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Quantitative Systems Pharmacology (QSP) informs *in vitro* to *in vivo* translation for PCSK9 antibody

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Presented at ACOP 2014

Quantitative Systems Pharmacology in Cardiovascular Disease: Applications and Approaches in Drug Development

Research Overview

- Client Research Challenge:
  - Understand how preclinical data might translate to clinical efficacy for monoclonal antibodies (mAbs) that target proprotein convertase subtilisin/kexin type 9 (PCSK9)
- Research Approach:
  - Developed a quantitative systems pharmacology (QSP) Platform that included *in vitro* and *in vivo* systems
  - Used QSP Platform to (1) reproduce and provide insight into existing results, and (2) extrapolate to novel scenarios
- Research Results:
  - QSP confirmed mechanisms that drive *in vitro* and *in vivo* mAb efficacy and half-life
    - Insight into the relative clinical efficacy and half-life of antibodies, based on characteristics measured *in vitro*
  - QSP showed that LDL:PCSK9 binding, a recently published finding, might affect *in vivo* dynamics that could reduce mAb efficacy
- Program Impact:
  - QSP pointed to characteristics that can improve mAb efficacy
  - QSP identified key mechanisms of PCSK9 dynamics to investigate in humans

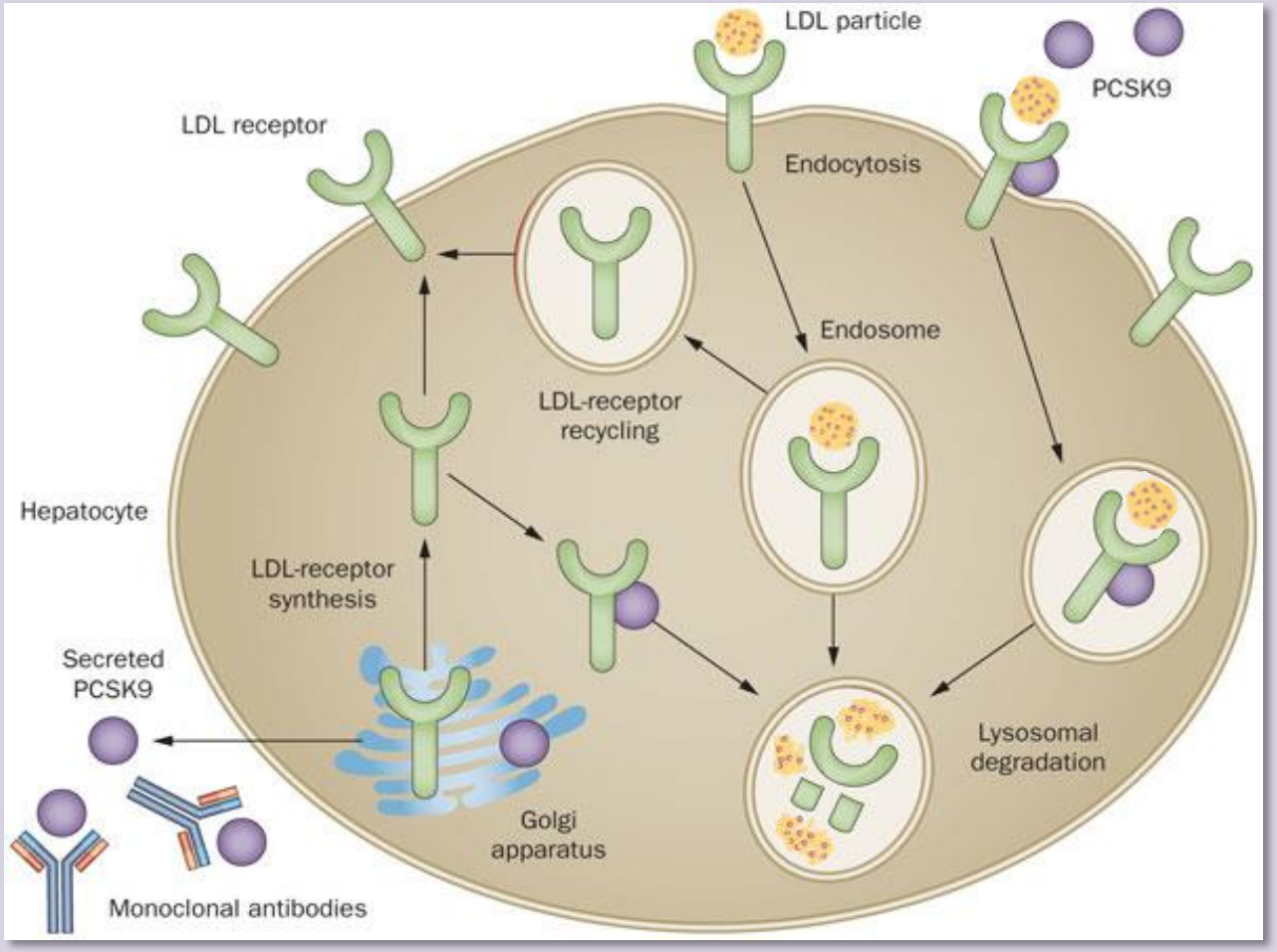
Discussion Outline

- Background: The role of PCSK9 in regulating LDL
- Overview of a graphical representation of the physiology in the QSP Platform
- Confirmation that QSP is qualified to investigate efficacy and half-life mechanisms
- Use of the QSP Platform to explore the implications of new data from the literature and new hypotheses

PCSK9 regulates the recycling of the LDL receptor (LDLR) by targeting the LDLR for degradation.

Strategy:

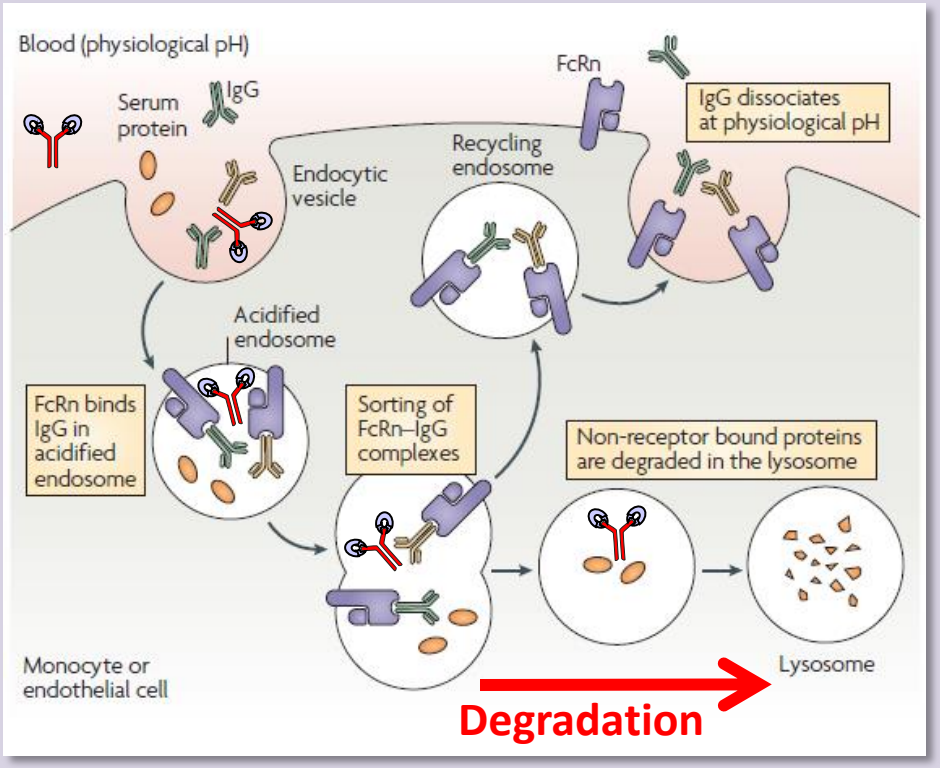
- Inhibiting PCSK9 with anti-PCSK9 mAbs will spare LDLRs for recycling.
- A greater abundance of LDLRs on the membrane will enhance LDL uptake.
- More LDL uptake will reduce serum LDL levels.



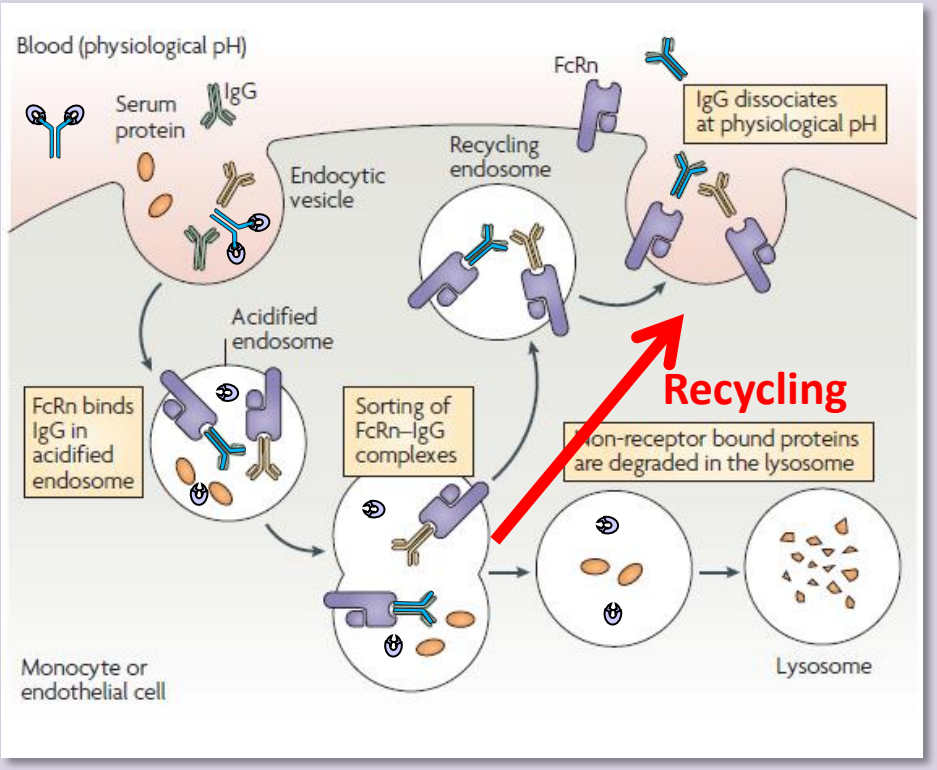
Adapted from Davidson (2013) Nature Reviews Cardiology 10:618

Anti-PCSK9 antibody can either be degraded along with PCSK9 or recycled via FcRn, depending on mAb binding at endosomal pH.

non-pH-sensitive mAb
PCSK9



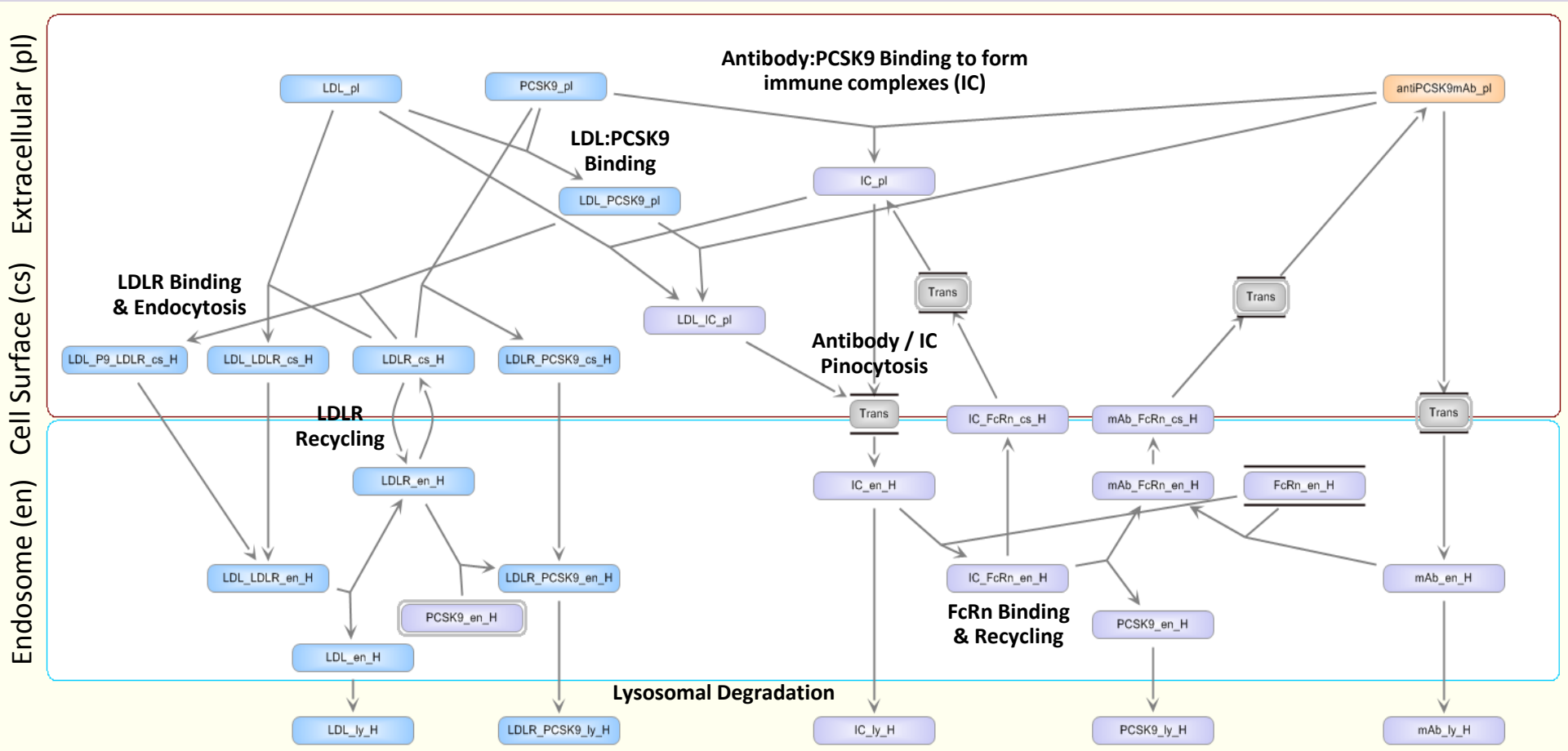
pH-sensitive mAb
PCSK9



Adapted from Roopenian and Akilesh (2007) Nature Reviews Immunology 7:715

The QSP Platform captures binding, recycling, and degradation mechanisms for LDL, LDLR, PCSK9, and anti-PCSK9 antibody.

The Hepatocyte Module of a PCSK9 PhysioPD™ Research Platform



In addition, the model includes antibody pinocytosis, degradation, and FcRn recycling dynamics in endothelial cells.

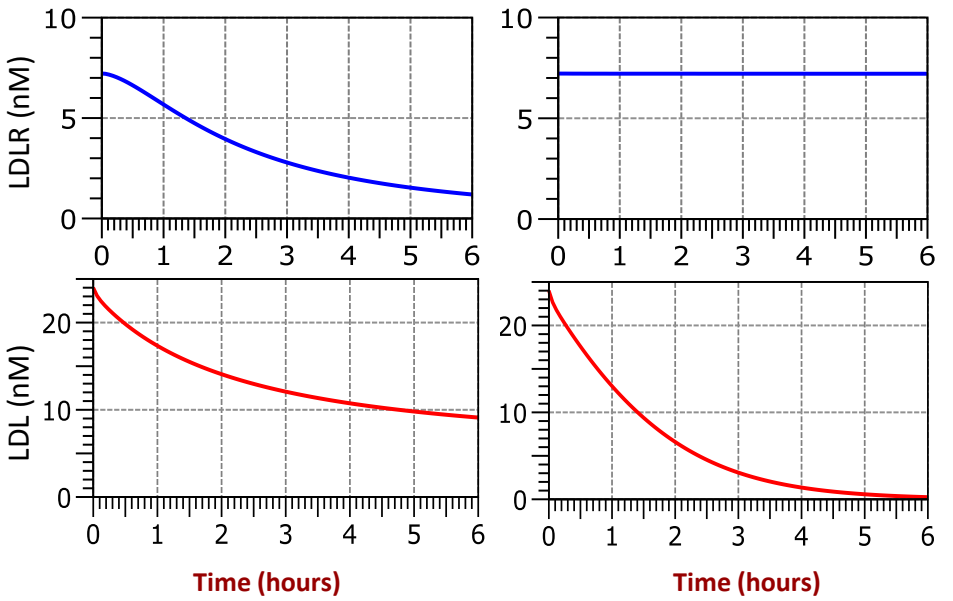
The Platform was qualified according to Rosa's Model Qualification Method (MQM), including comparison to data.

- Literature curation ensured relevant mechanisms were included in the Platform.
- Parameters were based on physiological values from public and proprietary data.
- Uncertainty and known variability in the data were noted for further assessment.
- Simulations of *in vitro* and *in vivo* protocols were compared to qualitative and quantitative expected results.

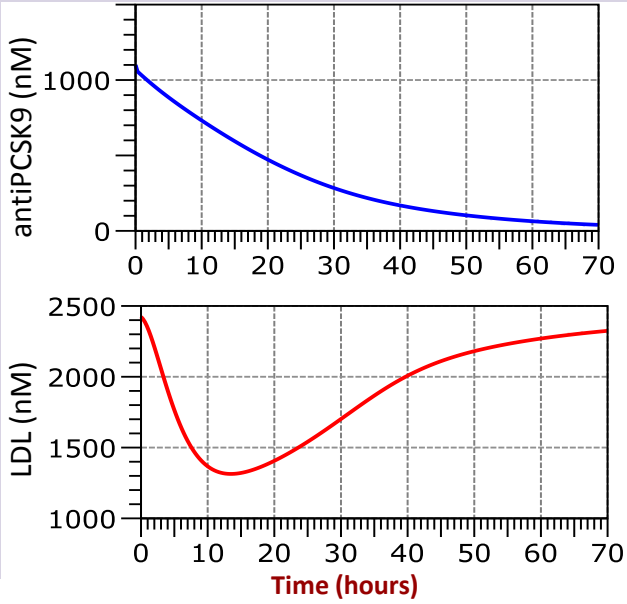
In vitro: LDL uptake in HepG2 cells: mAb inhibited PCSK9 effect on LDLR degradation

high [PCSK9], 0 mAb

high [PCSK9], high [mAb]

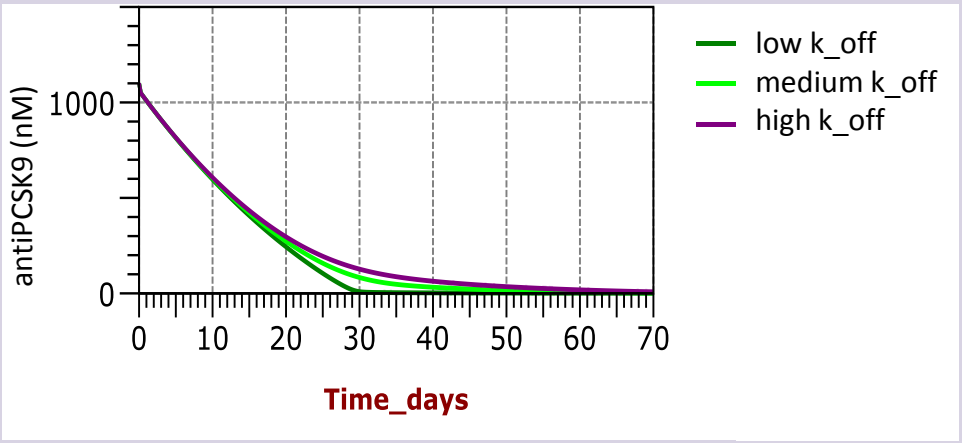


In vivo: serum mAb and LDL showed clinically appropriate dynamics



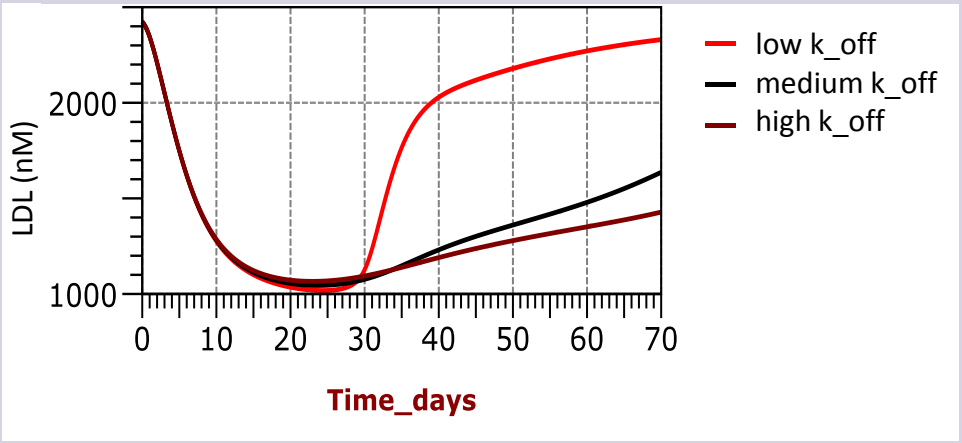
Parametric Analysis: Varying the endosomal off-rate of the antibody affected LDL clearance and antibody half-life

Plasma Antibody Concentration



- A higher k_{off} value increases the likelihood that the antibody dissociates from PCSK9 in the endosome; this dissociation favors mAb recycling

Plasma LDL Concentration



- The results are a prolonged antibody half-life (top chart) and extended LDL suppression (bottom chart)

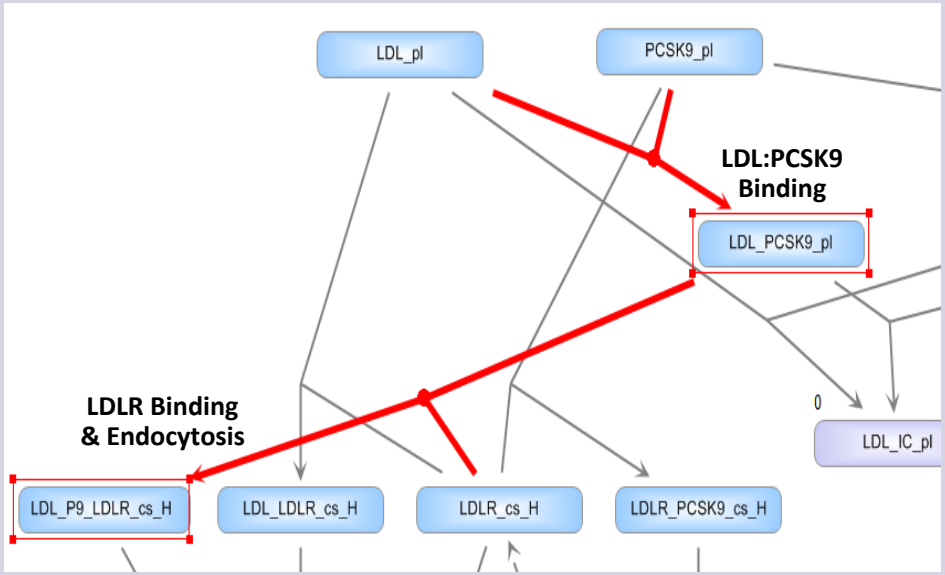
The Platform assessed implications of LDL:PCSK9 binding, based on current knowledge of PCSK9 mechanisms.

In 2013, Kosenko, et al.* showed:

i. In five normolipidemic subjects, 40% of plasma PCSK9 was bound to LDL

ii. PCSK9:LDL binding inhibited PCSK9:LDLR binding *in vitro*

iii. Under physiological-like conditions *in vitro*, PCSK9:LDL binding had no effect on LDL:LDLR binding



Research questions:

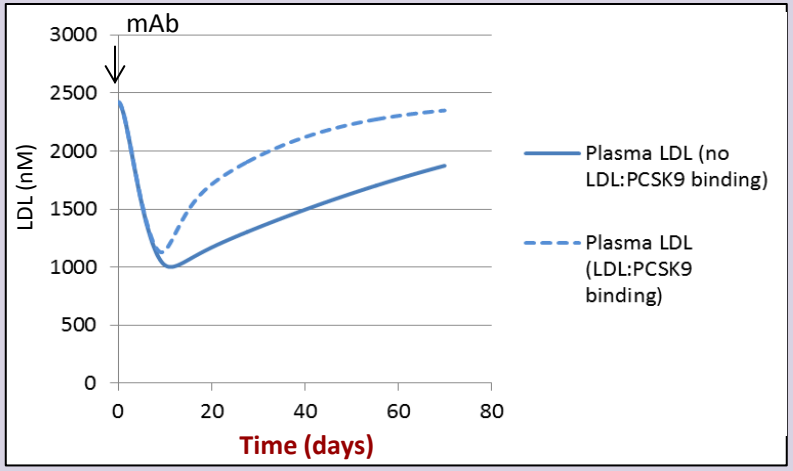
1. Under what conditions could PCSK9:LDL binding and inhibition of PCSK9:LDLR binding affect the clinical picture?
2. Are these observations consistent with available clinical data?
3. Could LDL:LDLR binding represent an endocytosis/clearance mechanism for PCSK9 bound to LDL?
   - What impact would this have under physiological conditions?

* Kosenko, T., M. Golder, et al. (2013) *J. Biol. Chem.* 288(12):8279-88.

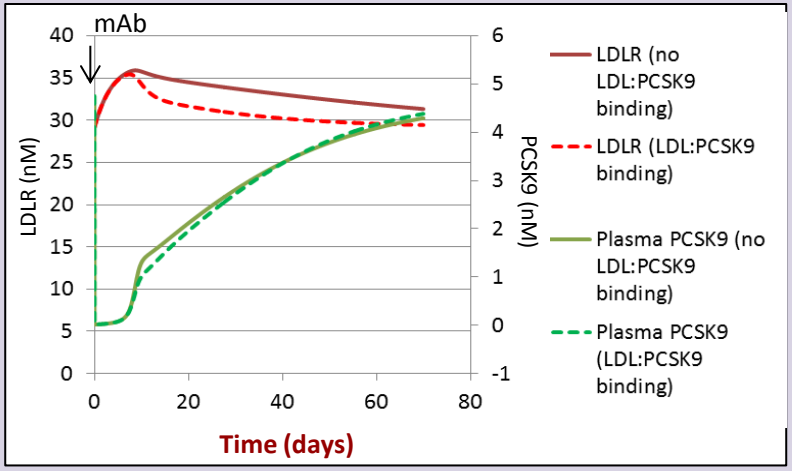
Simulations in the QSP Platform revealed possible clinical effects of LDL:PCSK9 binding and inhibition of LDLR degradation.

- Simulations were run in the presence (dashed lines) or absence (solid lines) of LDL:PCSK9 binding, starting with similar baseline conditions.
- Results
  - A given mAb dose was less efficacious when LDL:PCSK9 binding reduced LDLR clearance
  - The “no binding” scenario was more consistent with data; more clinical testing is needed
- Interpretation
  - If LDL binds 40% of PCSK9, the unbound PCSK9 must exert a greater effect on LDLR
  - mAbs that bind PCSK9:LDL have no added effect; thus, more mAbs are required to reduce LDL

SIMULATION: LDL response to antibody with or without LDL:PCSK9 binding



SIMULATION: LDLR and PCSK9 responses to antibody with or without LDL:PCSK9 binding



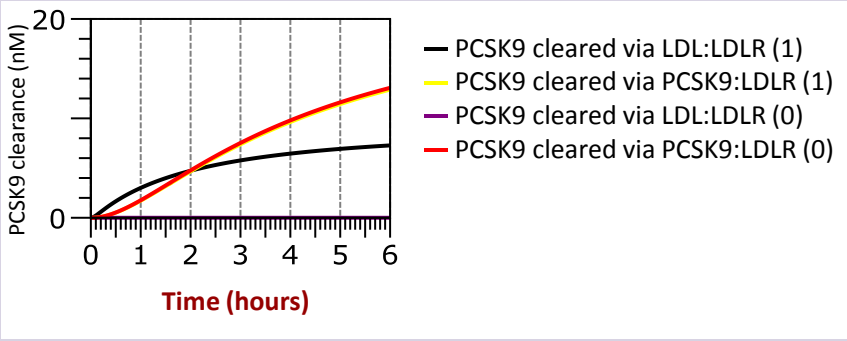
If LDL:LDLR binding is an endocytosis/clearance mechanism for PCSK9, what is its contribution to PCSK9 clearance?

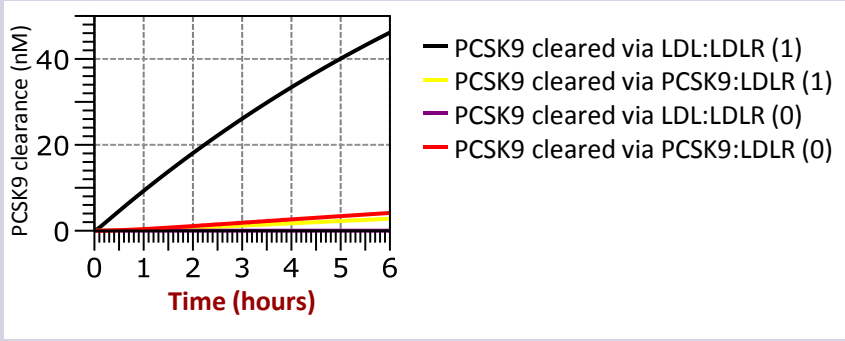
- At assay concentrations (left chart), PCSK9 clearance via LDL:LDLR binding (black/purple line) was similar to clearance via PCSK9:LDLR (yellow/red line)
- In physiological conditions (right chart), PCSK9 clearance via LDL:LDLR binding (black/purple line) was greater than clearance via PCSK9:LDLR (yellow/red line)
  - Suggests a testable implication of the findings in the Kosenko paper
- Remaining question: Is the mAb:PCSK9:LDL:LDLR complex endocytosed and cleared in this manner?

Simulations were run with (1) or without (0) PCSK9:LDL binding, and no mAb

PCSK9 clearance
Assay concentrations, [LDL] << [PCSK9]

LDLR level
"Physiological" concentrations





Simulations assume that PCSK9:LDL is endocytosed and cleared without binding to LDLR in the endosome.

Conclusions

- A single QSP Platform reproduced the existing *in vitro* and *in vivo* findings
- The QSP model confirmed mechanisms for anti-PCSK9 mAb efficacy and half-life
  - Endosomal off-rate was a key mechanistic driver
  - Platform can be used to assess the impact of different binding characteristics
- The QSP Platform could evaluate implications of reported LDL:PCSK9 binding
  - If PCSK9 binds LDL, as reported by Kosenko, et al., mAb efficacy may be reduced
    - Clinical data are needed to test whether this occurs in patients
  - If PCSK9 bound to LDL is endocytosed and cleared via PCSK9:LDL:LDLR binding, this could constitute significant PCSK9 clearance
- QSP modeling clarified connections between biological mechanisms and outcomes of interest

Acknowledgments

- Mike Reed
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