# An Integrated QSP Model of Lipoproteins with Liver Metabolism for Non-Alcoholic Fatty Liver Disease and Hyperlipidemia

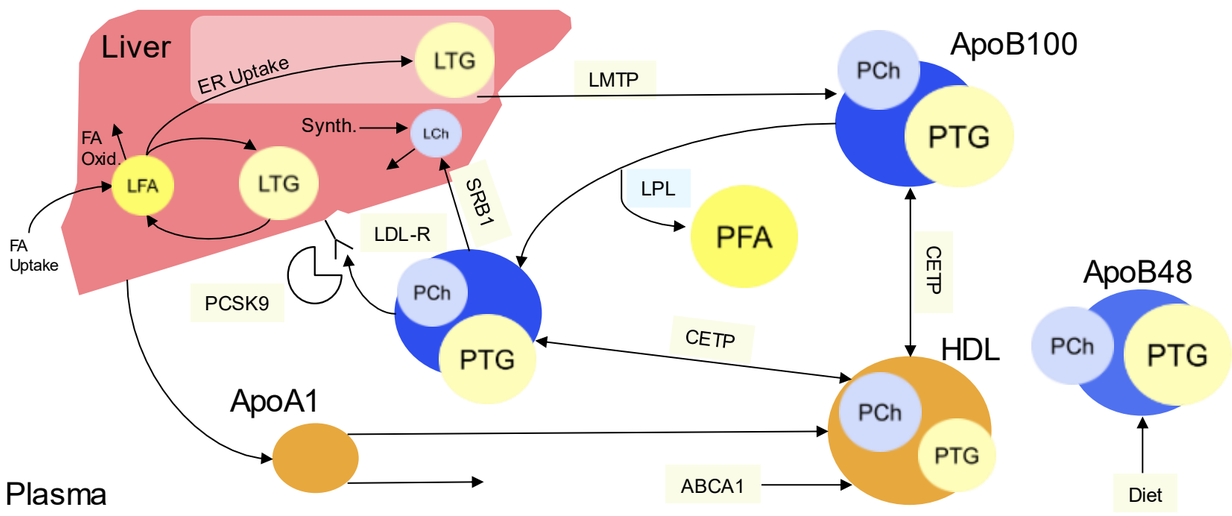
Theodore R. Rieger, Anna Sher, Tyler Cassidy, and C.J. Musante
Quantitative Systems Pharmacology, Pfizer Inc

*ACoP13, Oct 30 to Nov 2, 2022, Aurora Colorado*

## INTRODUCTION

- The liver is a key organ for metabolism of both lipids and cholesterol, as well as producing and clearing many circulating lipoproteins
- The central role of the liver makes it a compelling target organ for treatments for both non-alcoholic fatty liver disease [1] and hyperlipidemia [2,3]
- Given the interconnected nature of metabolism in the liver, a QSP model is an asset for guiding pharmaceutical development for the treatment of many cardiometabolic diseases
- **Here we integrate and build upon two published models [4,5] to develop a unified model of both lipid and lipoprotein metabolism**

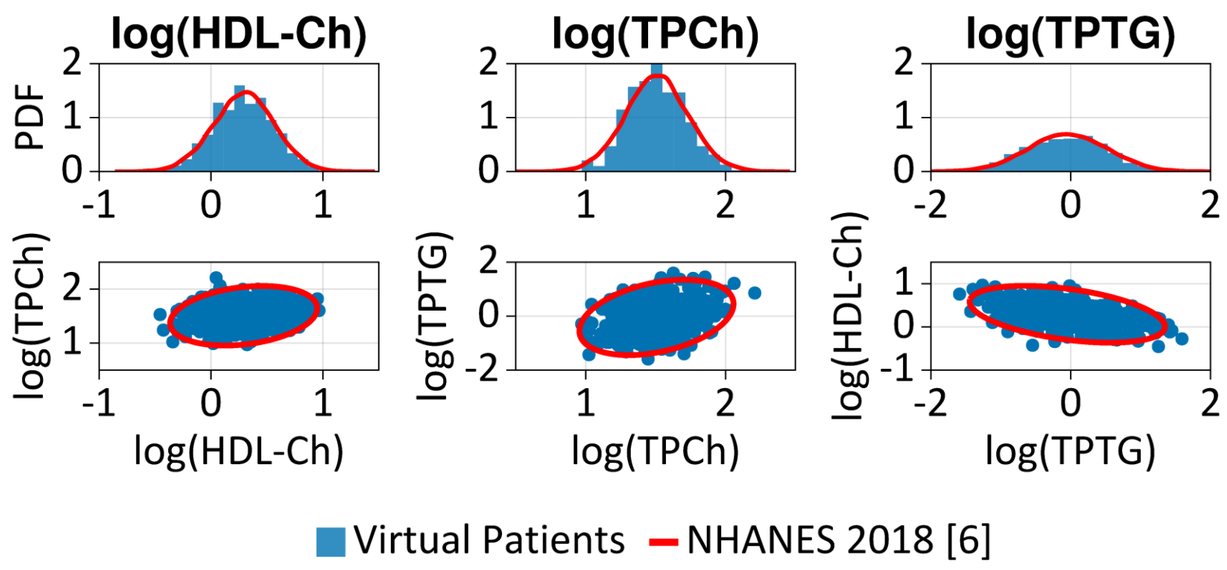
## AN INTEGRATED QSP MODEL OF LIVER METABOLISM AND LIPOPROTEINS




| Apo | Apolipoprotein | (L/P)Ch | Cholesterol (Liver or Plasma) | ER | Endoplasmic Reticulum | (L/P)FA | Fatty Acid (Liver or Plasma) | HDL | High Density Lipoprotein |
|---|---|---|---|---|---|---|---|---|---|
| HDL-Ch | HDL Cholesterol (apoA1 Ch) | TPCh | Total Plasma Ch (∑PCh) | (L/P)TG | Triglyceride (Liver or Plasma) | TPTG | Total Plasma TG (∑PTG) | VP/VPop | Virtual Patient/ Virtual Population |

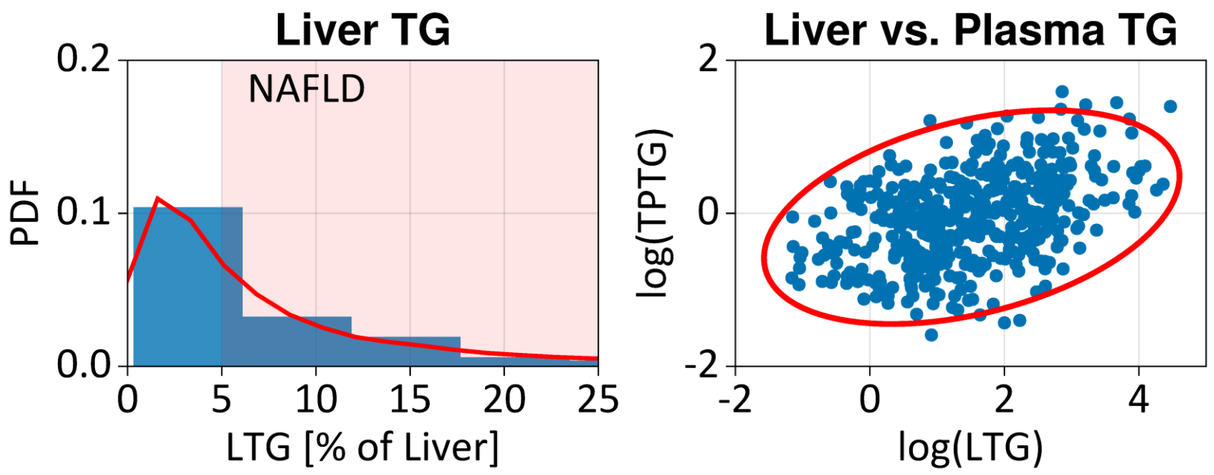
## DISTRIBUTION AND COMPARISON OF VPOP PLASMA BIOMARKERS TO DATA

### UNIVARIATE (TOP) AND BIVARIATE (BOTTOM) WITH DATA



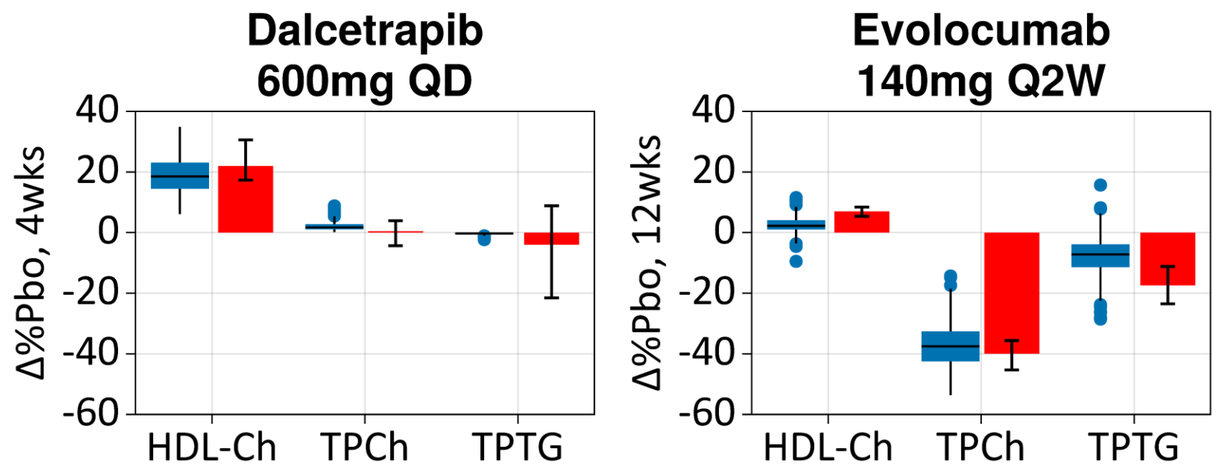

## LIVER TG AND NAFLD IN THE VPOP

### DIST. AT SS (LEFT) AND CORRELATION WITH TPTG (RIGHT)

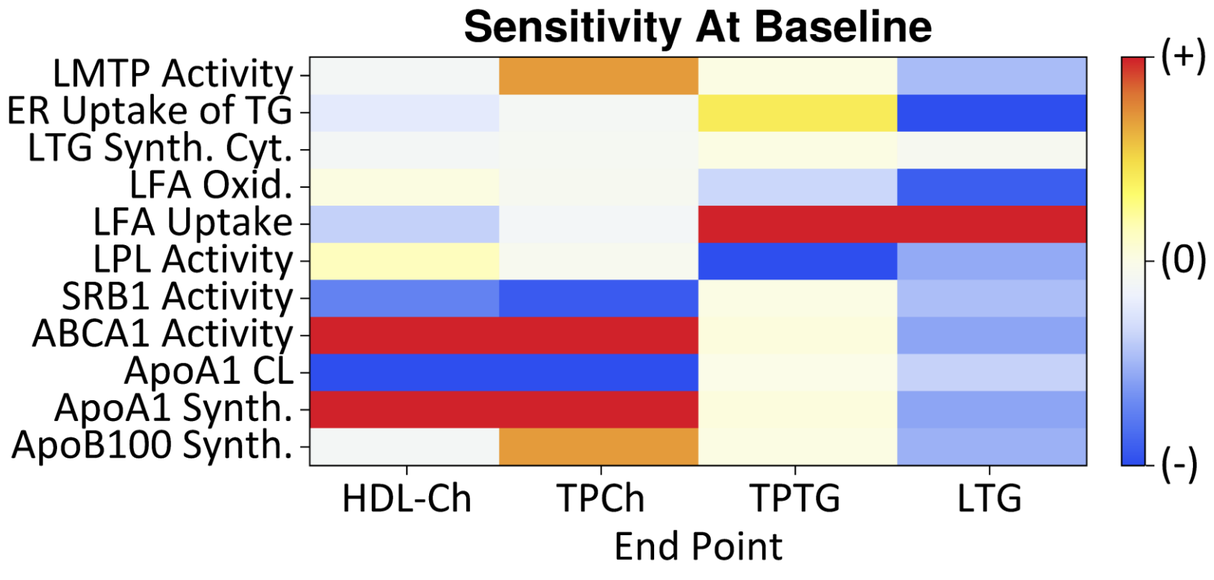



## VALIDATION: RESPONSE TO THERAPIES

### CETP INHIBITOR (LEFT) AND PCSK9 ANTIBODY (RIGHT)




## KEY DETERMINANTS OF CLINICAL ENDPTS.




## CONCLUSIONS AND REFERENCES

- The model successfully captures the steady state distributions of TPCh, HDL-Ch, TPTG, and LTG
- Simulations show a reasonable response of our Virtual Population to both CETPi and PCSK9ab
- Future work will consider special populations and additional regulators of interest (e.g., ApoCIII, ANGPTL4/5)

1. Arab et al. Ann. Rev. Path. 2018.
2. Stancu and Sima. J.Cell.Med. 2001.
3. Bergmark et al. Circulation. 2022.
4. Lu et al. CPT:PSP. 2015.
5. Rieger et al. Frontiers. 2022.
6. NHANES. 2017-2018.
7. Kotronen et al. JCI. 2007.
8. de Grooth et al. Circulation. 2002.
9. Zhang et al. BMC Med. 2015.