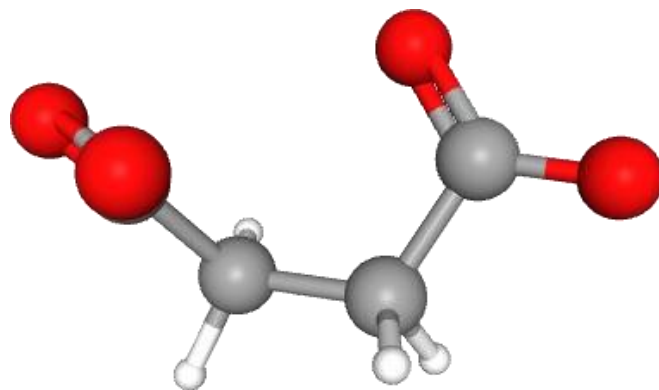


Development of a Succinate-Modulating Enzyme for Metabolic and Inflammatory Diseases

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TREBALL FINAL DE GRAU BIOTECNOLOGIA



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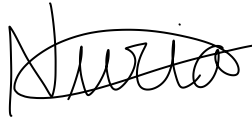
Doble grau de Biotecnologia + Bioquímica i Biologia molecular

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Jo, *Nuria González Lozano*, amb DNI 40565142L, soc coneixedor de la guia de prevenció del plagi a la URV *Prevenció, detecció i tractament del plagi en la docència: guia per a estudiants* (aprovada el juliol 2017)

(<http://www.urv.cat/ca/vidacampus/serveis/crai/que-us-oferim/formacio-competencies-nuclears/plagi/>) i afirmo que aquest TFG no constitueix cap de les conductes considerades com a plagi per la URV.

Tarragona, 02 de Setembre de 2025

A handwritten signature in black ink, appearing to read 'Nuria', written in a cursive style.

(signatura)

ACKNOWLEDGEMENTS

This work was carried out at SUCCIPRO, SL, a newly created spin-off of the Institut d'Investigació Sanitària Pere Virgili (IISPV) and the Universitat Rovira i Virgili (URV), focused on the development of succinate-modulating therapies for metabolic and inflammatory diseases. The project was conducted under the supervision of Dr. Carme Grau Bové, within a research initiative led by Dr. Isabel Huber Ruano and Dr. Sonia Fernández-Veledo. SUCCIPRO is headed by a team of outstanding researchers: Dr. Isabel Huber Ruano, with extensive experience in preclinical drug discovery, Dra. Sonia Fernández Veledo, an expert in metabolism, and Dr. Joan Vendrell Ortega, a clinical endocrinologist.

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AI-based language models were used during the writing process for minor linguistic refinement. No AI tools were involved in the generation, analysis, or interpretation of scientific content.

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ABSTRACT

Succinate is a metabolic intermediate produced by both host cells and gut microbiota, acting as a signaling molecule in immunity, fibrosis, and metabolism. Elevated succinate levels are consistently observed in Non-Alcoholic fatty liver disease (NAFLD) and Inflammatory Bowel Disease (IBD), and they contribute to their progression. Strategies to lower succinate levels could provide a novel therapeutic avenue. We hypothesized that a novel succinate-degrading enzyme, SD1 and two SD1-variants, could reduce succinate levels *in vivo*, therefore improving metabolic and inflammatory outcomes. The main objective was to assess their effects on succinate levels, however, more specific ones included producing the enzymes efficiently, and successfully testing them *in vivo*.

We worked with three potential therapeutic candidates, SD1 and two variants from SD1 obtained by semi-rational mutagenesis, which were tested in different mouse models. In the NAFLD-induced model, all three were evaluated, whereas in the DSS model (to simulate IBD), only SD1 was tested. The *in vivo* outcomes were then analyzed through different techniques: histological, qPCR, and ELISA. Culture optimization of the therapeutic variants was also carried out in parallel with the *in vivo* studies.

From the overall results, the hypothesis is partially supported. SD1 and one variant showed promising improvements in the NAFLD mouse model, while SD1 demonstrated favorable effects in the acute DSS model, although the impact was less pronounced in the relapse setting. Additionally, the cultivation process was successfully optimized, representing an important methodological improvement. Further studies are needed to clarify the mechanisms underlying the observed effects, particularly in the DSS relapse model, and to guide the complete development of the therapeutic strategy.

KEY WORDS: succinate, inflammation, metabolic disease, non-alcoholic fatty liver disease, inflammatory bowel disease.

INSTITUTION DETAILS

Succipro is a biotechnology spin-off founded in 2022 from the Pere Virgili Health Research Institute (IISPV-CERCA) and the Universitat Rovira i Virgili (URV), located in Tarragona, Spain. The company develops succinate-modulating therapies aimed at metabolic and inflammatory diseases.

The Institut d'Investigació Sanitària Pere Virgili (IISPV) is a biomedical research institution affiliated with the Universitat Rovira i Virgili. It brings together research groups from hospitals and academic centers across Catalonia and focuses on areas such as oncology, neuroscience, metabolism and nutrition, infectious diseases, cardiovascular and respiratory health, and environmental health.