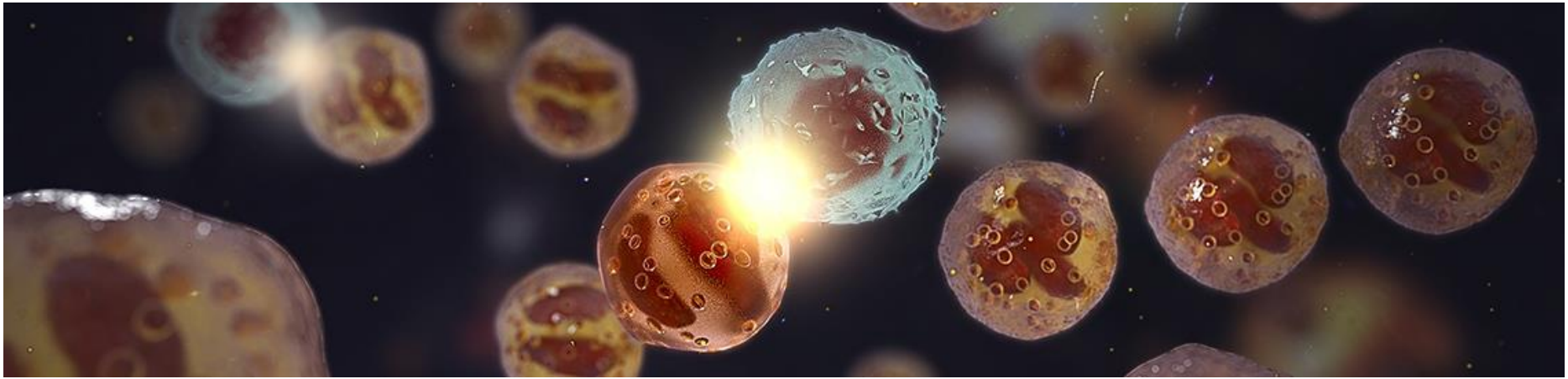
A Mechanistic Model of Lipoprotein Metabolism and Kinetics for Cardiovascular Disease Targets

James Lu

ASCPT 2016, San Diego

March 2016

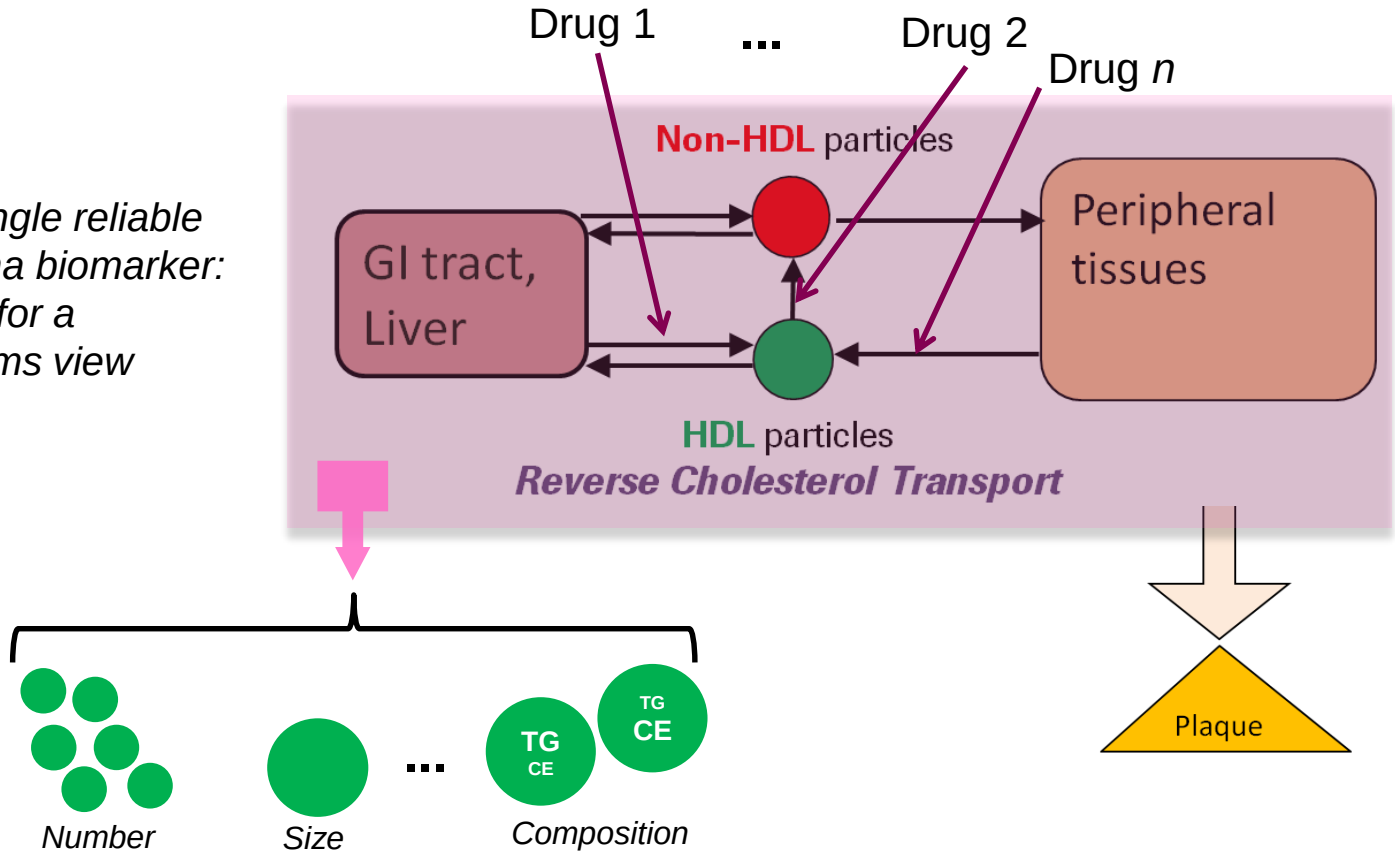


Outline

- Why platform models?
- Case studies: drug development & scientific impacts
- Considerations in platform building
- Disease platforms in drug safety

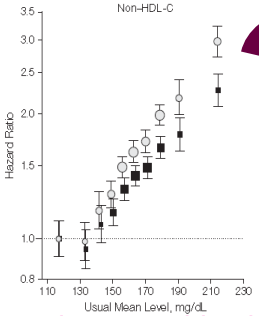
Challenge: assessing Reverse Cholesterol Transport

No single reliable plasma biomarker: need for a systems view

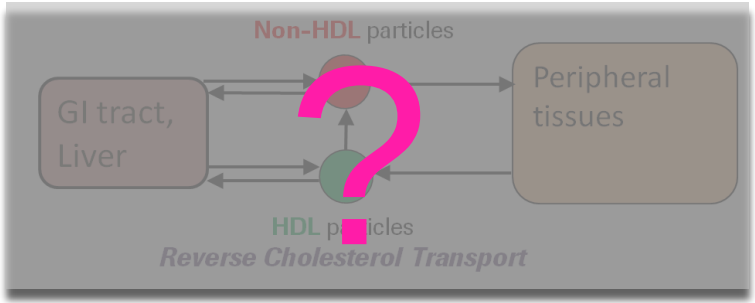


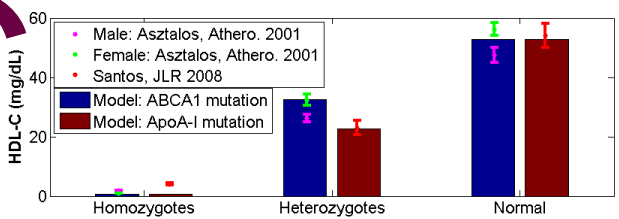
The case for an integrative platform model

- Individual data sets can be perplexing to understand in isolation
- System feedbacks can be pieced together from multiple data sources/projects

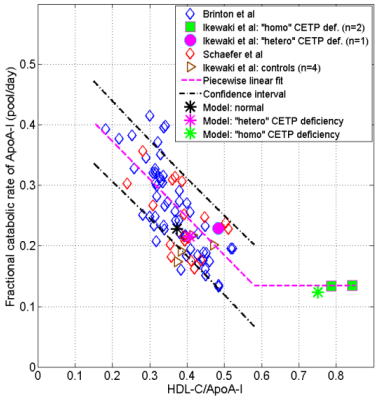


Disease epidemiology

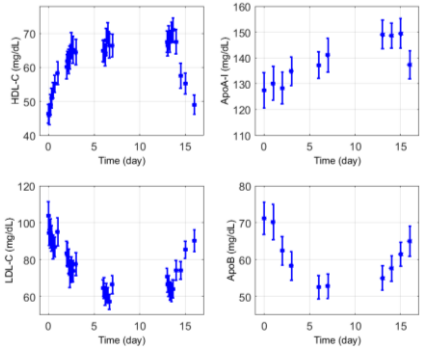




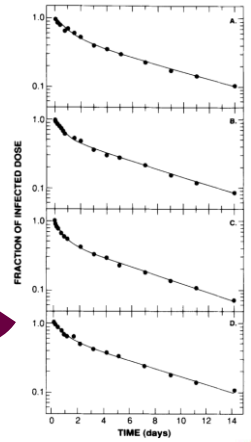
Inborn errors of lipid metabolism



Correlations in populations



Drug data



Tracer kinetics studies

Platform models as knowledge repository

Tracer kinetics models

Initial platform model

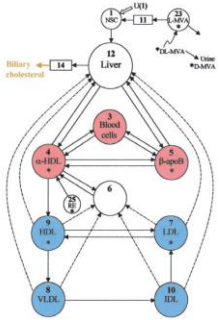
Refined platform model

State-of-art simulatable repository

- In-vitro data
- Mutation phenotypes
- ...

- MAD data

Bayesian update from prior knowledge



Schwartz et al, JLR (2004)

Evaluation of HDL-modulating interventions for cardiovascular risk reduction using a systems pharmacology approach[S]

Kapil Gadkar,[1,2,*] James Lu,[1,†] Srikumar Sahasranaman,* John Davis,* Norman A. Mazer,[†] and Saroja Ramanujan*

ORIGINAL ARTICLE

Analysis of "On/Off" Kinetics of a CETP Inhibitor Using a Mechanistic Model of Lipoprotein Metabolism and Kinetics

J Lu[1]*, Y Cleary[1], C Maugeais[2], CI Kiu Weber[3] and NA Mazer[1]

OPEN ACCESS Freely available on

An *In-Silico* Model of Lipoprotein Metabolism and Kinetics for the Evaluation of Targets and Biomarkers in the Reverse Cholesterol Transport Pathway

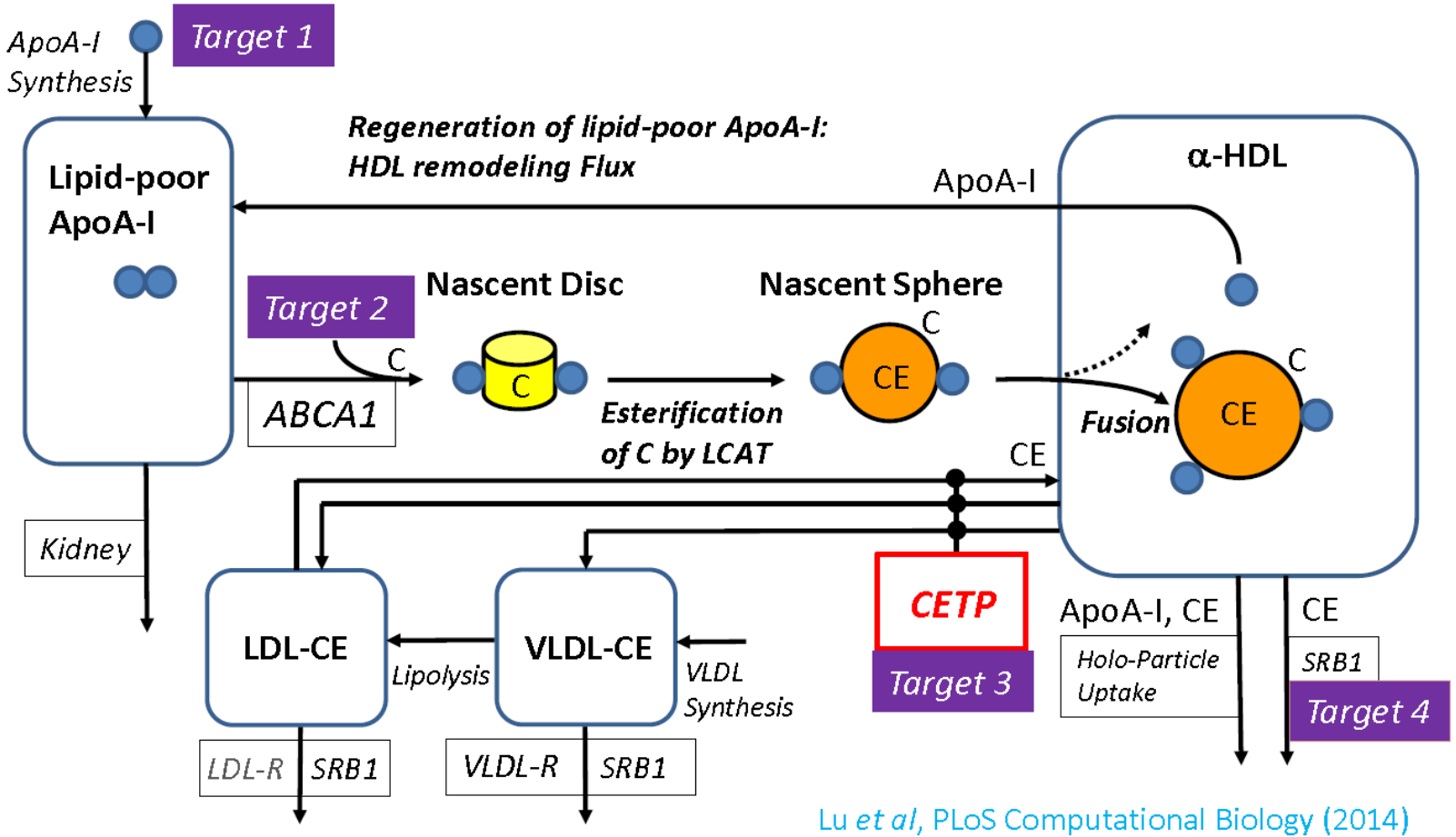
James Lu[1]*, Katrin Hübner[2], M. Nazeem Nanjee[3], Eliot A. Brinton[4], Norman A. Mazer[1]

REVIEW

For reprint orders, please cont

Mathematical models of lipoprotein metabolism and kinetics: current status and future perspective

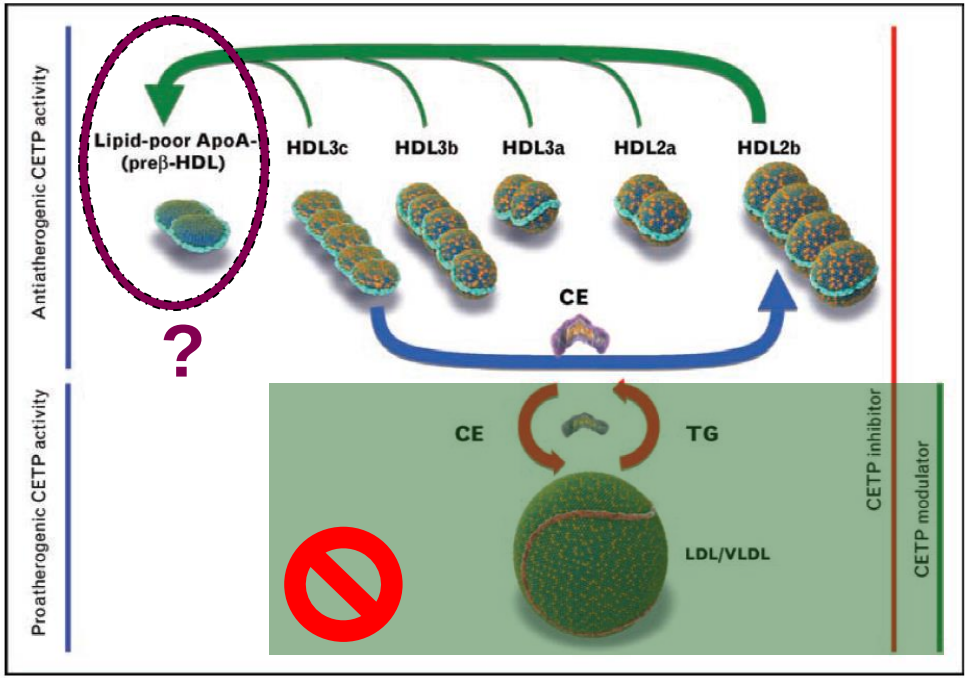
Schematic diagram of the initial LMK model



Lu *et al*, PLoS Computational Biology (2014)

Use model to test hypothesis on the role of CETP

- Role of CETP in the generation of lipid-poor ApoA-I (pre-β HDL):
  – Optimal level/schedule of CETP inhibition to maximize anti-atherogenic activity?



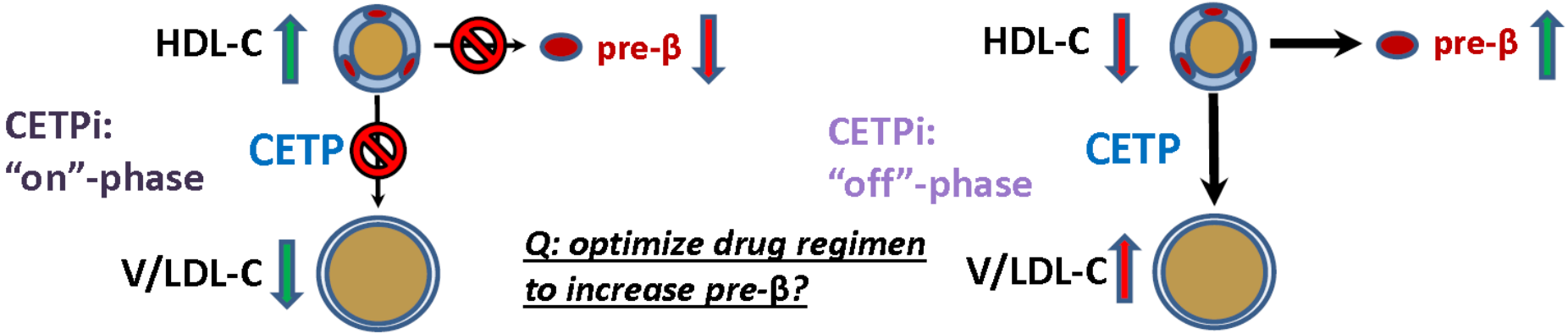
Evaluate the hypothesis in view of surface/volume consideration of HDL particles

Niesor, Curr Opin Lipidol. 2011

Evaluating “on/off” hypothesis of a CETP inhibitor

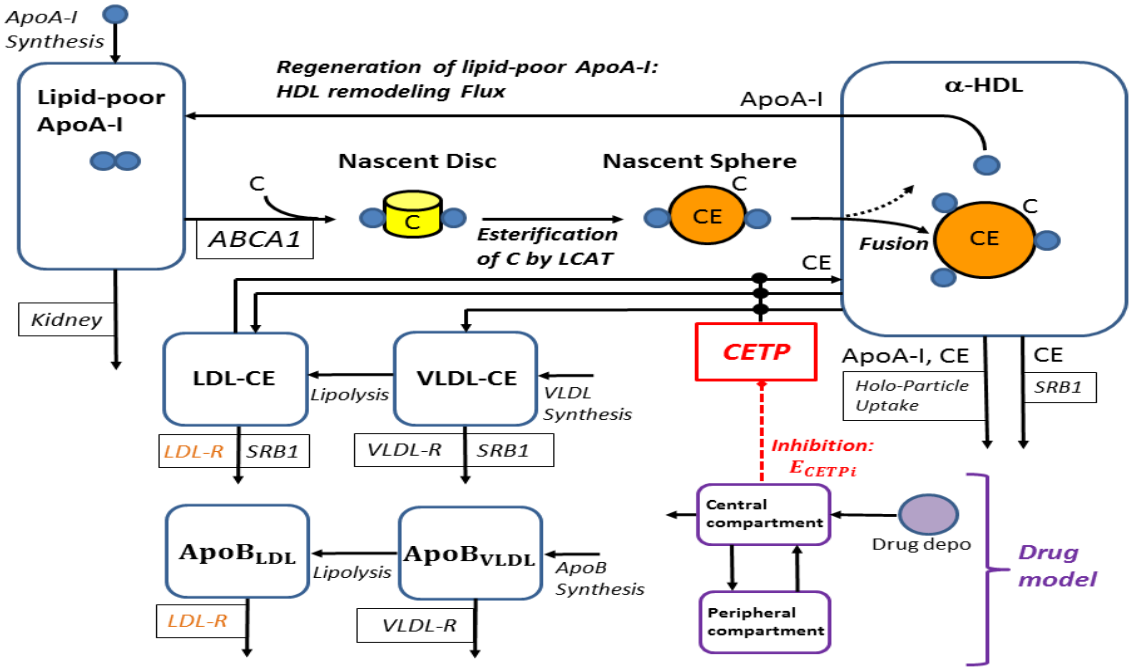
- Plasma protein **CETP** is a key mediator in cholesterol metabolism:
  - Transfer of cholesteryl ester (CE) from **HDL** to **LDL** and **VLDL**

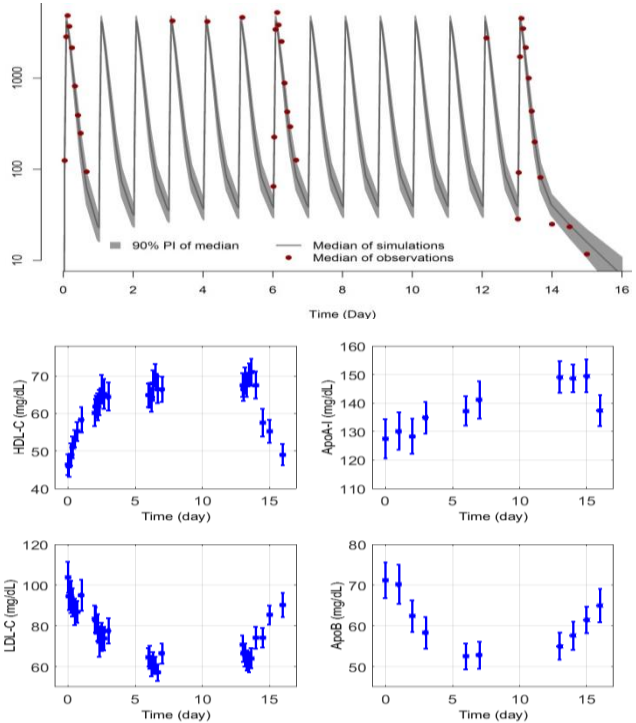
  - Is there a way to optimize schedule?



Refine model using newly acquired clinical data

- Addition of modules to describe data
- Pharmacology model: PK parameters
- Refine parameter values from new data



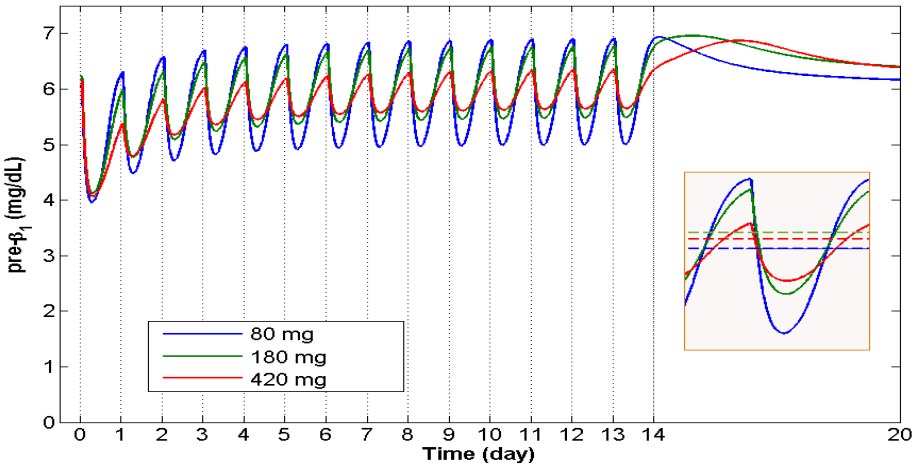


Lu *et al*, CPT:Pharmacometrics and Systems Pharmacology (2015)

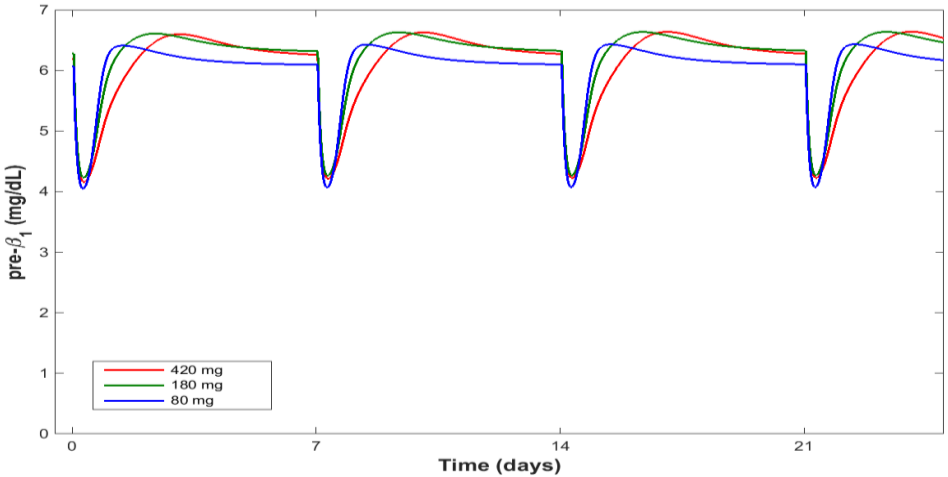
Evaluating “on/off” hypothesis of a CETP inhibitor

- Model prediction for pre-β dynamics:
  - Large amplitude oscillations; no net increase when averaged over time

Daily dosing



Weekly dosing



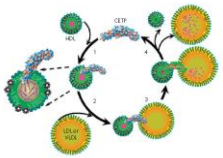
Lu *et al*, CPT:Pharmacometrics and Systems Pharmacology (2015)

HDL interventions beyond CETP

- Failures of CETP inhibitors to impact CVD risk

CETP inhibitors boost 'good' cholesterol to no avail

Eli Lilly's decision to stop phase 3 studies of its cholesteryl ester transfer protein (CETP) inhibitor evacetrapib in patients with atherosclerotic cardiovascular disease adds another expensive, late-stage failure to a drug class that has confounded the pharma industry's expectations for a decade. This drug class was once bullishly pursued by big pharma originally because its effects on raising high-density lipoprotein cholesterol (HDL-c) were considered to be comple-



sensitivity for weaker efficacy signals, but it has a longer follow-up period, of four years versus 2.75 years for evacetrapib. The Merck study also excluded patients with acute coronary syndrome—heart attack or unstable angina—whereas Lilly's ACCELERATE study did not.

REVEAL passed an interim futility test in November, but the study's results are not due out until early 2017. Many critics have already written off its prospects, however, pointing to

Nat. Chem. Biol. 8, 342–349 (2012)

Sheridan, Nat. Biotech. (2016)

Cholesteryl ester transfer protein: ace of spades, queen of hearts, or the joker?

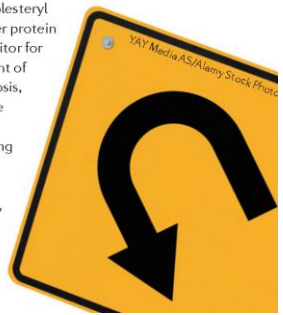
*Norman E. Miller**

Magdalen College, Oxford University, Oxford, UK

Miller, Frontiers in Pharmacology (2015)

CETP set-back, again

Eli Lilly halted a Phase III trial of its evacetrapib after an interim analysis found that the lipid-modulating drug had a low probability of being effective. Lilly is now the third big pharma company to scrap a Phase III cholesteryl ester transfer protein (CETP) inhibitor for the treatment of atherosclerosis, reducing the odds for the few remaining companies, including Merck & Co., that are still invested in the space. The first high-profile



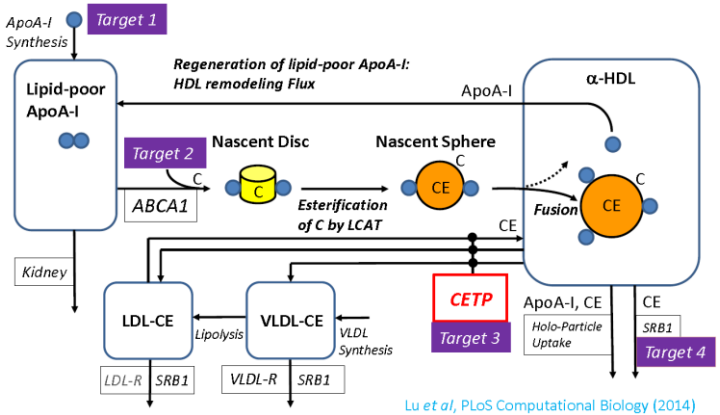
Mullard, Nat. Rev. Drug Disc. (2015)

- What other interventions could impact not only HDL-C but also RCT rate?
  - Correlation vs causal
  - Need systems understanding

Evaluation of HDL-modulating interventions for cardiovascular risk reduction using a systems pharmacology approach[5]

Kapil Gadkar,[1,2,*] James Lu,[1,†] Srikumar Sahasranaman,[*] John Davis,[*] Norman A. Mazer,[†] and Saroja Ramanujan[*]

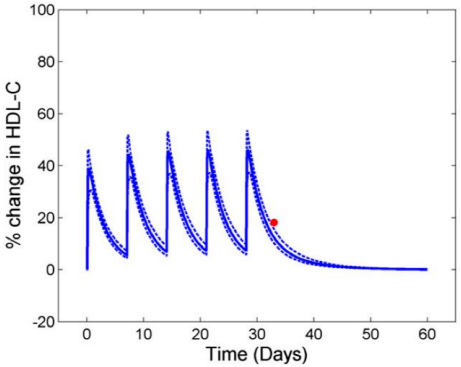
Genentech Research and Early Development,[*] South San Francisco, CA; and Roche Pharma Research and Early Development,[†] Clinical Pharmacology, Disease Modeling Group, Roche Innovation Center Basel, Basel, Switzerland

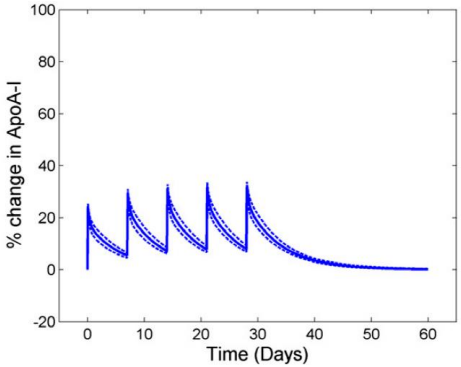


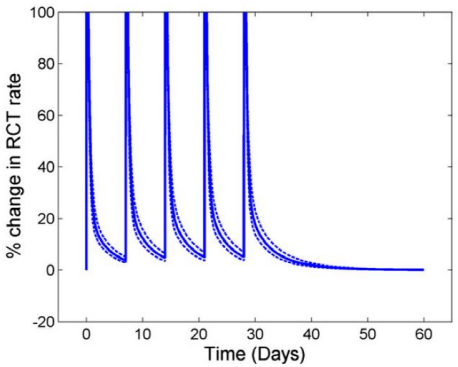
Lu *et al*, PLoS Computational Biology (2014)

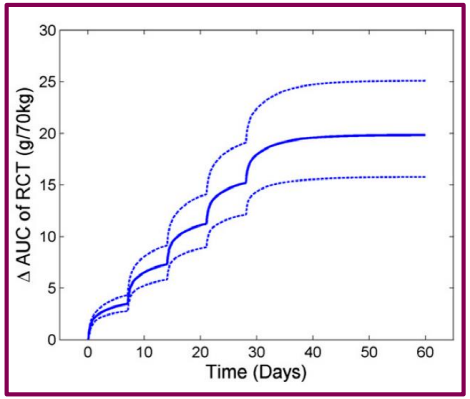
Supporting decisions: evaluation of HDL interventions

- Simulation of reconstituted HDL infusions

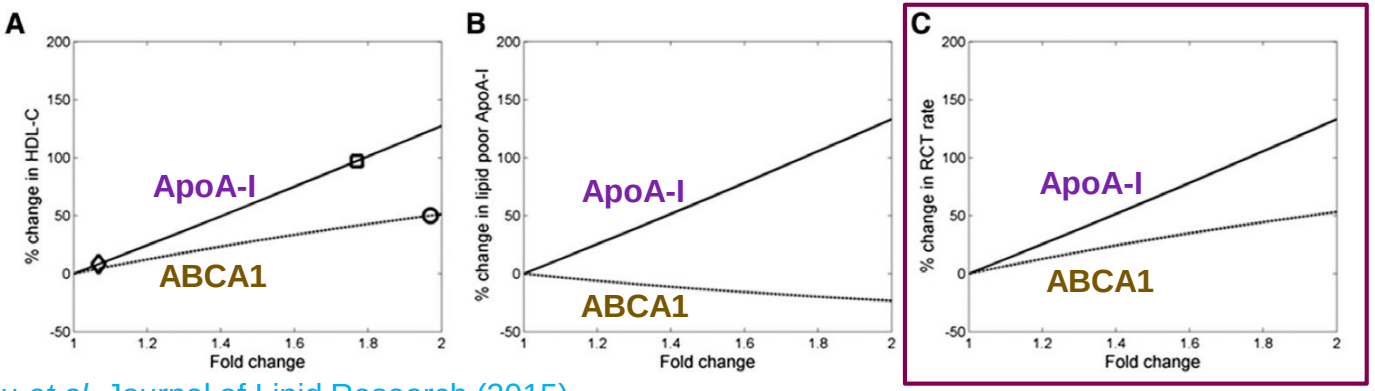






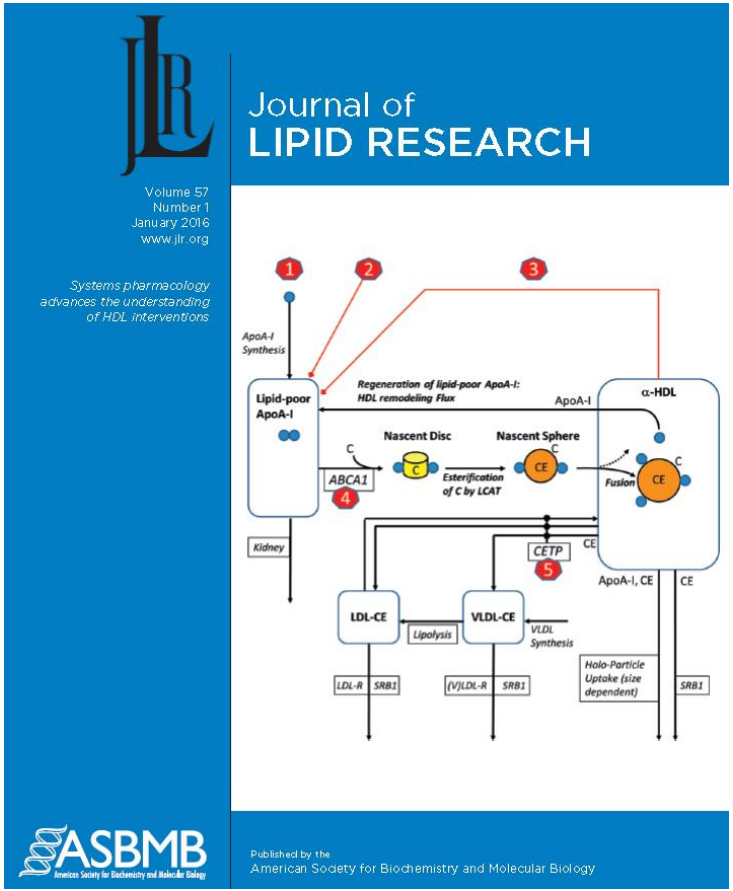


- Differentiation between up-regulating ApoA-I or ABCA1 on the RCT rate?

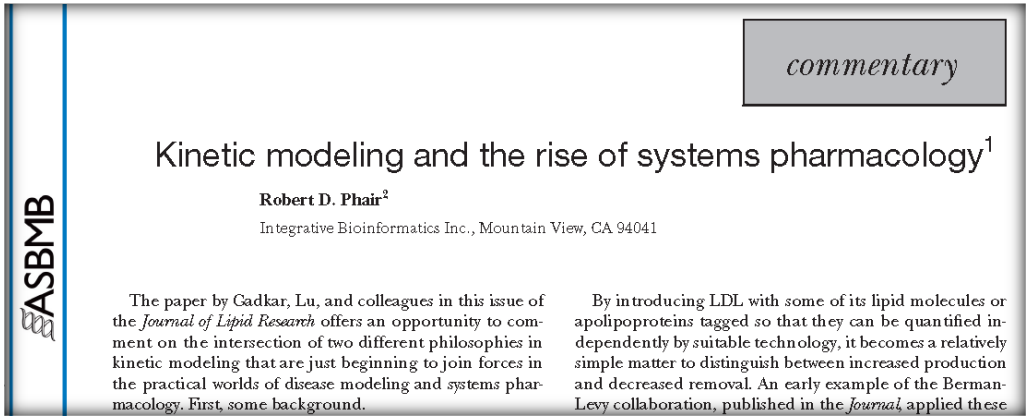


Gadkar & Lu *et al*, Journal of Lipid Research (2015)

Scientific impact: evaluation of HDL interventions



- Getting onto the cover of Journal of Lipid Research (Jan 2016):
  - *Systems pharmacology advances the understanding of HDL interventions*


commentary

Kinetic modeling and the rise of systems pharmacology[1]

Robert D. Phair[2]
Integrative Bioinformatics Inc., Mountain View, CA 94041

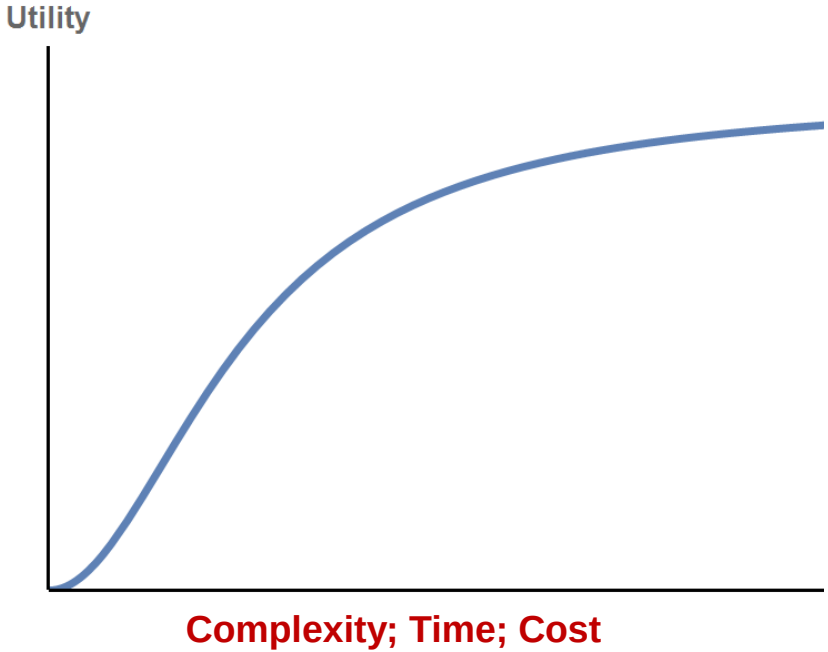
The paper by Gadkar, Lu, and colleagues in this issue of the *Journal of Lipid Research* offers an opportunity to comment on the intersection of two different philosophies in kinetic modeling that are just beginning to join forces in the practical worlds of disease modeling and systems pharmacology. First, some background.

By introducing LDL with some of its lipid molecules or apolipoproteins tagged so that they can be quantified independently by suitable technology, it becomes a relatively simple matter to distinguish between increased production and decreased removal. An early example of the Berman-Levy collaboration, published in the *Journal*, applied these

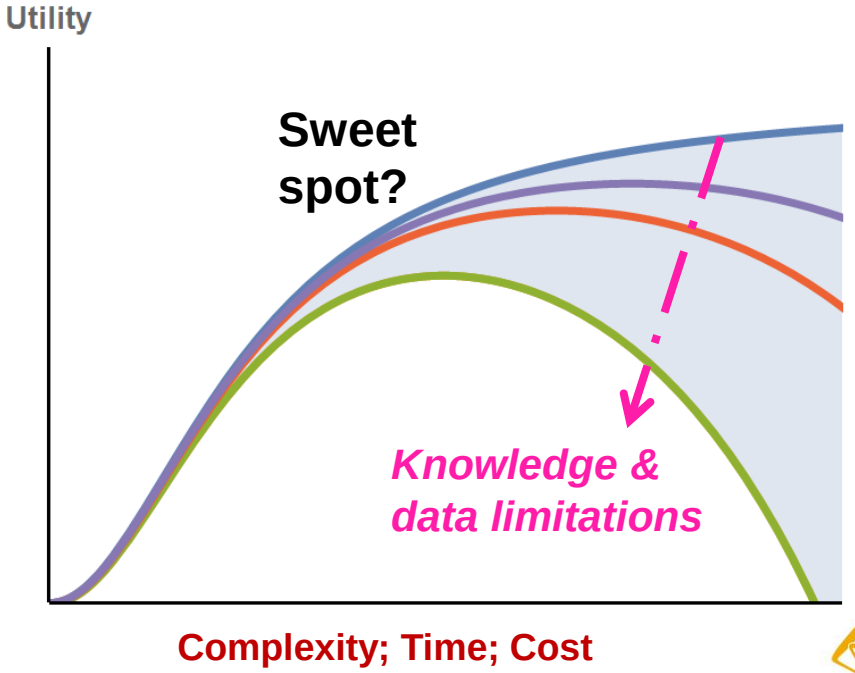
- Commentary by R. D. Phair:
  - "*It behooves all of us to challenge this model with additional protocols and data sets.*"

Considerations in platform building

- Ideal scenario:
  - Detailed biological knowledge
  - Rich, high quality data

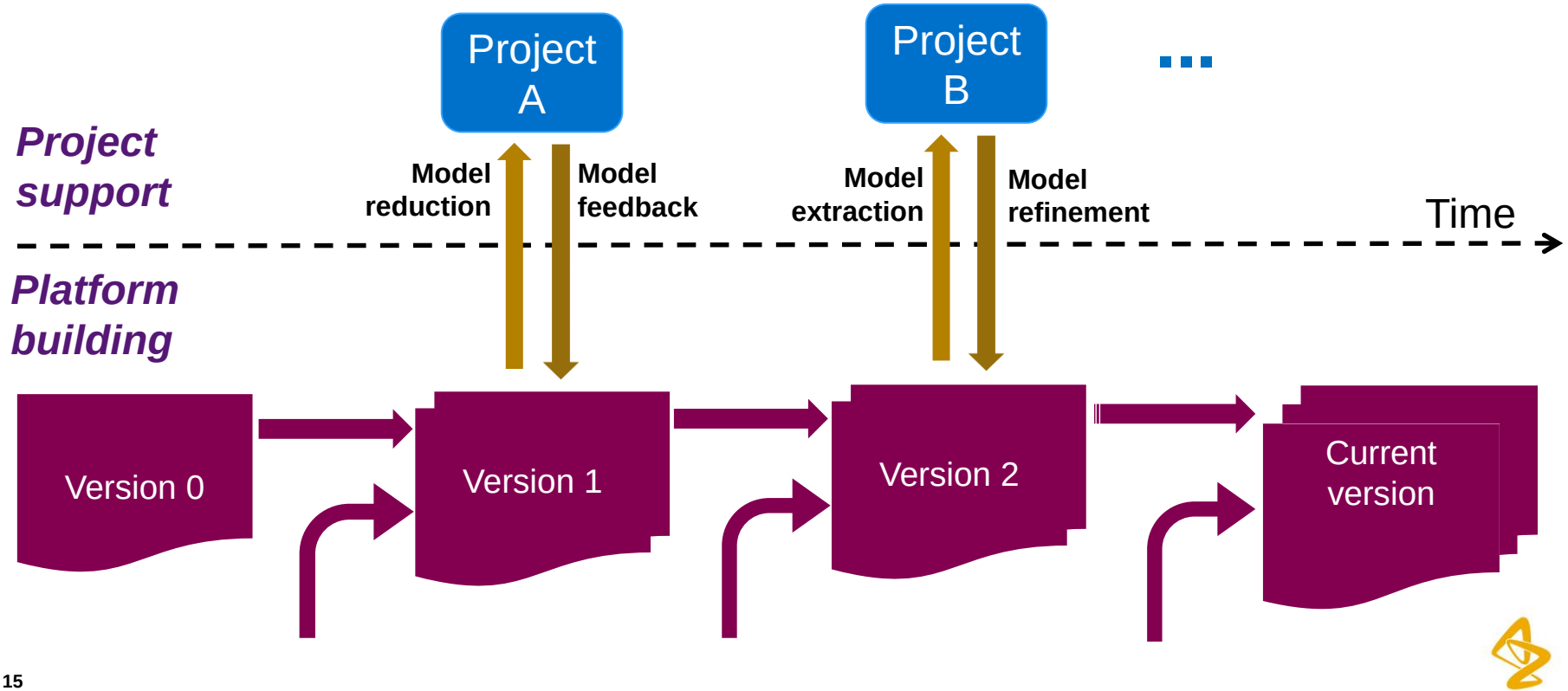


- Real-world scenario:
  - Gaps in biological knowledge
  - Sparse, noisy data



Development and use of platform models

- Platform building and project support can go hand-in-hand

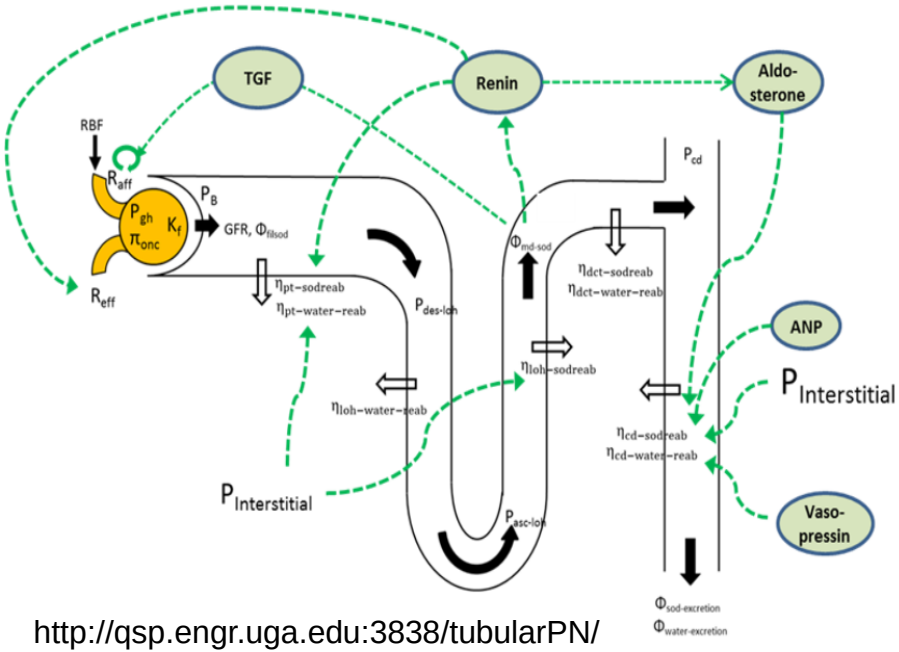


Disease platform for safety assessment: kidney injury

- How is the risk of drug-induced kidney injury affected by pathophysiology (e.g., chronic kidney disease)?

- Learn across compounds: characterize system properties via different nephrotoxicity patterns

- Project the impacts on kidney function to patient populations (nephron number, GFR, filtration coefficient, ...)



http://qsp.engr.uga.edu:3838/tubularPN/

Yeshi Gebremichael, Melissa Hallow (Univ. of Georgia)
Harish Shankaran, Jay Mettetal (Drug Safety & Metabolism, AZ)
Gabriel Helmlinger (Quantitative Clinical Pharmacology, AZ)

Acknowledgement

Roche

- N. Mazer
- C. Maugeais
- Y. Cleary
- C. Kiu-Weber
- D. Schwab
- C. Diack
- C. Weber
- J.-E. Charoin
- R. Peck

Genentech

- K Gadkar
- S. Sahasranaman
- S. Ramanujan

Astrazeneca

- H. Shankaran
- J. Mettetal
- T. Collins
- R. McDougall
- T. Yamamoto
- R. Jansson-Loefmark
- G. Helmlinger

Academic

- K. Huebner
- M. Nanjee
- E. Brinton
- N. Miller
- Y. Gebremichael
- M. Hallow

Confidentiality Notice