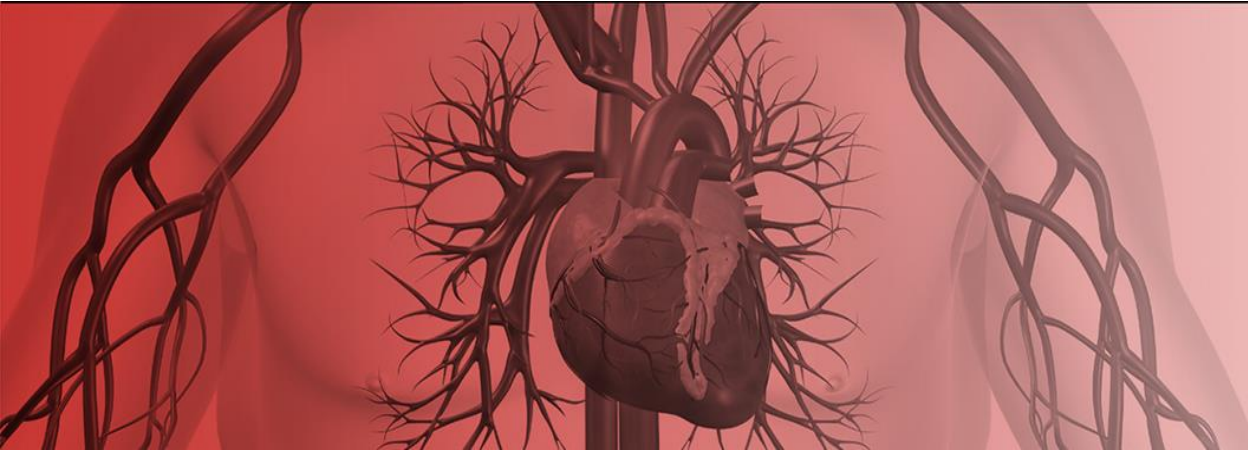

Application of a mechanistic, systems model of lipoprotein metabolism and kinetics (LMK) to target selection and biomarker identification in the reverse cholesterol transport (RCT) pathway

James Lu & Norman Mazer

Clinical Pharmacology, F. Hoffman-La Roche

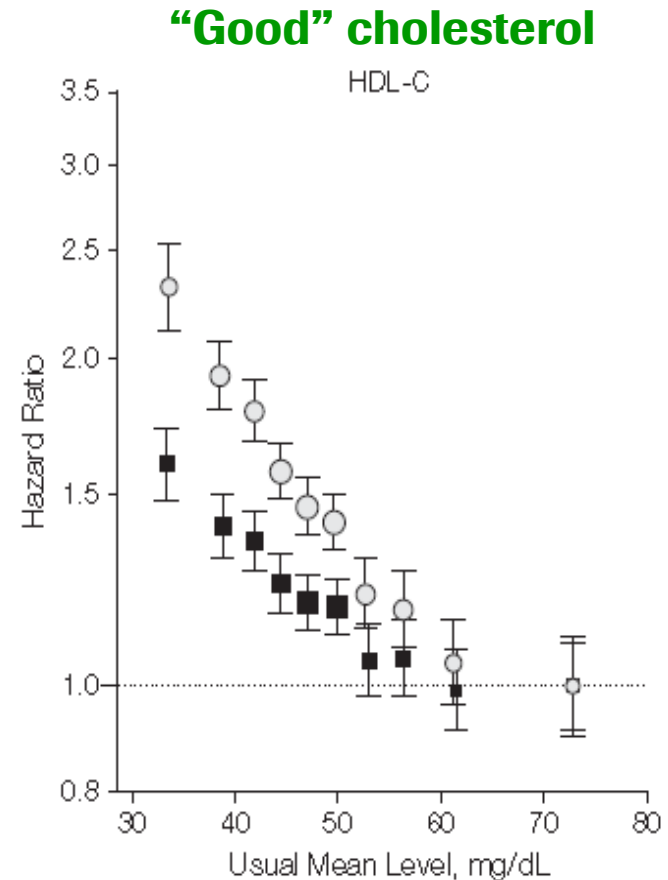
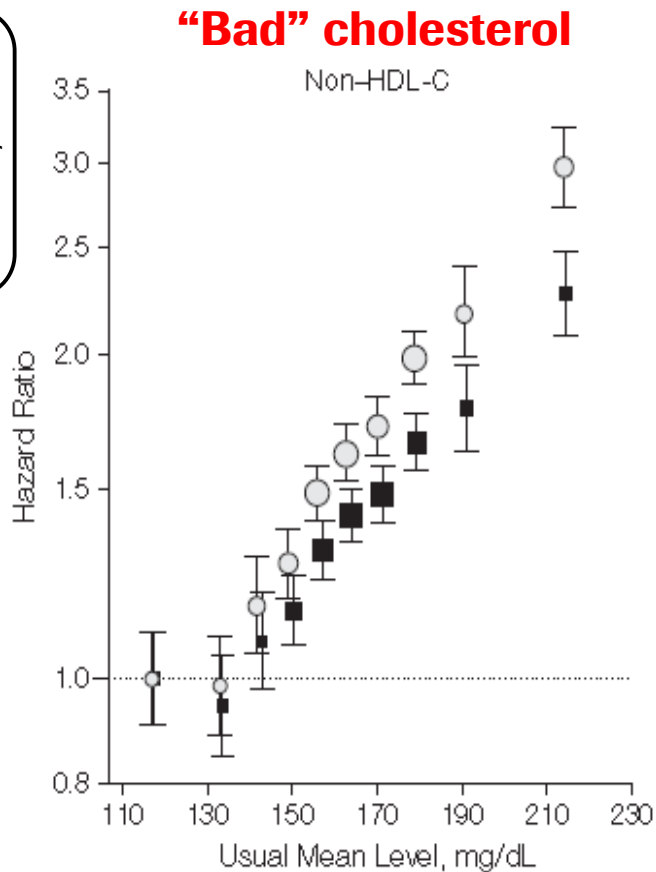
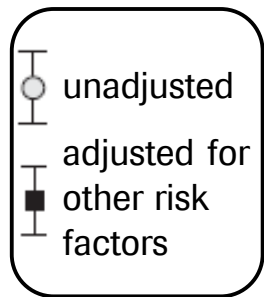


Relationship of cardio-vascular risk to cholesterol levels

FROM EPIDEMIOLOGY TO TARGETS

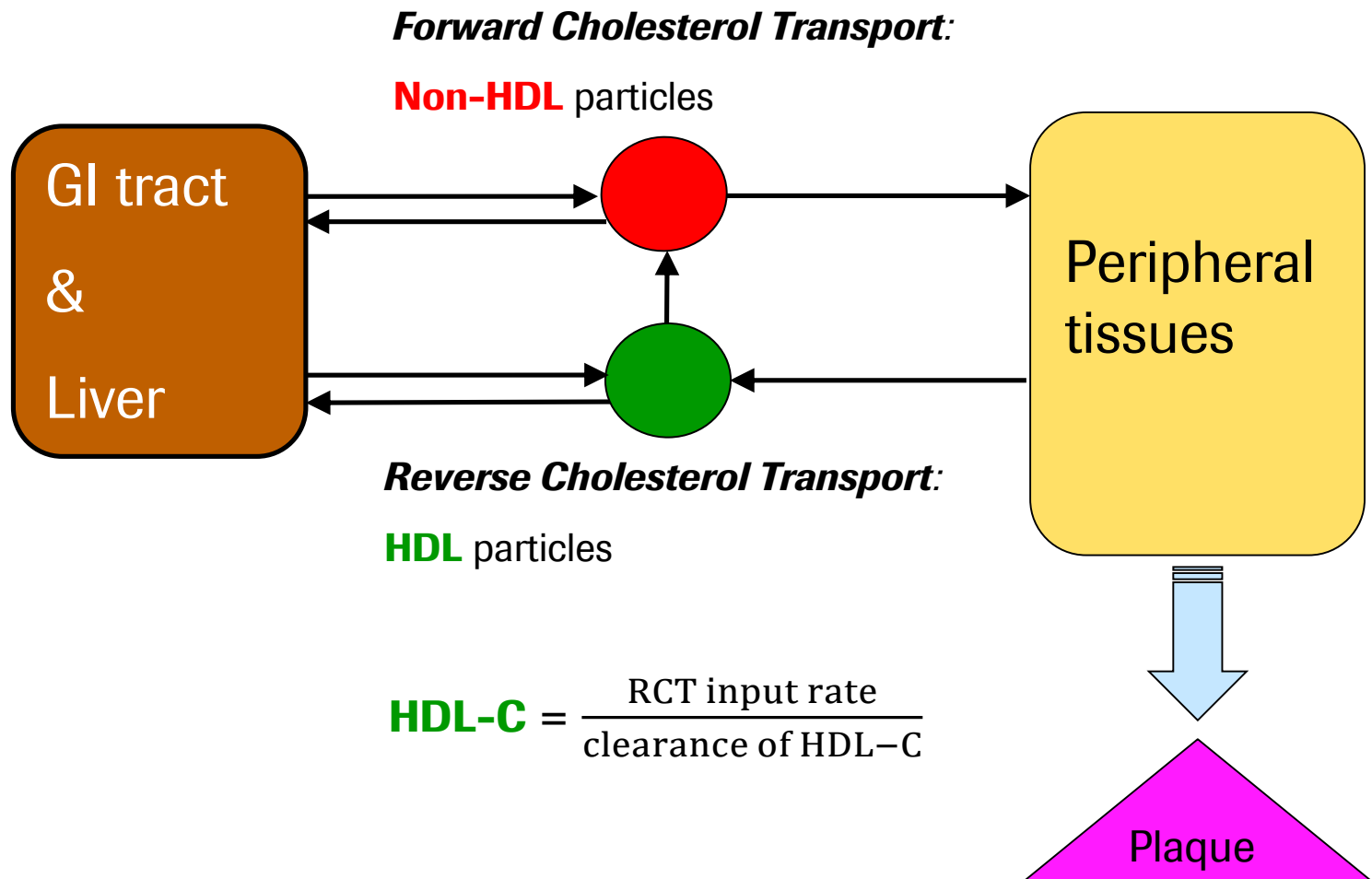
HDL-C and cardio-vascular risk

- Association of cholesterol levels with coronary heart disease
 - Total-C = **non-HDL-C** + **HDL-C**



Reverse Cholesterol Transport: linking HDL-C to cardio-vascular risk

- Reverse cholesterol transport (RCT): cholesterol removal from peripheral tissues (e.g., macrophages) back to the liver, mediated by HDL particles



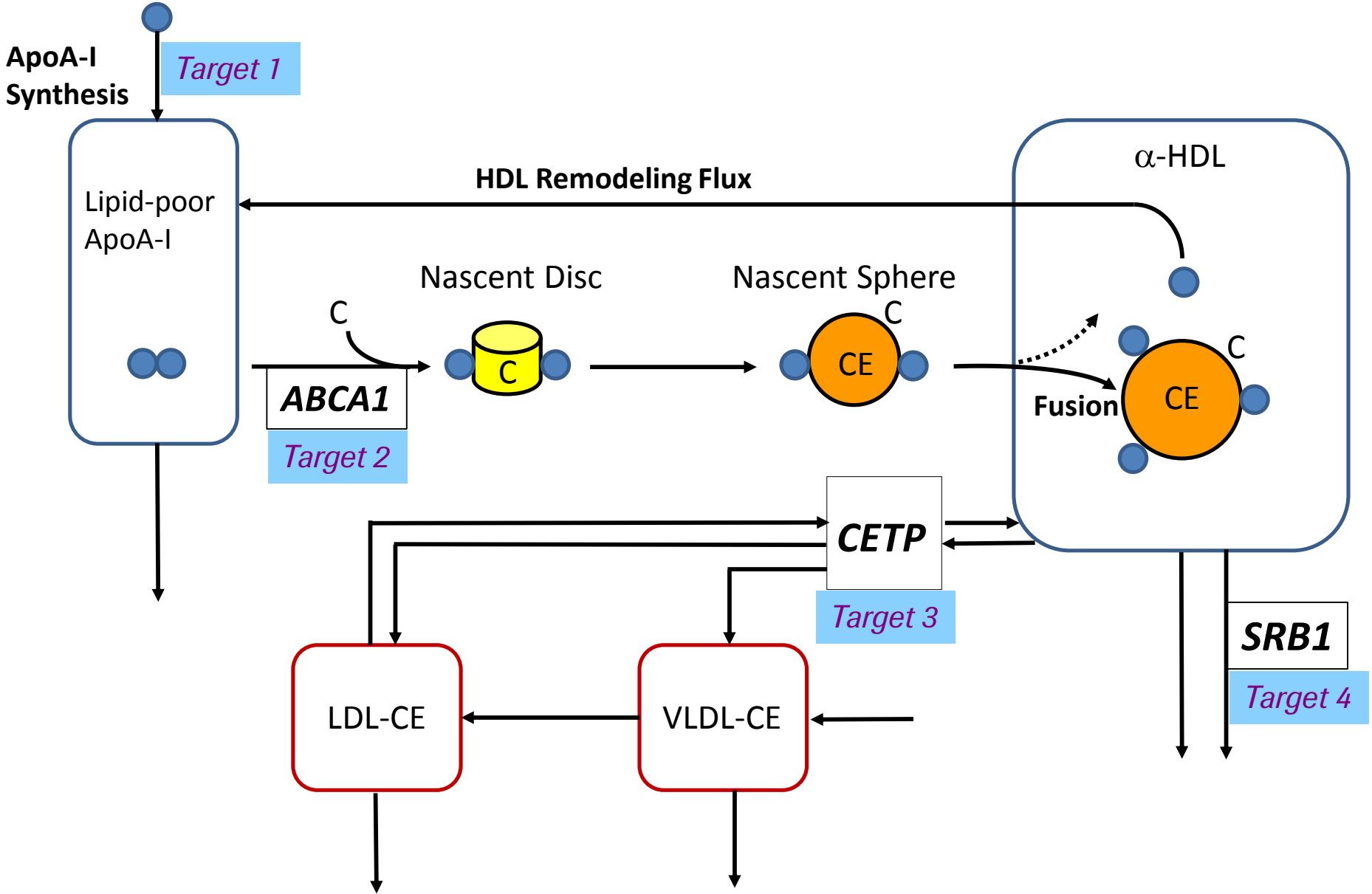
Can the promise of HDL-C raising therapies be fulfilled?

- Unexpected failures of HDL-C raising therapies
 - CETP inhibitors (Torcetrapib, Dalcetrapib)
 - Niacin (HPS2-THRIVE)
- Targeting HDL-C levels: mis-understanding of the connection between HDL-C and CV risk?
 - HDL functionality rather than quantity: e.g., RCT rate
- What conclusions should be drawn for other targets in the pathway?

Pathway representation & quantification

MODEL DEVELOPMENT & CALIBRATION

Schematic diagram: targets in pathway



Model calibration

- Bayesian methodology: *maximum a posteriori* (MAP)
 - Prior estimates (k_{prior}) + calibration data (d) \rightarrow posterior values (k_{MAP})
 - Nonlinear least squares minimization:

$$\min_k (k - k_{prior})^T C_k^{-1} (k - k_{prior}) + (G(k) - d)^T C_d^{-1} (G(k) - d) \rightarrow k_{MAP}$$

Where, k_{prior} : prior parameter estimate;

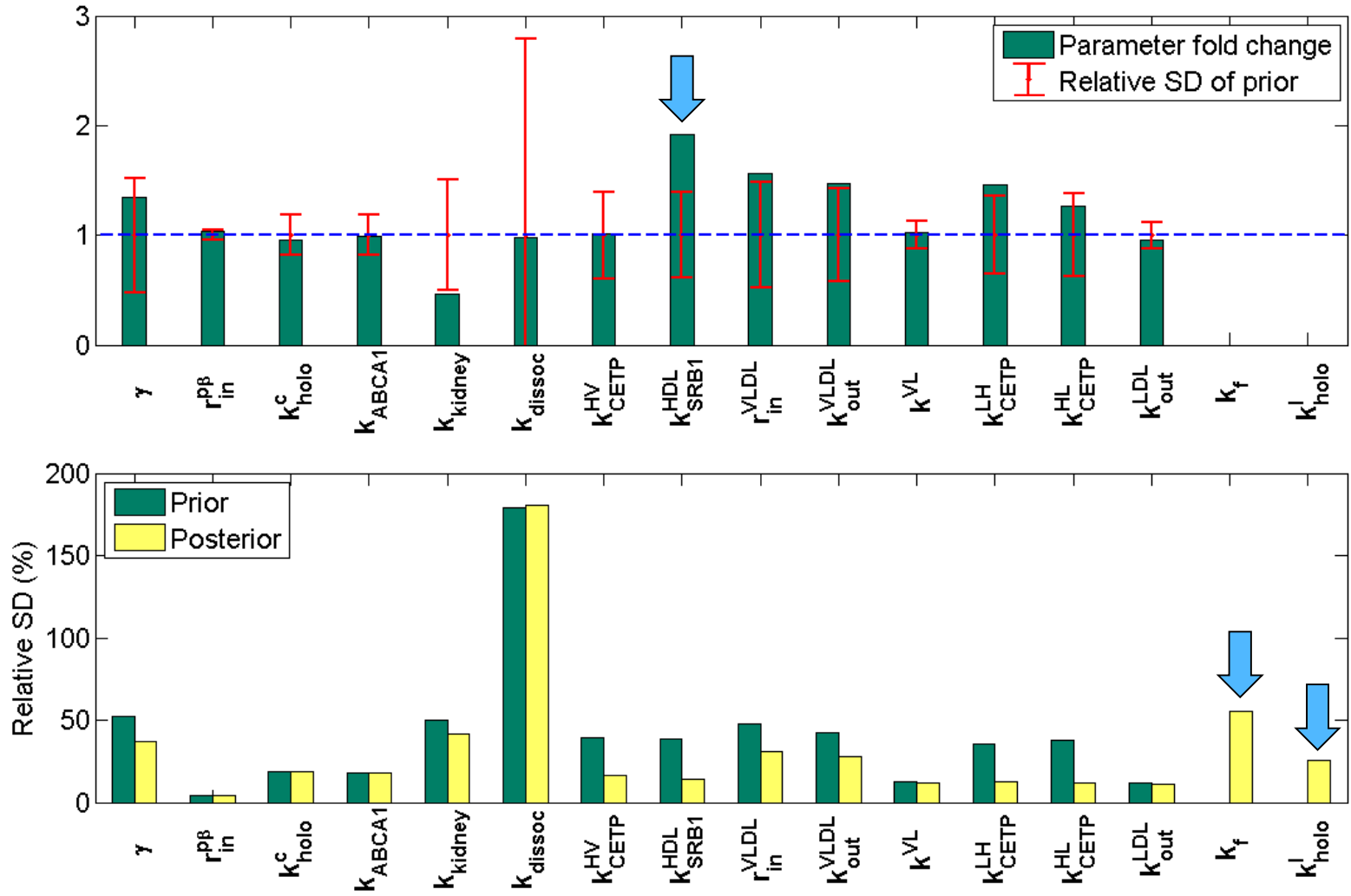
C_k and C_d : covariances for parameters and data (with adjustments);

$G(k)$: model simulation in reproducing data d .

- Prior estimates of parameters
 - Number of literature references: **11**
 - Informative priors: **14/16** parameters
- Calibration data
 - Number of literature references: **8**
 - Number of data values: **15**

Posterior parameter values and uncertainty

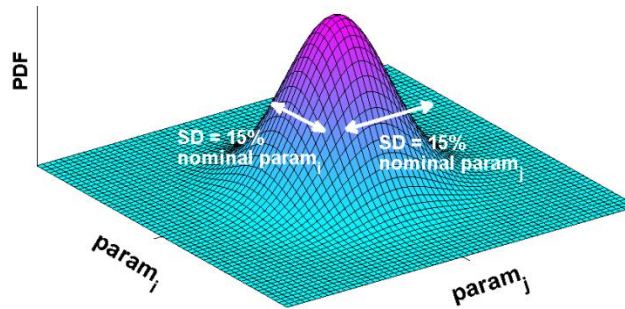
- Fold changes in posterior values and estimates of confidence intervals using Fisher Information Matrix



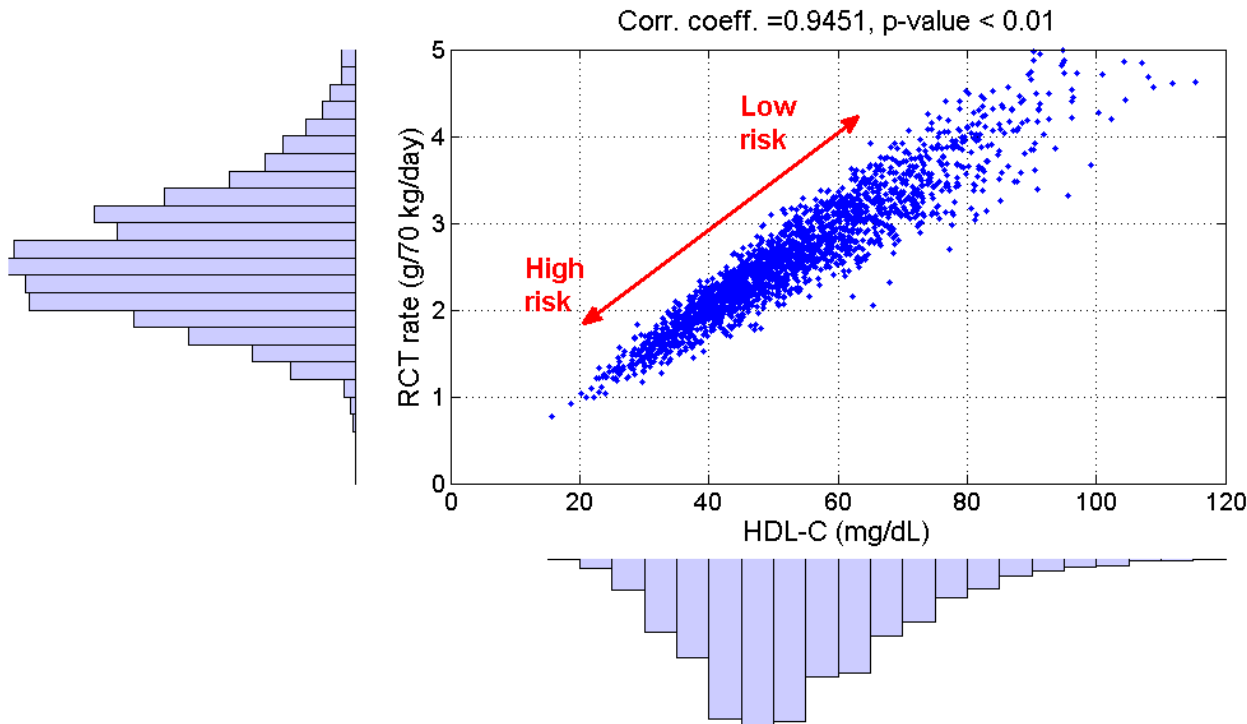
Correlation analysis using a virtual population



- Relationships between biomarkers can be studied within a *virtual population*



- Model offers an explanation for the association between HDL-C and CV risk



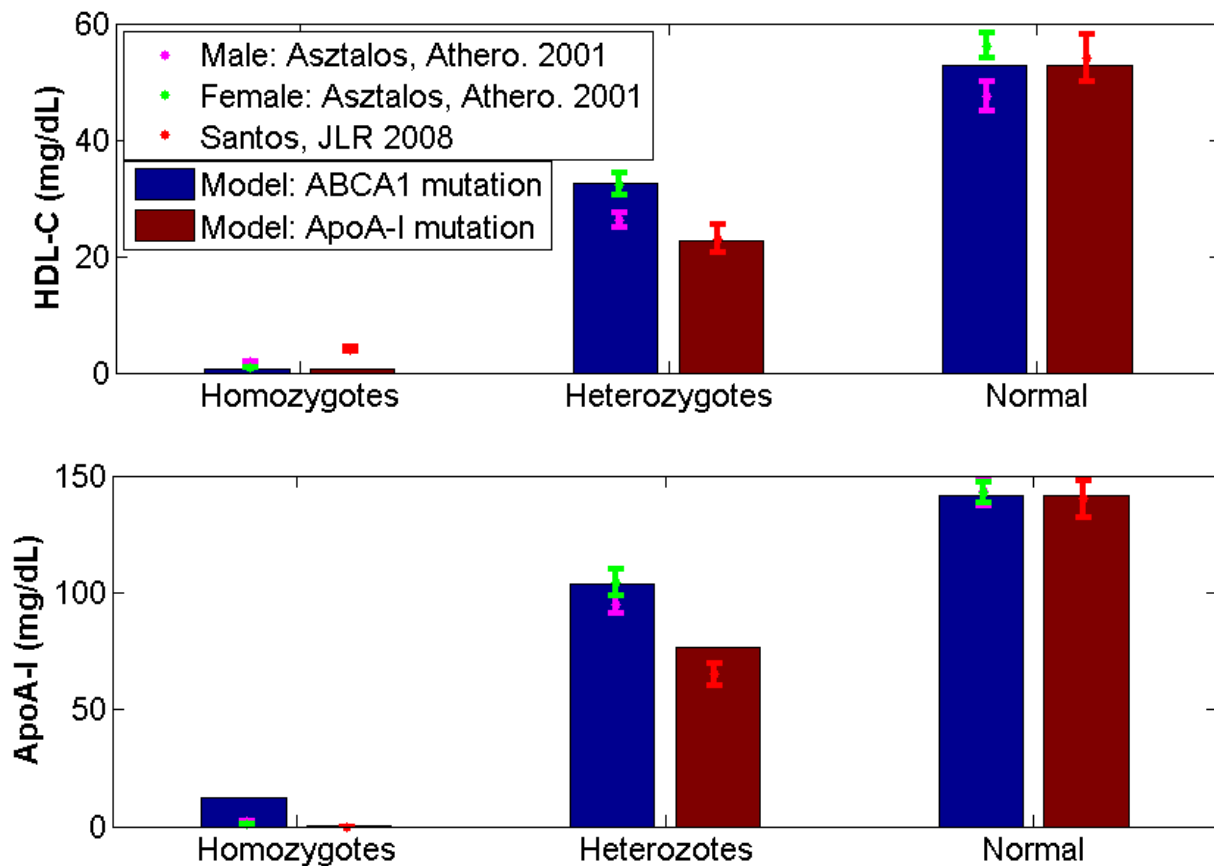
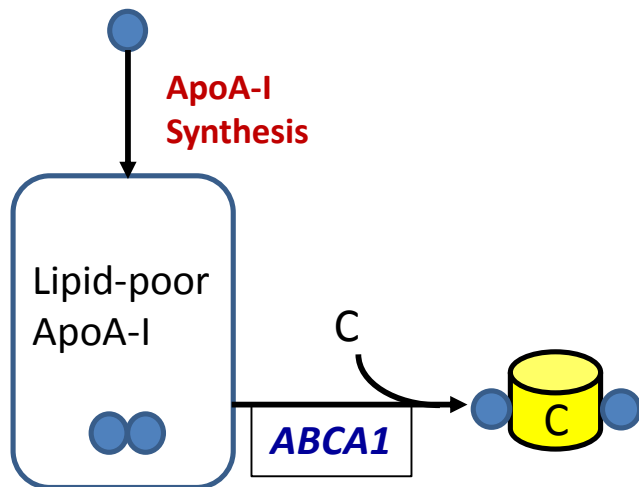
Assessment of HDL-C raising targets

TARGET MODULATION

Model validation on targets of interest

- **ApoA-I** and **ABCA1** are important targets in RCT pathway
 - Validate model by simulating **heterozygous** & **homozygous** mutations

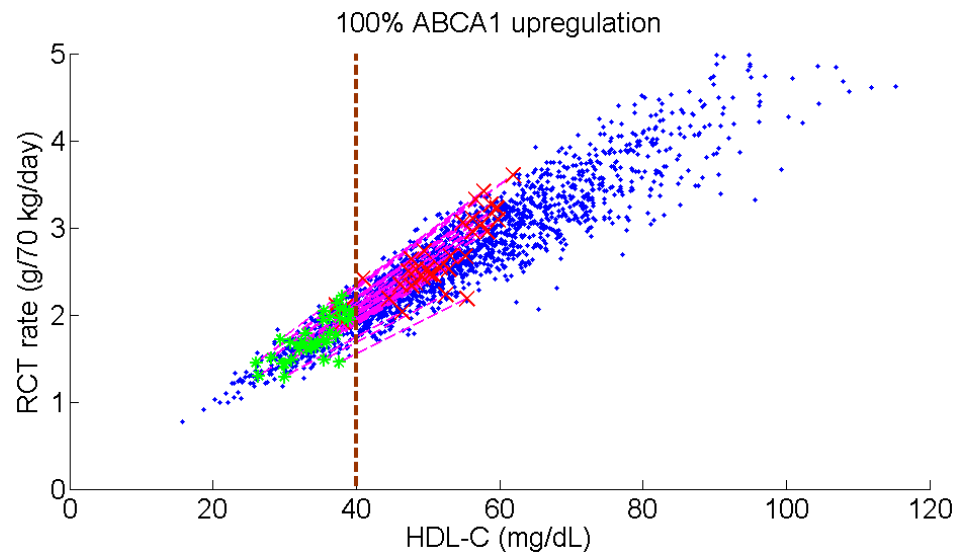
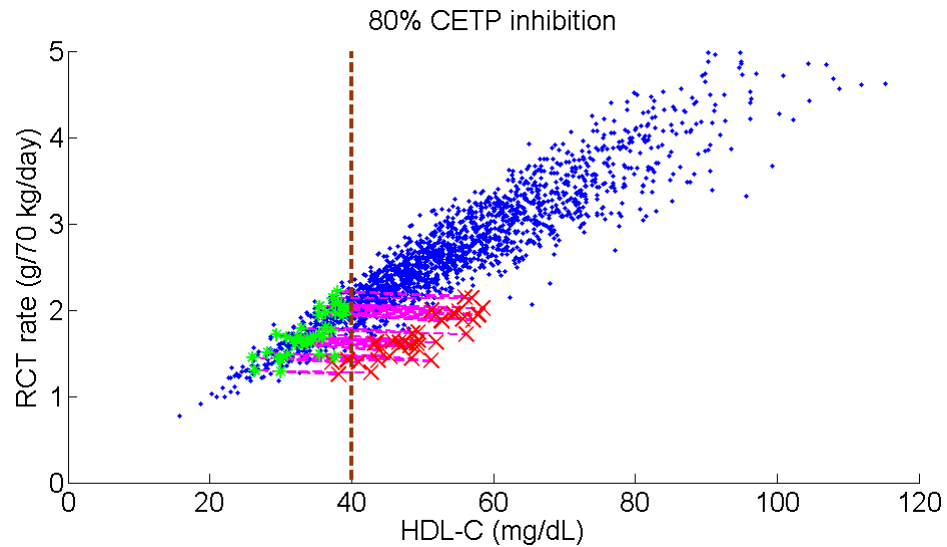
Set **ApoA-I synthesis** rate & **ABCA1 activity** to **50%** and **0%** of normal



Comparison of Target Modulations



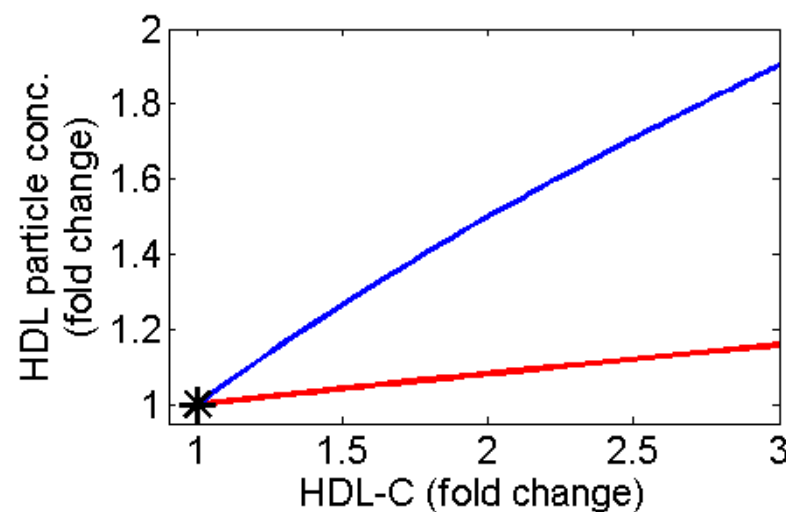
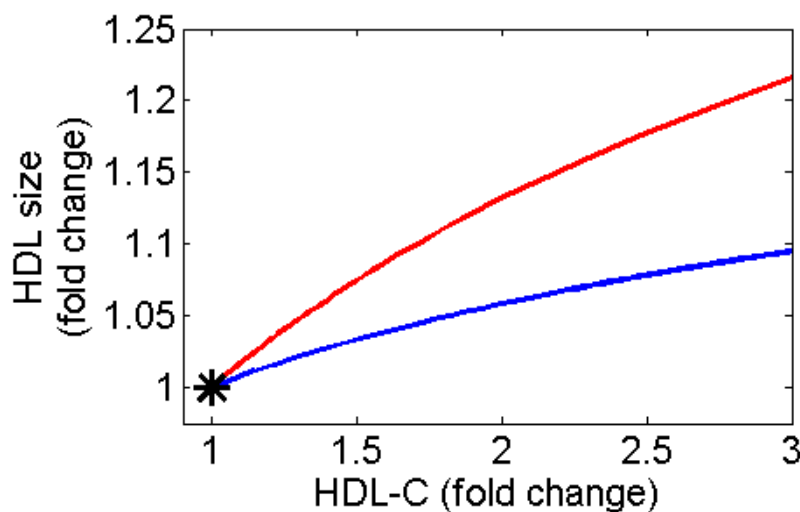
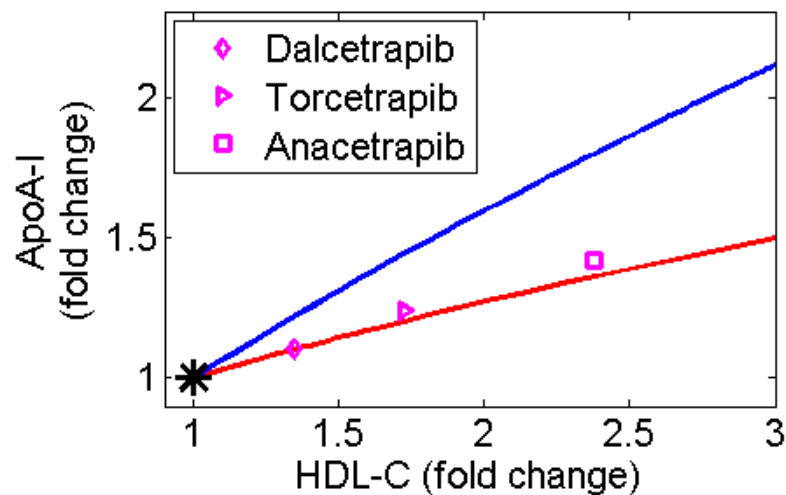
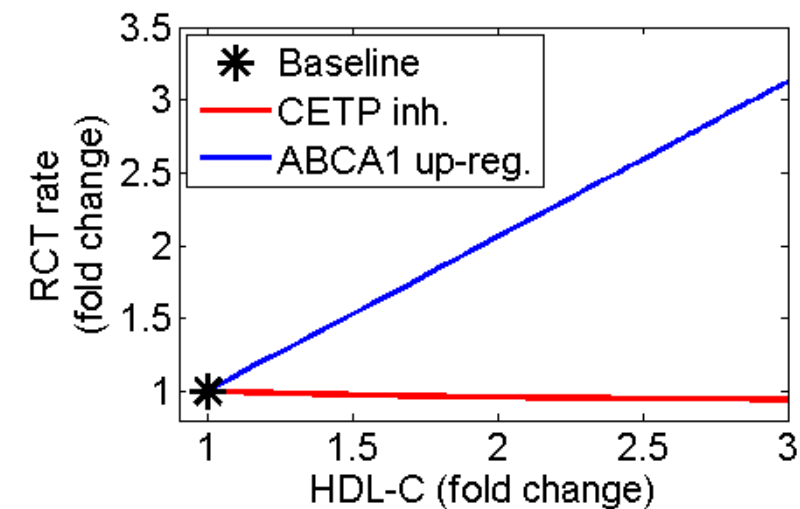
- Predicted HDL-C & RCT changes: **CETP inhibition** vs **ABCA1 up-regulation**



Model predictions on lipoprotein biomarkers



- The changes in RCT rate and biomarkers depend on the MoA

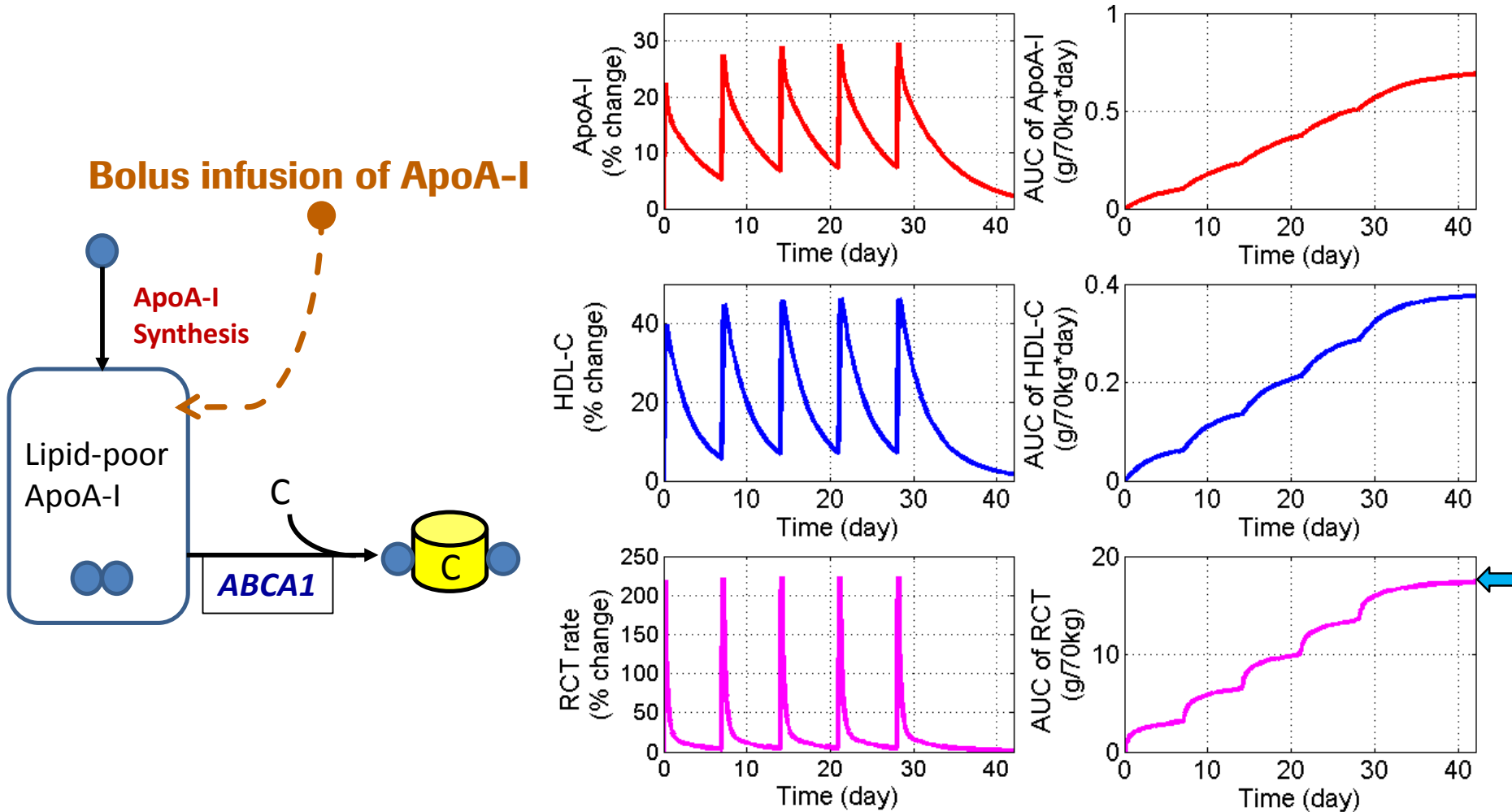


CETP inhibitors: Schwartz et al, NEJM '12; Clark et al, ATVB '04; Cannon et al, NEJM '10

Contextualize drug mechanism within disease biology

OPTIMIZE DOSAGE REGIMEN

Simulation of ApoA-I infusion therapy



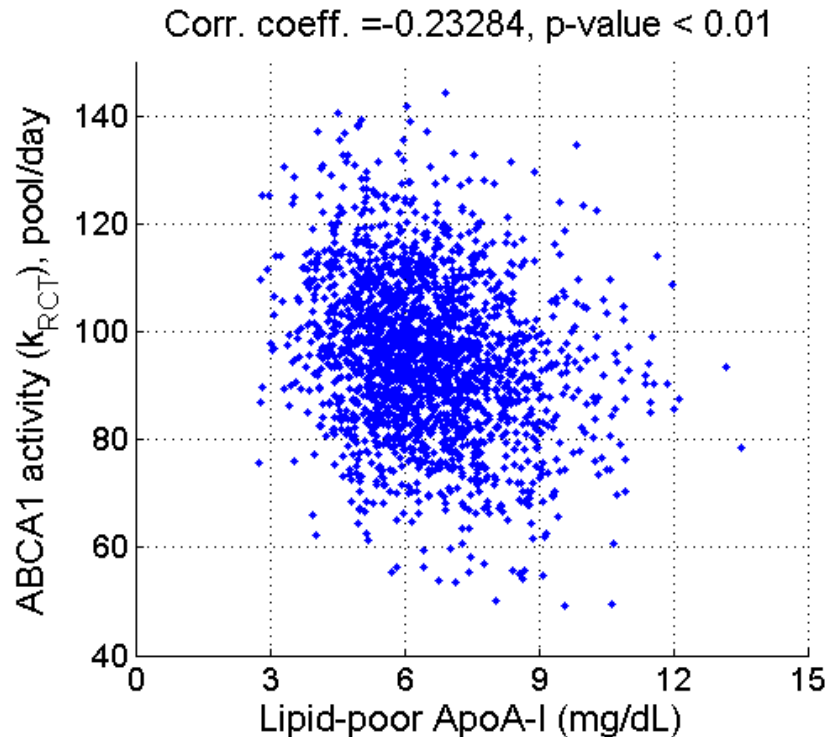
- Optimize formulation & dose schedule: maximize cholesterol removal

Model-based approach for

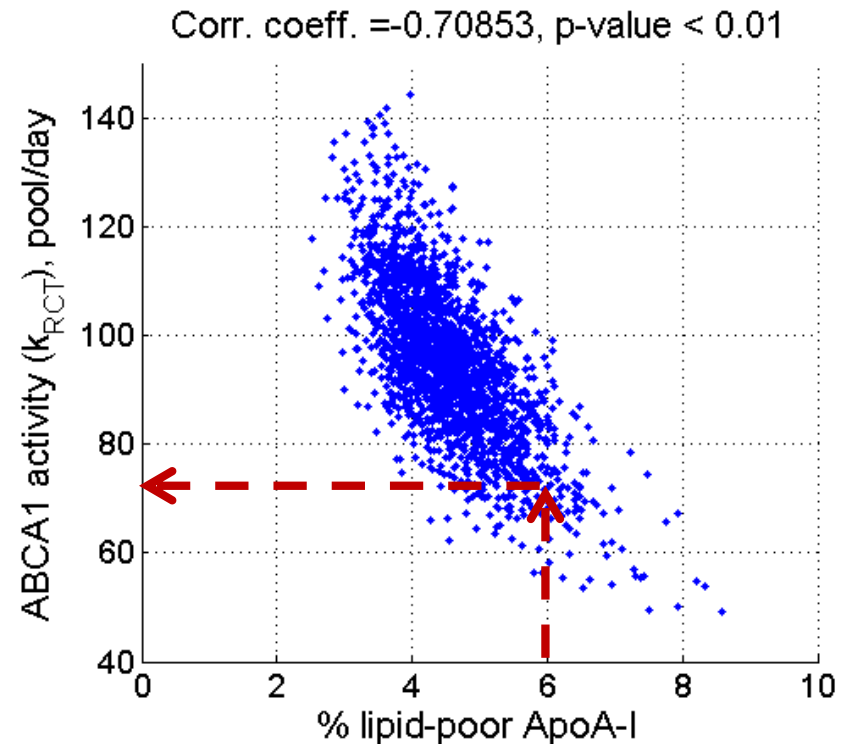
BIOMARKER IDENTIFICATION

The right biomarker for ABCA1 activity

- *In-vivo*, whole-body ABCA1 activity is difficult to assess experimentally
- Infer the most effective lipoprotein-based surrogate for ABCA1 activity



Poor indicator of ABCA1 activity



Robust marker of ABCA1 activity

Conclusions

- Mechanistic modeling:
 - Integrates state-of-art biology with prior experimental & observational data
 - Leverages the explosion in biological data
 - Contextualizes drug mechanisms within the disease biology
 - Quantifies effect of drugs on disease progression
 - Broad potential impacts within drug discovery & development
 - Assess targets, biomarkers, dosage; reconfirm MoA, ...
- LMK model:
 - Quantifies linkage between HDL-C and RCT
 - Provides explanation for failure of CETP inhibition
 - Identifies better targets for impacting cardio-vascular risk

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Doing now what patients need next