USING QUANTITATIVE SYSTEMS PHARMACOLOGY IN EARLY DISCOVERY: EVALUATING THE ADIPOSE AS A TARGET TISSUE TO TREAT NON-ALCOHOLIC FATTY LIVER DISEASE

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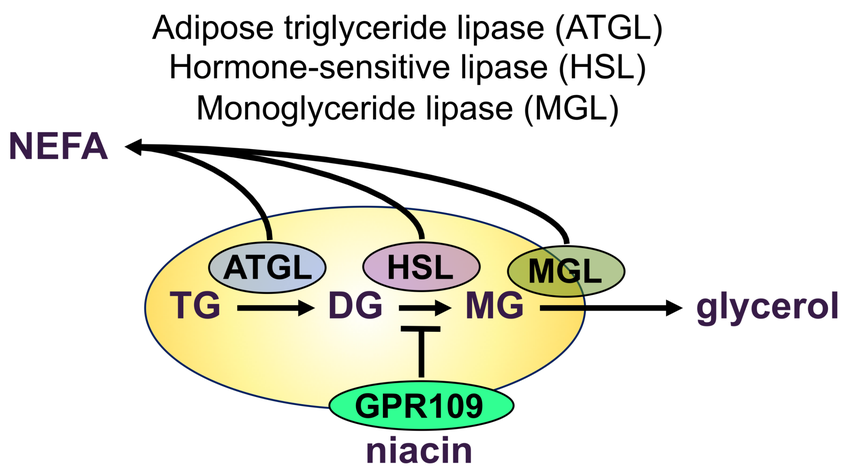
SCAN ME

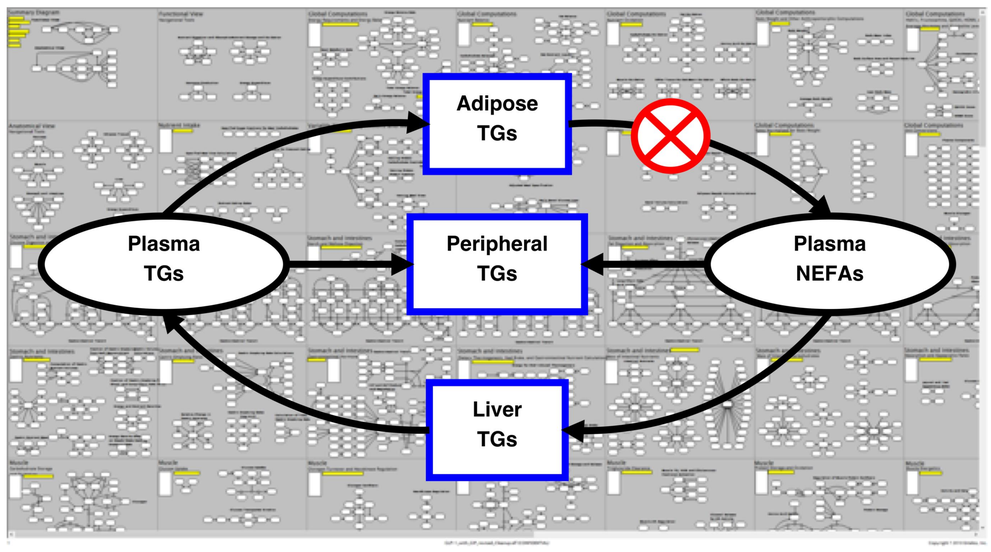
INTRODUCTION

- Non-alcoholic fatty liver disease (NAFLD) is a progressive disorder that begins with liver steatosis
- Non-esterified fatty acid (NEFA) flux from the adipose appears to be a large contributor to liver lipids[1]
- ***To find new treatments for NAFLD, we used a QSP model to simulate the sensitivity of liver steatosis to reducing the flux of NEFAs***
- We based our model on a GPR109a agonist that has previously been in the clinic[2,3]

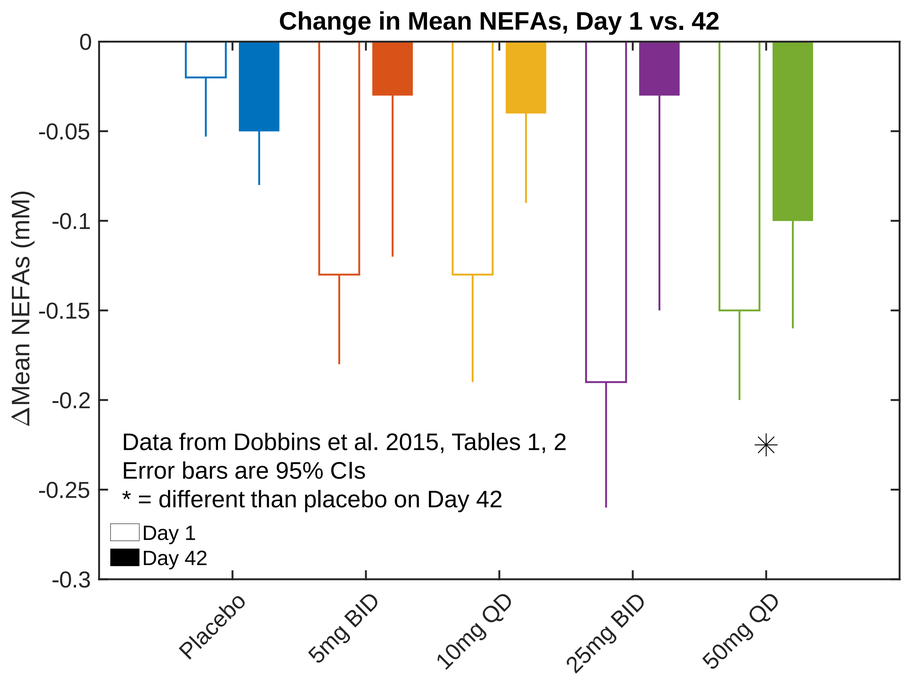
Illustration of the process of lipolysis and GPR109



QSP model: Pfizer-Modified Entelos Metabolism PhysioLab®



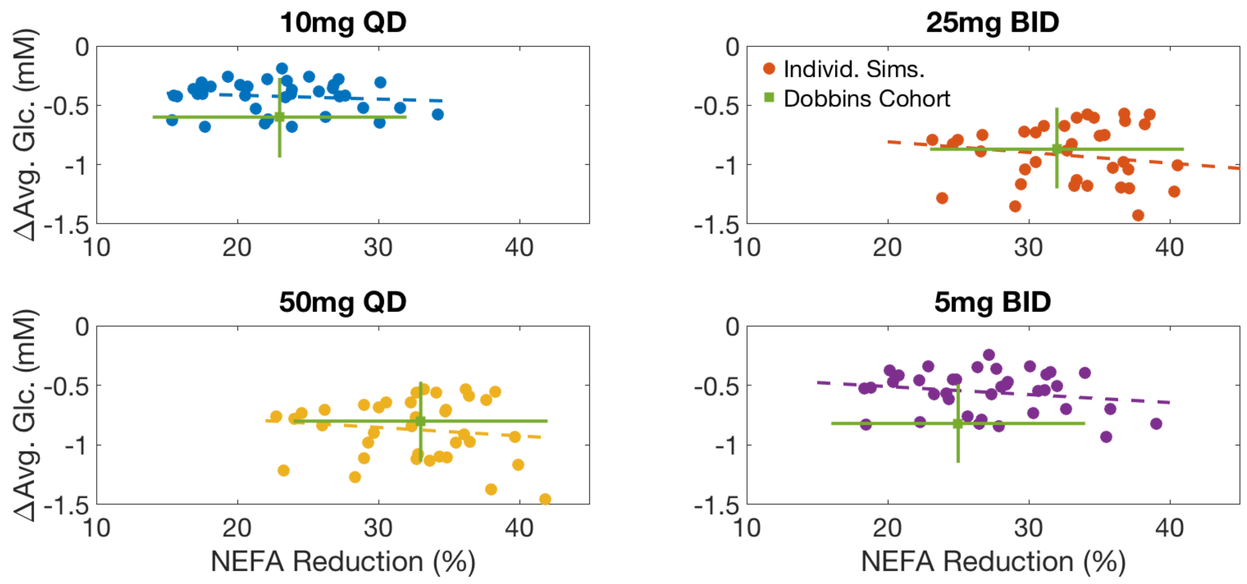
Acute NEFA reduction by a GPR109a agonist in patients with type 2 diabetes (T2D)



Calibrate PK to Phase I (Dobbins) data → Incorporate in-house data on PPB and EC50 → Simulate acute (2d) dosing and verify model predictions → Simulate chronic therapy w/o adaptation

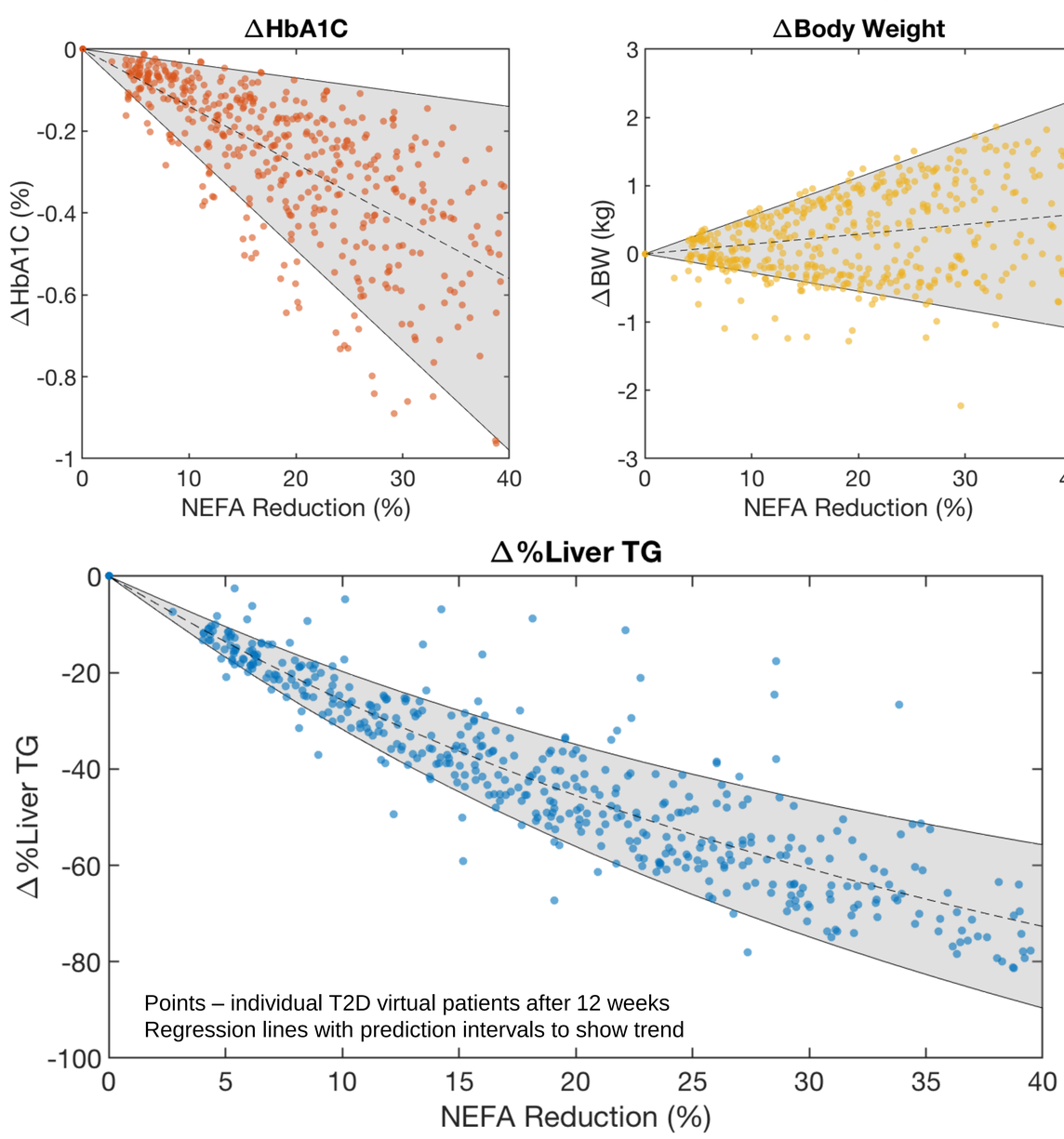
RESULTS

Simulation of two days of GPR109a therapy in a cohort of T2D virtual patients



The QSP model captured the acute response of a GPR109a agonist without any fitting.

Extrapolation of QSP model simulations to 12 weeks of dosing



- ***QSP modeling predicts that reducing NEFA flux to the liver should be a potent method for reducing liver fat***
- Future work should focus on identifying developable approaches for achieving sustained reductions in NEFA flux

REFERENCES AND ACKNOWLEDGEMENTS

1. Lambert et al. Gastro. 2016.
2. Dobbins et al. Eur. J. Pharmacol. 2013.
3. Dobbins et al. Eur. J. Pharmacol. 2015.

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