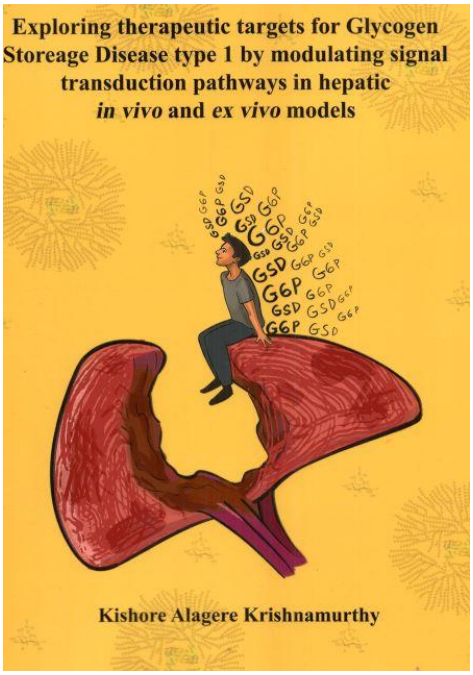

Samenvatting proefschrift
K. Alagere Krishnamurthy

'Exploring therapeutic targets for Glycogen Storeage Disease type 1 by modulating signal transduction pathways in hepatic *in vivo* and *ex vivo* models'

Promotiedatum: 25 september 2024

Supervisors:
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This PhD thesis explores the regulation of glucose 6-phosphatase (G6PC)-independent glucose production in hepatic Glycogen Storage Disease (GSD) types Ia and Ib, with the objective of optimizing glucose homeostasis and reducing hepatic glycogen accumulation and hepatomegaly. Building on prior findings, the research primarily focuses on the role of carbohydrate-responsive element-binding protein (ChREBP) in modulating glucose and glycogen metabolism, especially when G6PC function is compromised.

In an acute GSD Ib model, induced by inhibiting the G6P transporter SLC37A4 via S4048, ChREBP was observed to play a critical role in regulating glucose metabolism. Downregulation of ChREBP through short-hairpin RNA (shRNA) exacerbated the GSD Ib phenotype, leading to increased hepatic glycogen accumulation and further reductions in blood glucose levels. This downregulation also elevated glucokinase (GCK) mRNA and protein levels, independently of GCKR regulation, suggesting ChREBP may act as a transrepressor of the *Gck* gene. Interestingly, even though predicted ChREBP target genes like *Gys2* and *Pygl* had reduced expression and protein levels, fluxes through glycogen metabolism pathways were increased, indicating that metabolite- and hormone-driven flux regulation predominated over enzyme-driven effects during hepatic ChREBP normalization.

On the other hand, a novel *ex vivo* model using precision-cut liver slices (PCLS) was developed to further investigate hepatic glucose production and AMPK signaling. The PCLS model validated key findings related to glucose production in GSD not only from the murine models but also from the patient samples (including GSD I patients), offering a promising platform for studying inborn errors of metabolism and potential therapeutic interventions.

In conclusion, this research offers new insights into ChREBP's role and AMPK signaling in hepatic glucose and glycogen metabolism. Its future implications set the stage for further studies

Aan de publicatie van dit proefschrift werd een financiële bijdrage geleverd door de Nederlandse Vereniging voor Hepatologie.

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that will utilize both *in vivo* and *ex vivo* models to focus on the detailed mechanisms of ChREBP-mediated and AMPK-mediated regulation and its clinical applications.

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