

Quantitative Systems Toxicology Approach Integrates Simcyp PBPK and Core Hepatocyte Metabolism: a Case Study with Valproic Acid

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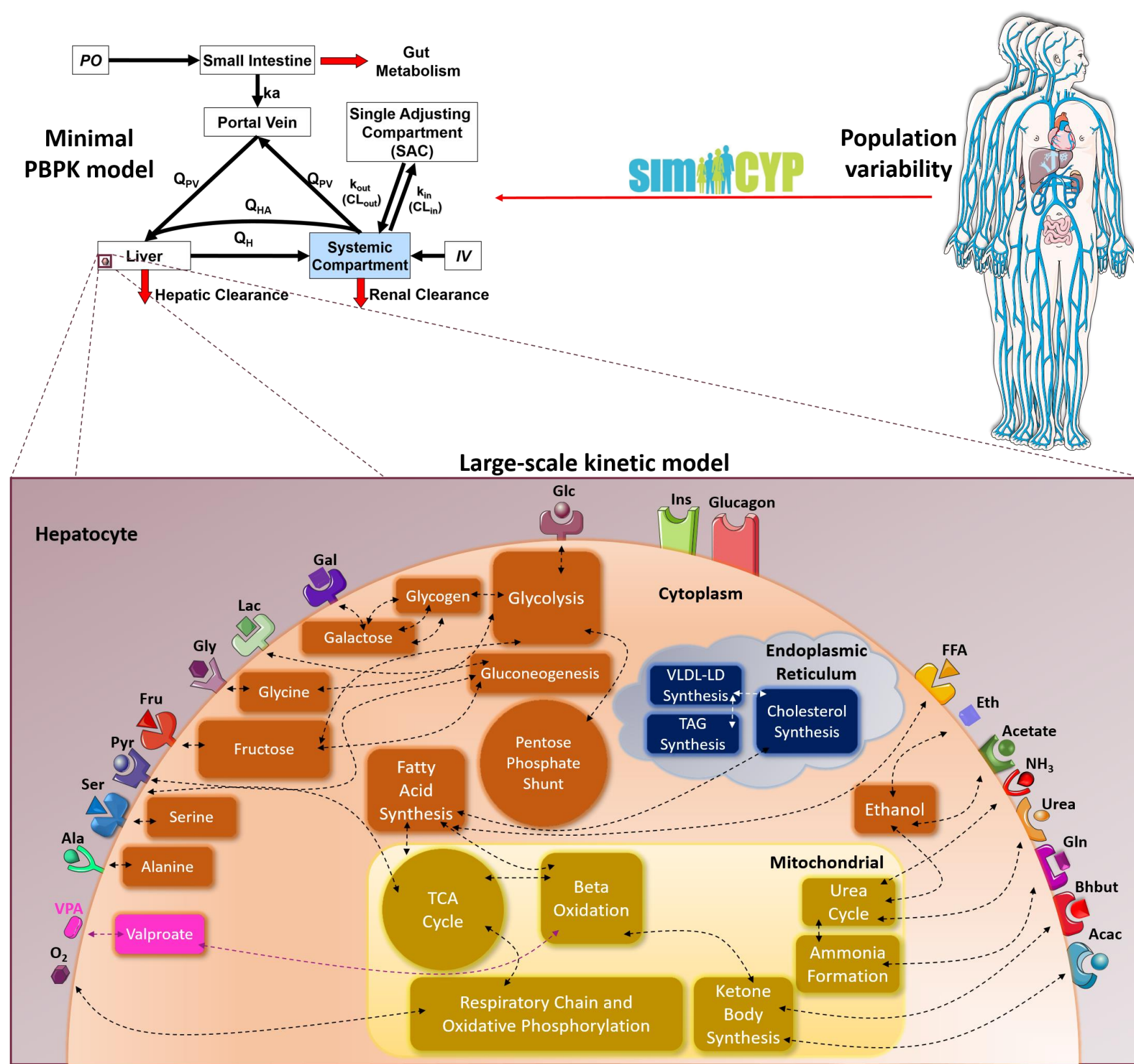
Quantitative systems toxicology modelling approach characterizes effect of valproic acid on lipid metabolism



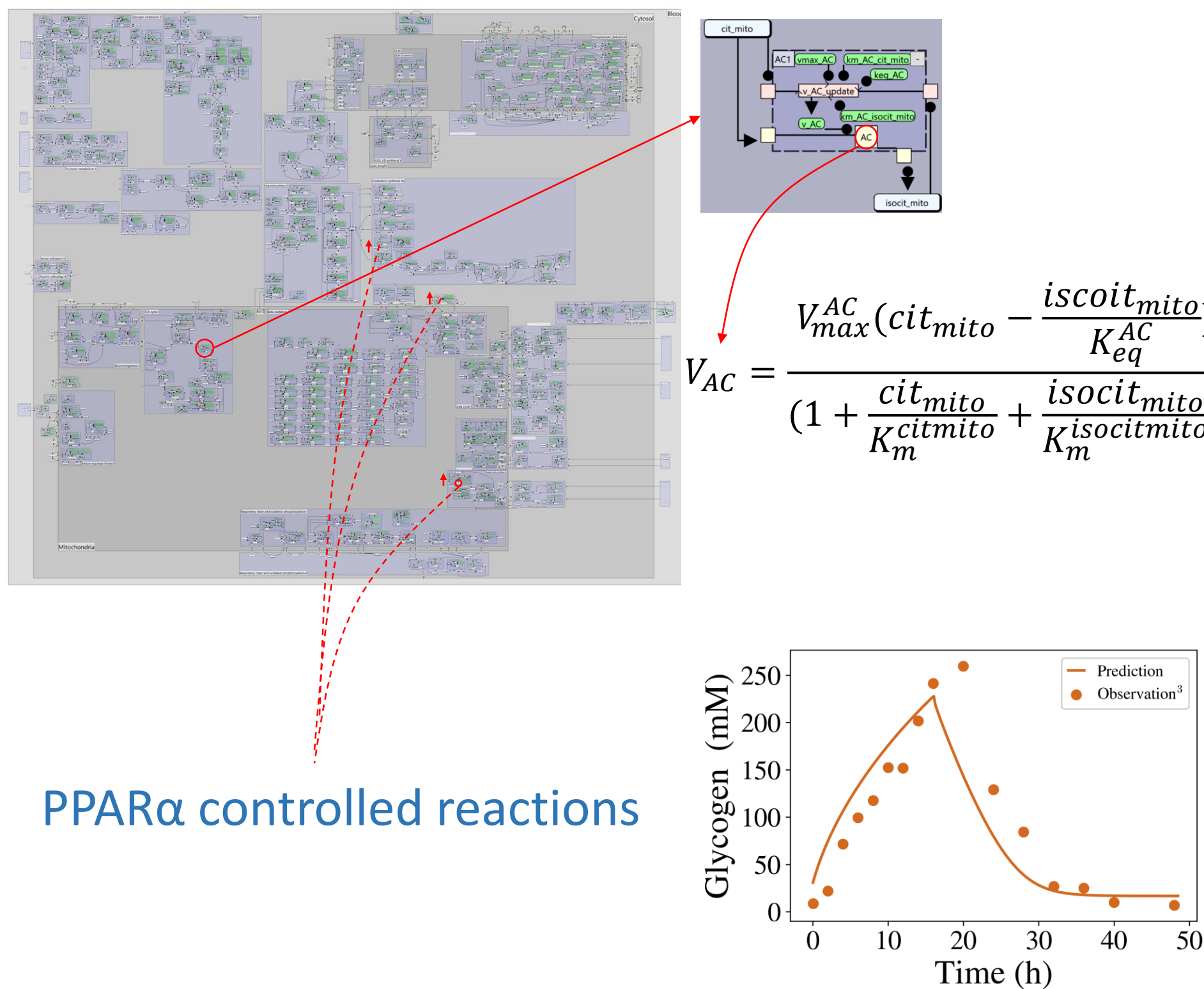
Introduction

- Valproic acid (VPA) is a treatment for epilepsy and bipolar disorder
- A known side effect is induction of hepatic steatosis¹ (lipid accumulation)
- We mechanistically examine and quantify the effect of VPA exposure on lipid metabolism
- We develop a general quantitative systems toxicology (QST) approach integrating Simcyp PBPK with core hepatic metabolism² regulated by PPARα and insulin signalling

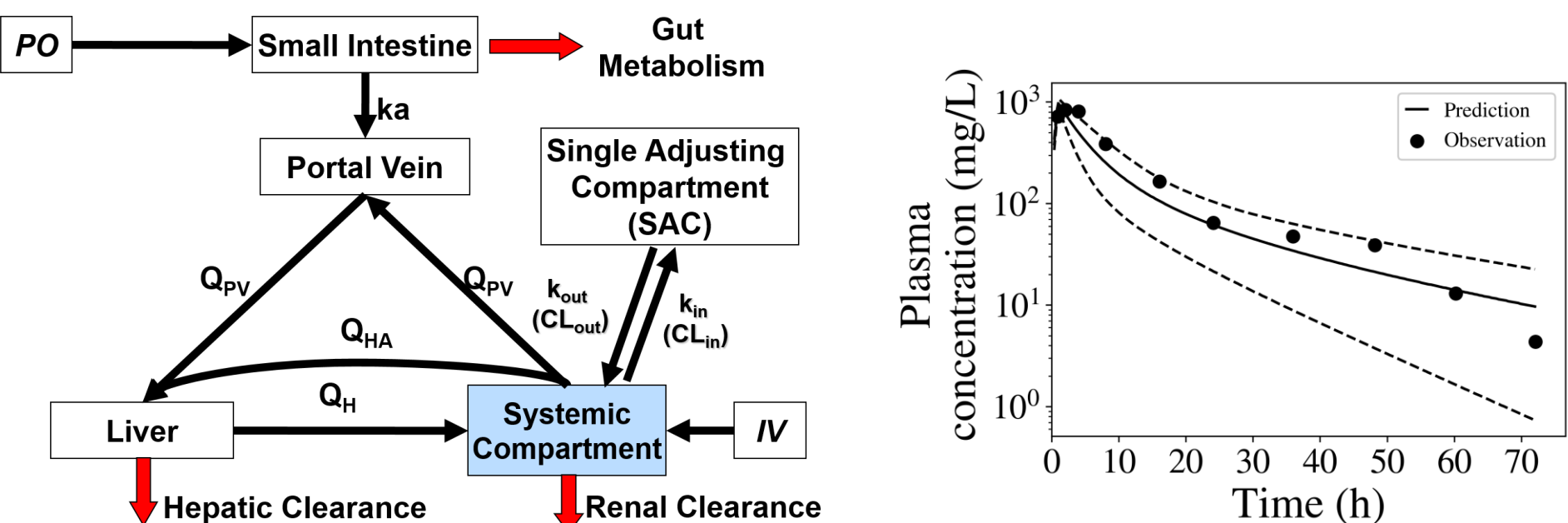
Multi-scale QST model



Schematic representation of QST approach

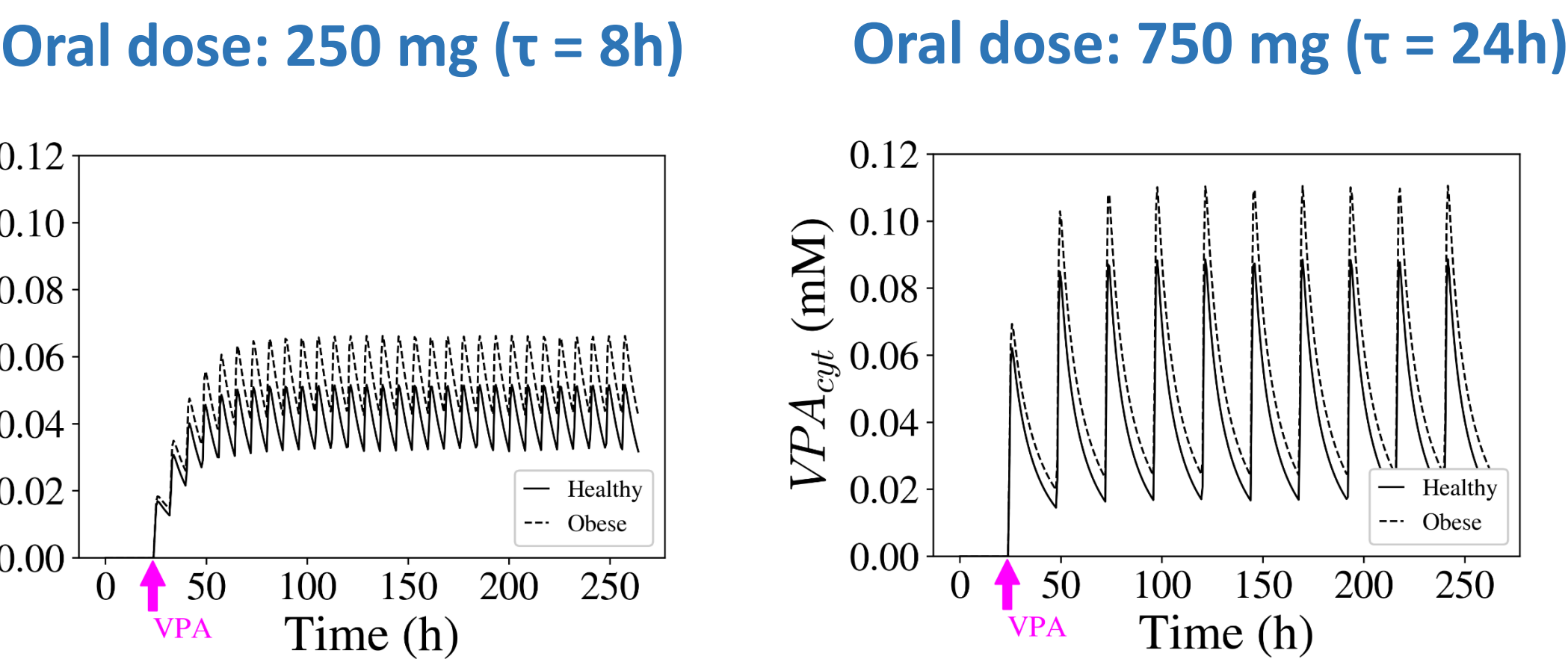


PPARα controlled reactions

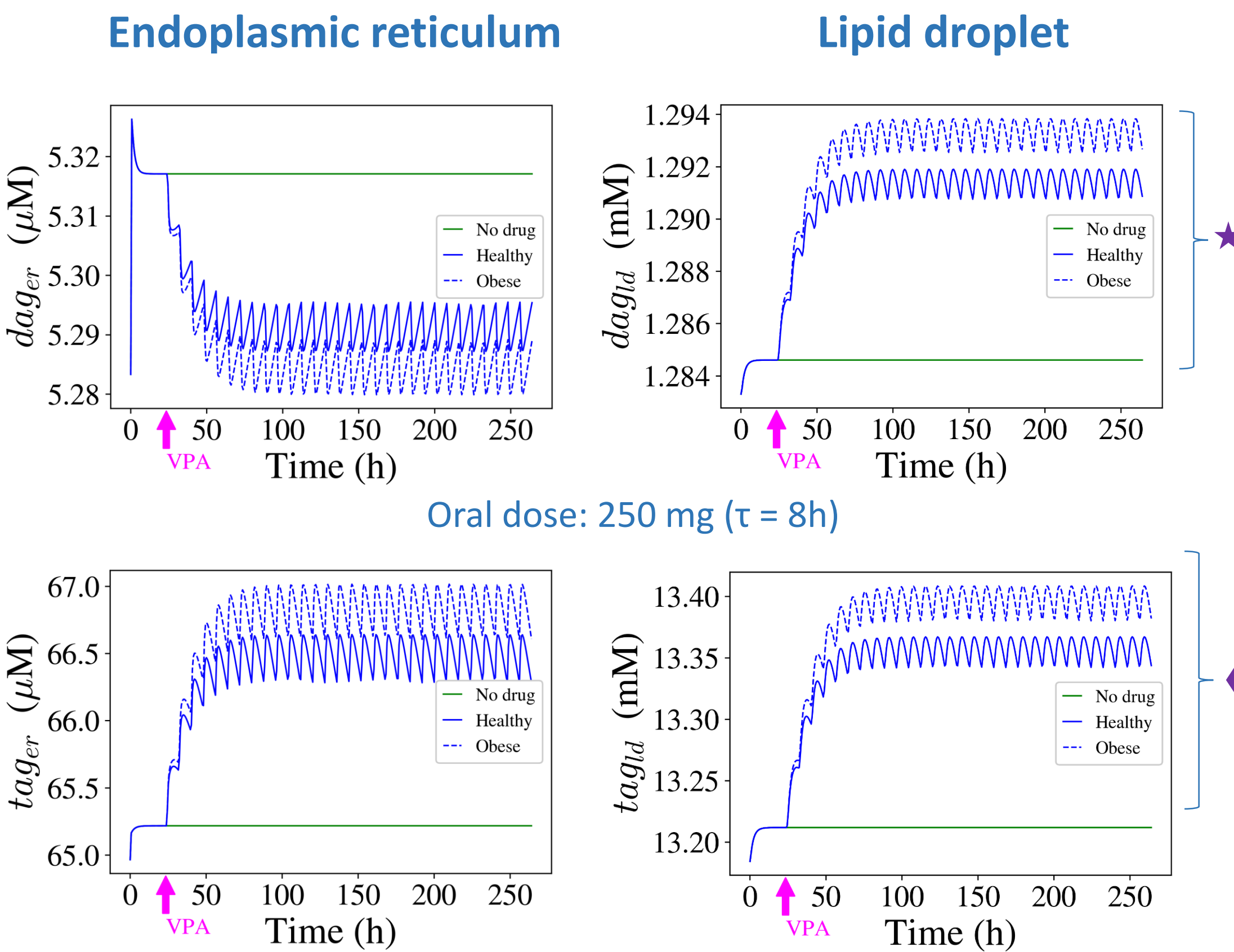


Models are verified independently

Liver concentration of VPA



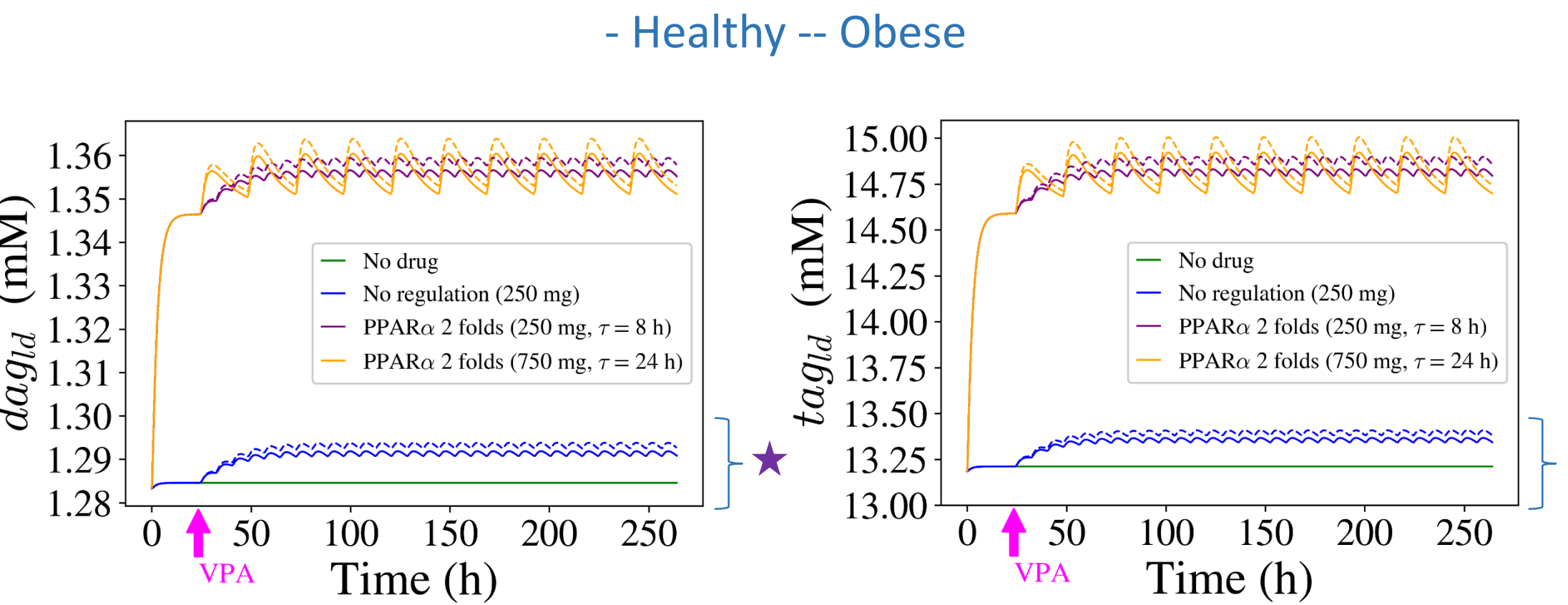
Effect of VPA on lipid metabolism



VPA causes persistent disturbance in lipid metabolism

Effect of PPARα on lipid metabolism

- PPARα is a key regulator of fatty acid metabolism



PPARα regulation enhances the effect of VPA

Discussion

- We developed a general QST modelling approach to evaluate liver toxicity
- We identify that chronic treatment with VPA results in a persistent disruption in lipid metabolism
- We explore the impact of lipid dysregulation in obese individuals
- We are further evaluating how PPARα regulation affects lipid concentration

Additional Information

Reactions regulated by PPARα⁴

Enzyme	Reaction
AAT	$akg_{cyt} + ala_{cyt} \rightarrow glu_{cyt} + pyr_{cyt}$
ACC1/ACC2	$acoa_{cyt} + atp_{cyt} \rightarrow adp_{cyt} + p_{cyt} + malcoa_{imm}$
ACSL1/ACSL4/ACSL5	$atp_{cyt} + c16_{cyt} + coa_{cyt} \rightarrow amp_{cyt} + c16coa_{cyt} + pp_{cyt}$
ALDR	$gra_{cyt} + nadph_{cyt} \rightarrow glyc_{cyt} + nadp_{cyt}$
ALDDH1/ALDDHII	$aald_{cyt} + nad_{cyt} \rightarrow acetate_{cyt} + nadh_{cyt}$
ALDDH _{gra}	$gra_{cyt} + nad_{cyt} \rightarrow glycerate_{cyt} + nadh_{cyt}$
ASL	$arg_{succ_{cyt}} \rightarrow arg_{cyt} + fum_{cyt}$
CACT	$c16car_{cyt} + car_{mito} \rightarrow car_{cyt} + c16car_{mito}$ $valcar_{cyt} + car_{mito} \rightarrow car_{cyt} + valcar_{mito}$
CPS	$2 atp_{mito} + NH_3_{mito} \rightarrow 2 adp_{mito} + cmp_{mito} + p_{mito}$
CPT1	$c16coa_{cyt} + car_{cyt} \rightarrow c16car_{cyt} + coa_{cyt}$ $valcoa_{cyt} + car_{cyt} \rightarrow valcar_{cyt} + coa_{cyt}$
G6P _{er}	$glc6p_{er} \rightarrow glc_{er} + p_{er}$
Glyck	$atp_{cyt} + glyc_{cyt} \rightarrow adp_{cyt} + g3p_{cyt}$
GLNASE	$gln_{mito} \rightarrow gln_{mito} + NH_3_{mito}$
HMG _{syn_cyt}	$acoa_{cyt} + kc4coa_{cyt} \rightarrow coa_{cyt} + hmgcoa_{cyt}$
HMG _{syn}	$acoa_{mito} + kc4coa_{mito} \rightarrow coa_{mito} + hmgcoa_{mito}$
ME	$mal_{cyt} + nadp_{cyt} \rightarrow nadph_{cyt} + pyr_{cyt}$
OTC	$cmp_{mito} + orn_{mito} \rightarrow ct_{mito} + p_{mito}$
PEPCK	$gtp_{cyt} + oaa_{cyt} \rightarrow gdp_{cyt} + pep_{cyt}$

References

- Luef, G., M. Rauchenzauner, M. Waldmann, W. Sturm, A. Sandhofer, K. Seppi, E. Trinkka et al. "Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug treatment." *Epilepsy research* 86, no. 1 (2009): 42-47.
- Berndt, Nikolaus, Sascha Bulik, Iwona Wallach, Tilo Wünsch, Matthias König, Martin Stockmann, David Meierhofer, and Hermann-Georg Holzütter. "HEPATOKIN1 is a biochemistry-based model of liver metabolism for applications in medicine and pharmacology." *Nature communications* 9, no. 1 (2018): 2386.
- Friedmann, Bernice, Edward H. Goodman Jr, and Sidney Weinhouse. "Effects of glucose feeding, cortisol, and insulin on liver glycogen synthesis in the rat." *Endocrinology* 81, no. 3 (1967): 486-496.
- Maldonado, Elaina M., Vytautas Leoncikas, Ciarán P. Fisher, J. Bernadette Moore, Nick J. Plant, and Andrzej M. Kierzek. "Integration of genome scale metabolic networks and gene regulation of metabolic enzymes with physiologically based pharmacokinetics." *CPT: pharmacometrics & systems pharmacology* 6, no. 11 (2017): 732-746.



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