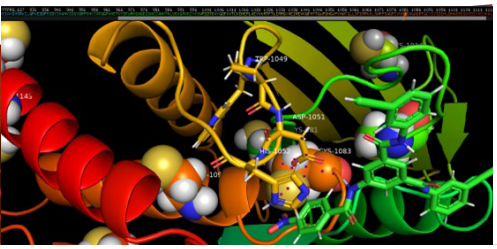

PROTEIN TYROSINE PHOSPHATASE RECEPTOR KAPPA (PTPRK) INHIBITORS FOR TREATING OBESITY-INDUCED PATHOLOGIES

KEYWORDS

- Obesity-induced pathologies
- Hepatocellular Carcinoma (HCC)
- Small Molecule Inhibitor
- Protein Tyrosine Phosphatase

Collaboration type
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THE TECHNOLOGY IN A NUTSHELL

Small molecule inhibitors of Protein Tyrosine Phosphatase Receptor Kappa (PTPRK) for use in the treatment of obesity and obesity-induced pathologies including metabolic dysfunction-associated steatotic liver disease (MASLD) and hepatocellular carcinoma (HCC).

STATE OF THE ART

Obesity, which affects more than 650 million individuals worldwide, is a well-established risk factor for MASLD which can in turn progress to HCC. With an increasing number of patients developing obesity-related liver complications, there is a pressing need to develop drugs based on new therapeutic approaches for the treatment of such diseases. Protein Tyrosine Phosphatases represent in this perspective a new class of emerging drug targets of specific interest, remaining still largely unexplored.

THE INVENTION

Fat accumulation, *de novo* lipogenesis, and glycolysis are key drivers of hepatocyte reprogramming and the consequent MASLD. Obesity leads to dysregulated expression of hepatic protein tyrosine phosphatases (PTPs). Among PTPs, PTPRK has been found by the inventors to be increased in steatotic hepatocytes and positively correlated with lipogenic signaling. In addition, the inventors demonstrated that silencing PTPRK in hepatoma cell lines resulted in reduced colony-forming ability and that PTPRK knock-out mice developed smaller tumours upon hepatocarcinogenesis induction, thereby shedding light on the key role of PTPRK in regulating hepatic glycolysis, lipid metabolism and tumour development.

In this context, the inventors have developed a series of small molecules PTPRK inhibitors providing new therapeutic possibilities for the treatment of obesity-associated liver diseases. The hit compounds series present a high stability and molecular affinity for the catalytic site of PTPRK and are amenable to a drug development program further to the validation of their specific inhibition activity on the PTPRK target through enzymatic activity assays using the recombinant PTPRK intracellular domain. The first *in vitro* results on cell lines also confirm the effect of those small molecules inhibitors on cancer cell lines growth. Pre-clinical *in vivo* studies in C57BL/6 mice demonstrate in addition that those compounds also induce a decrease of weight and body fat in obese mice opening thereby opportunities for obesity treatment

KEY ADVANTAGES OF THE TECHNOLOGY

- Inhibition of PTPRK's catalytic activity with IC_{50} in the µM range amenable to lower concentrations upon hit to lead optimization.
- *In vitro* inhibition of cancer lines growth.
- *In vivo* demonstration of body fat reduction upon treatment of obese mice.
- Small molecules presenting no toxicity as assayed on Zebrafish larvae.

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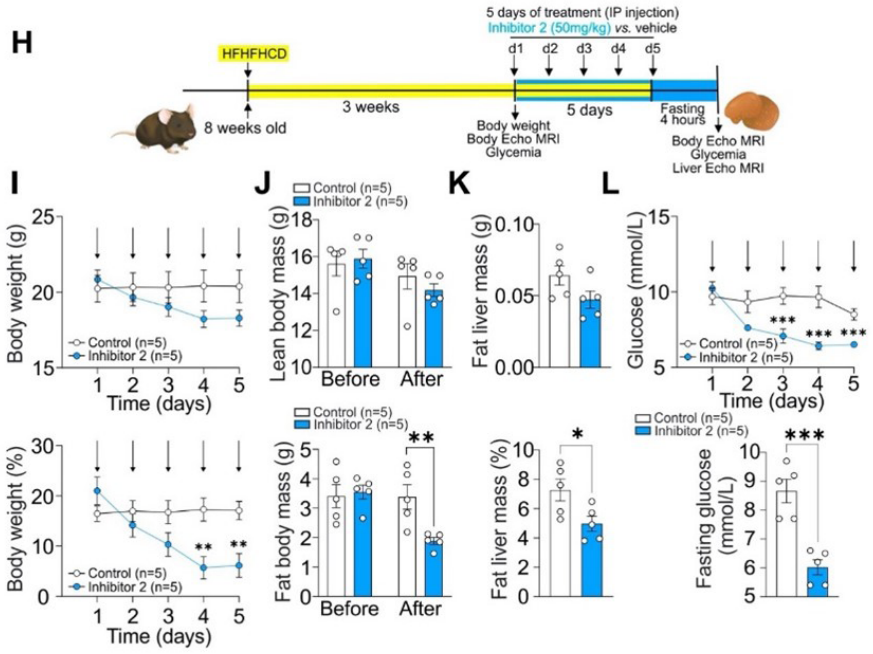
TECHNOLOGY READINESS LEVEL

1 2 **3** 4 5 6 7 8 9

TRL-3 Proof of concept: *in vitro* inhibition of hepatic cancer lines and first *in vivo* results showing potential for development of obesity treatment.

POTENTIAL APPLICATIONS

- Treatment of obesity
- Treatment of obesity induced HCC and other related hepatic diseases, such as MASLD



H) *In vivo* assessment of PTPRK Inhibitor 2 was conducted in C57Bl/6 male mice. The mice were treated with vehicle or 50mg/kg PTPRK Inhibitor 2 for 5 days. (I-L) Body weight was measured daily (I), and body composition were measured before and after the treatment (J). Liver composition analysis was performed (K) and glycaemia levels were assessed daily (L). The reported data are presented as mean±SEM. Statistical significance is indicated as * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

THE TEAM

Prof Esteban Gurzov has dedicated his scientific career to investigate the pathogenic mechanisms of obesity and diabetes and the discovery of novel therapeutics. In 2017, he received a tenured Associate Researcher/Chercheur Qualifié position from the FRS-FNRS to direct the Signal Transduction & Metabolism Laboratory. In 2019, he was awarded with a European Research Council (ERC) Consolidator Grant. He is also a WELBIO Investigator since 2019 and was recipient of one of the 2021 AstraZeneca Foundation Award.

The Signal Transduction & Metabolism Laboratory, located on the academic hospital campus aims at translating research discoveries to the clinic through a combined use of molecular biology, stem cells research, animal models of metabolic disorders and human samples.

Prof José Antonio is a specialist in structural proteomics and bioinformatics and has in this framework been very active in the *in silico* design of peptidic protein-kinase inhibitors. His expertise also encompasses molecular docking approaches for drug discovery including research on inhibitors of Dengue and Zika RNA-dependent RNA polymerase and more recently on Protein Tyrosine Phosphatases inhibitors. He heads the Bioactive Molecules Design and Development research group at the Institute of Research, Development, and Innovation in Healthcare Biotechnology of the Miguel Hernandez University at Elche. He also spent 2 years at the European Molecular Biology Laboratory (EMBL) in Heidelberg where he contributed to the development of the website for ADAN database of protein modular domains implied in protein-protein interactions.

RELEVANT PUBLICATIONS

> PTPRK regulates glycolysis and de novo lipogenesis to promote hepatocyte metabolic reprogramming in obesity, *Nat Commun* **15**, 9522 (2024)

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