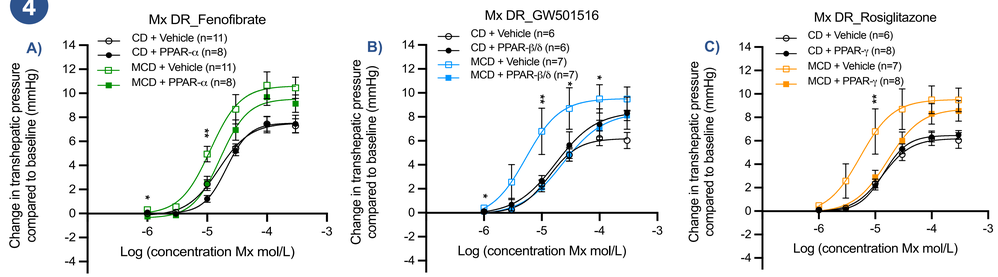

Figure 4: Dose-response methoxamine

In the vehicle-treated groups, MCD rats are **hyperreactive** to Mx compared to CD rats.
Lanifibranor normalised Mx hyperreactivity in MCD rats.
A) PPAR-α agonist: Partial improvement of Mx hyperreactivity.
B) PPAR-β/δ agonist: Overall normalisation of Mx hyperreactivity, comparable to lanifibranor.
C) PPAR-γ agonist: Normalisation of Mx hyperreactivity in similar ways to lanifibranor.

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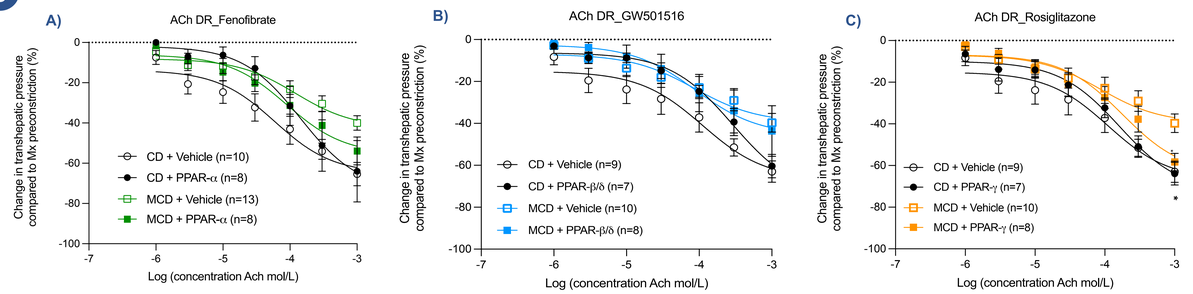

Figure 5: Dose-response acetylcholine

In the vehicle-treated groups, MCD rats are **hyporeactive** to ACh compared to CD rats. **Lanifibranor** normalised ACh hyporeactivity in MCD rats.
A) PPAR-α agonist: No normalisation of ACh hyporeactivity in MCD rats. At the highest doses it tends to cause some improvement.
B) PPAR-β/δ agonist: No normalisation of ACh hyporeactivity in MCD rats.
C) PPAR-γ agonist: No normalisation of ACh hyporeactivity, however, there is improvement at the highest doses.

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Metabolism, alcohol and toxicity
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