Converting human genetic insights into new medicines

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SVP, Program Value Enhancement
Pfizer Worldwide R&D

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Human genetic insights which drove drug R&D yielding new medicines (excludes cancer & enzyme deficiencies)

Genetic insight	Disease Association	Year Public disclosure	Approval of new medicine & disease indication
PNLIP	Steathorrhea	1964	1999 Obesity
Factor-2	Familial bleeding disorder	1969	2000 Thrombosis
Factor-X	Familial bleeding disorder	1970	2008 Venous Thromboembolism Atrial Fibrillation
GPIIb/IIIa	Glanzmann's Thrombasthenia	1974	1997 Percutaneous Coronary Intervention
ApoB	Hypobetalipoproteinemia	1987	2013 Familial Hypercholesterolemia
CaSR	Familial hypocalciuric hypercalcemia	1993	2004 Hypercalcemia
MTTP	Familial abetalipoproteinemia	1995	2012 Familial Hypercholesterolemia
CCR5	HIV	1996	2007 HIV
Leptin	Childhood Obesity	1997	2014 Leptin-deficient Lipodystrophy
SGLT2	Glucosuria	2002	2013 Type-2 Diabetes
PCSK9	Familial Hypercholesterolemia Atherosclerosis	2003 2006	2015 Hypercholesterolemia

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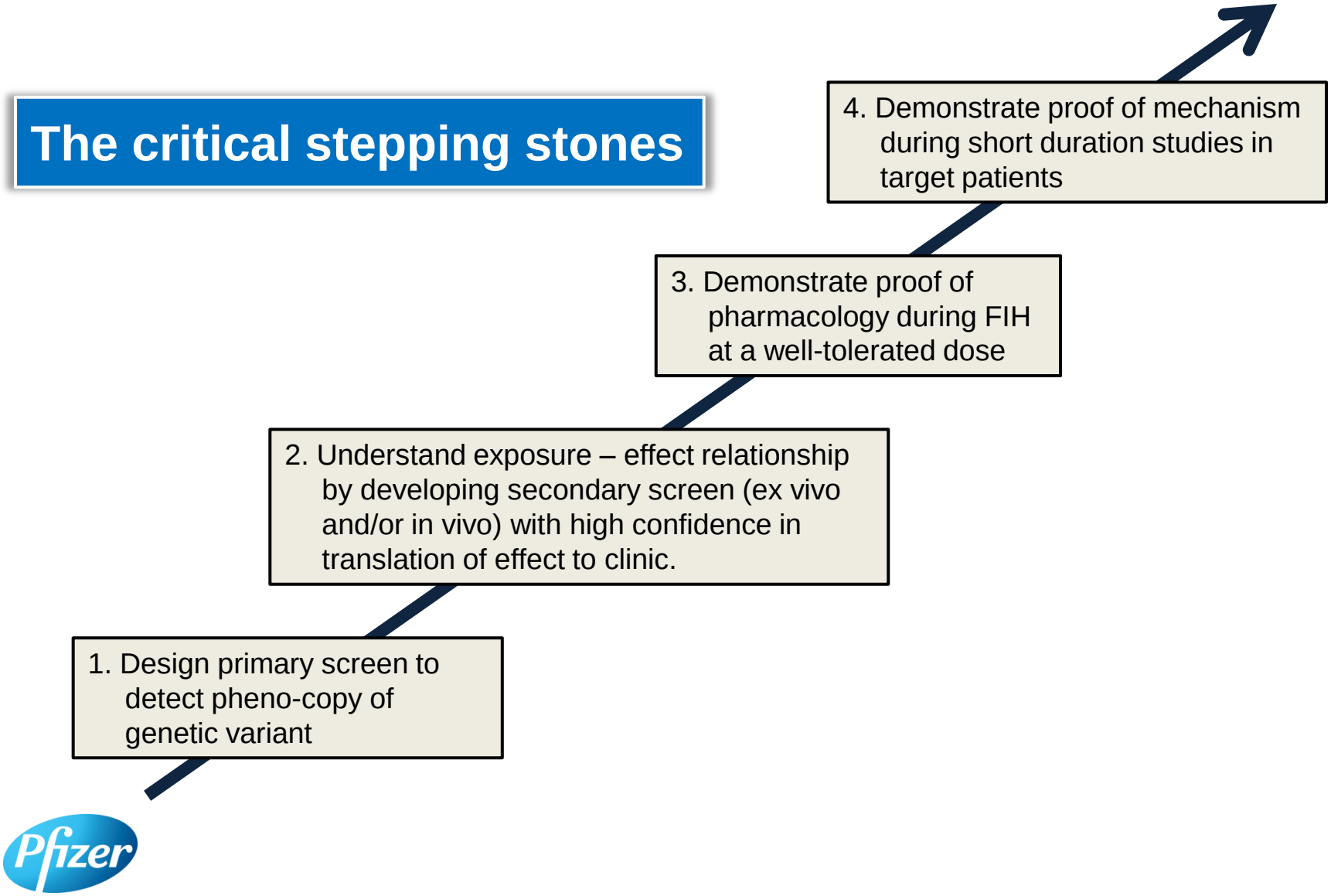
‘Foundational’ path to novel medicine; discover candidate, confirm it will test therapeutic hypothesis in human



1. Design primary screen to detect pheno-copy of genetic variant

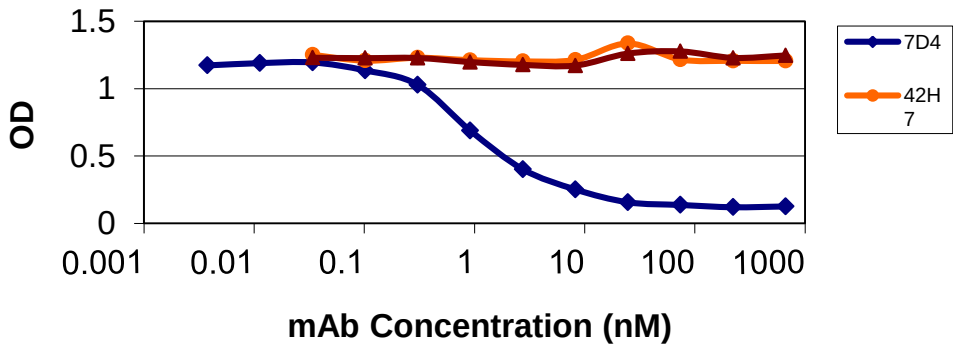
The Ideal; Biological knowledge of PCSK9 enabled design of *in vitro* screen to detect mAb phenocopying PCSK9 LOF

A.

recombinant PCSK9 (nM)	100							0
7D4 (nM)	1600	800	400	200	100	50	0	0

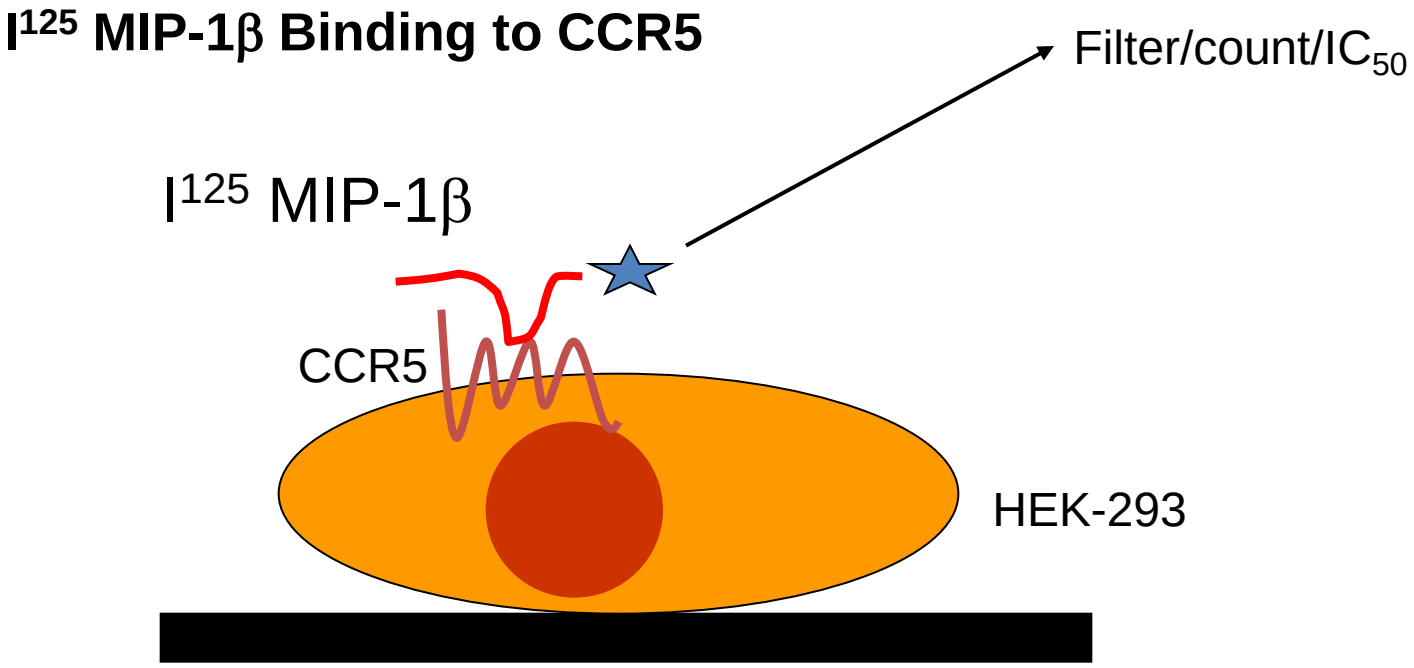
B.

Hu PCSK9 (0.4nM) Binding to Immobilized hu LDLr Extracellular Domain

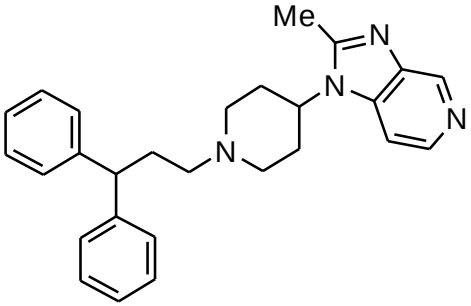


Frequent Reality; leap(s) of faith required to bridge gap(s) in the path

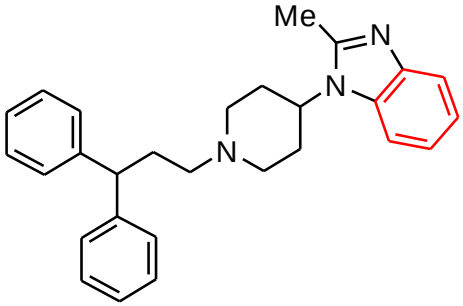
Does conformational change in CCR5 receptor with high affinity antagonist pheno-copy Δ32 CCR5 allele?



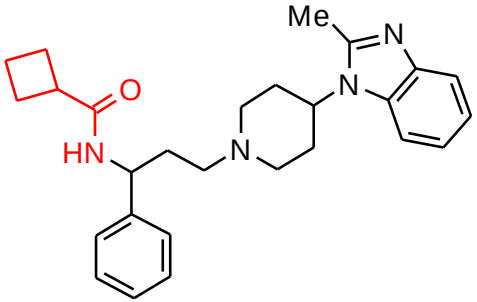
Successful leap because of rapid feedback on compounds pheno-copying Δ32 by reducing HIV replication *ex vivo*



UK-107,543
IC_{50}(MIP-1β) 0.6 uM
AV inactive

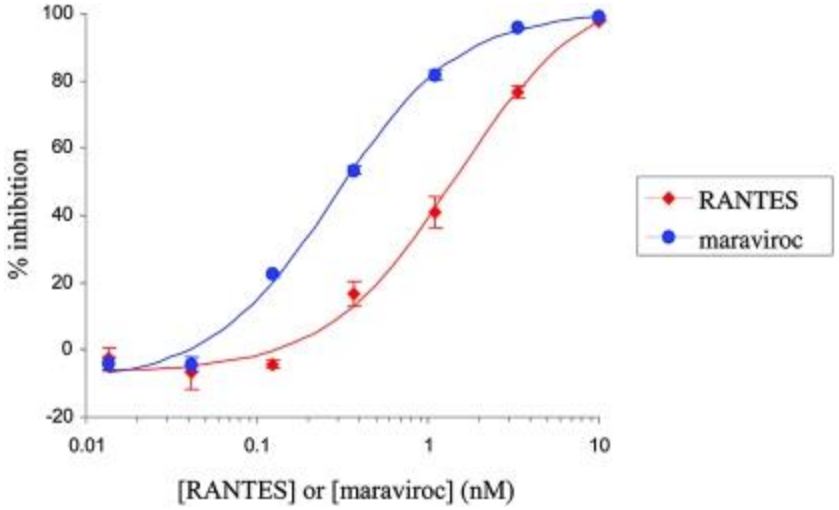


UK-370,907
IC_{50}(MIP-1β) 2 nM
AV inactive



UK-372,673
IC_{50}(MIP-1β) 40 nM
AV IC_{90} 75 nM

Concentration-effect response for maraviroc-dependent inhibition of HIV strain Ba-L replication in human peripheral blood lymphocytes (blue) vs. RANTES (red)



2. Understand exposure – effect relationship by developing secondary screen (in vivo) with high confidence in translation to clinic.

SGLT2 inhibition

↓

Urinary Glucose Excretion (UGE)
Secondary in vivo screen

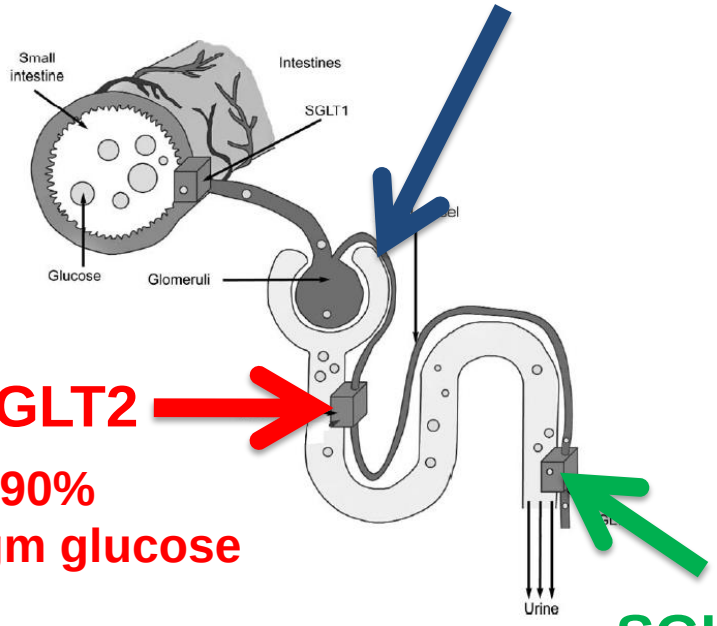
↓

Lower plasma glucose

↓

HbA1c reduction

Glucose filtration 180 gm / day



SGLT2

90%

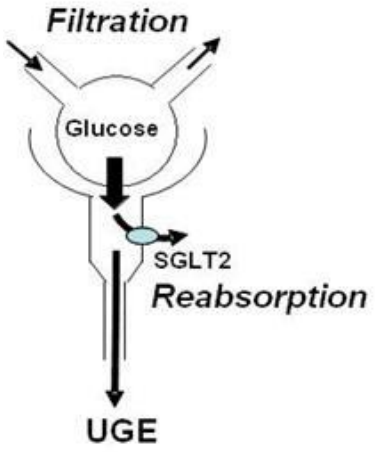
~162 gm glucose

SGLT1

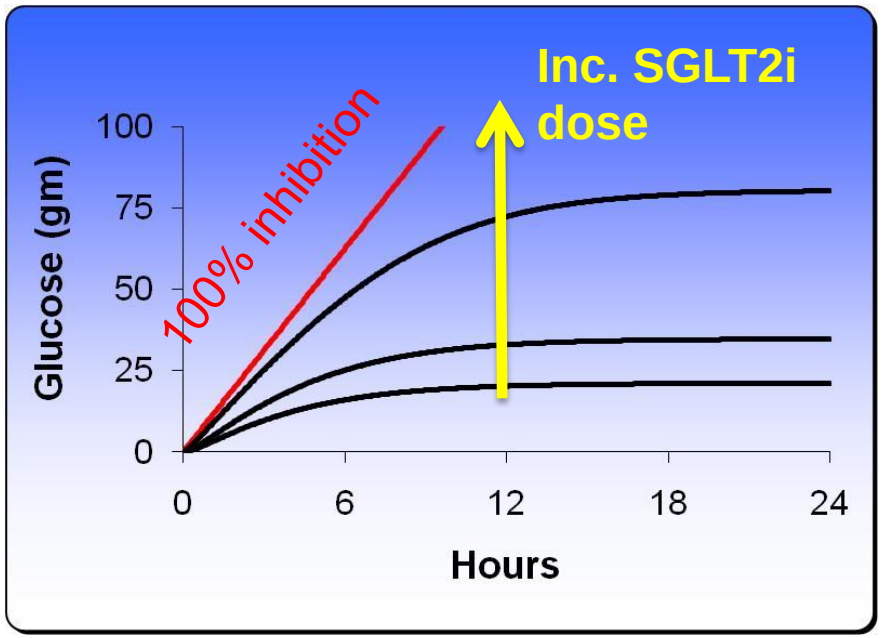
10%

~18 gm glucose

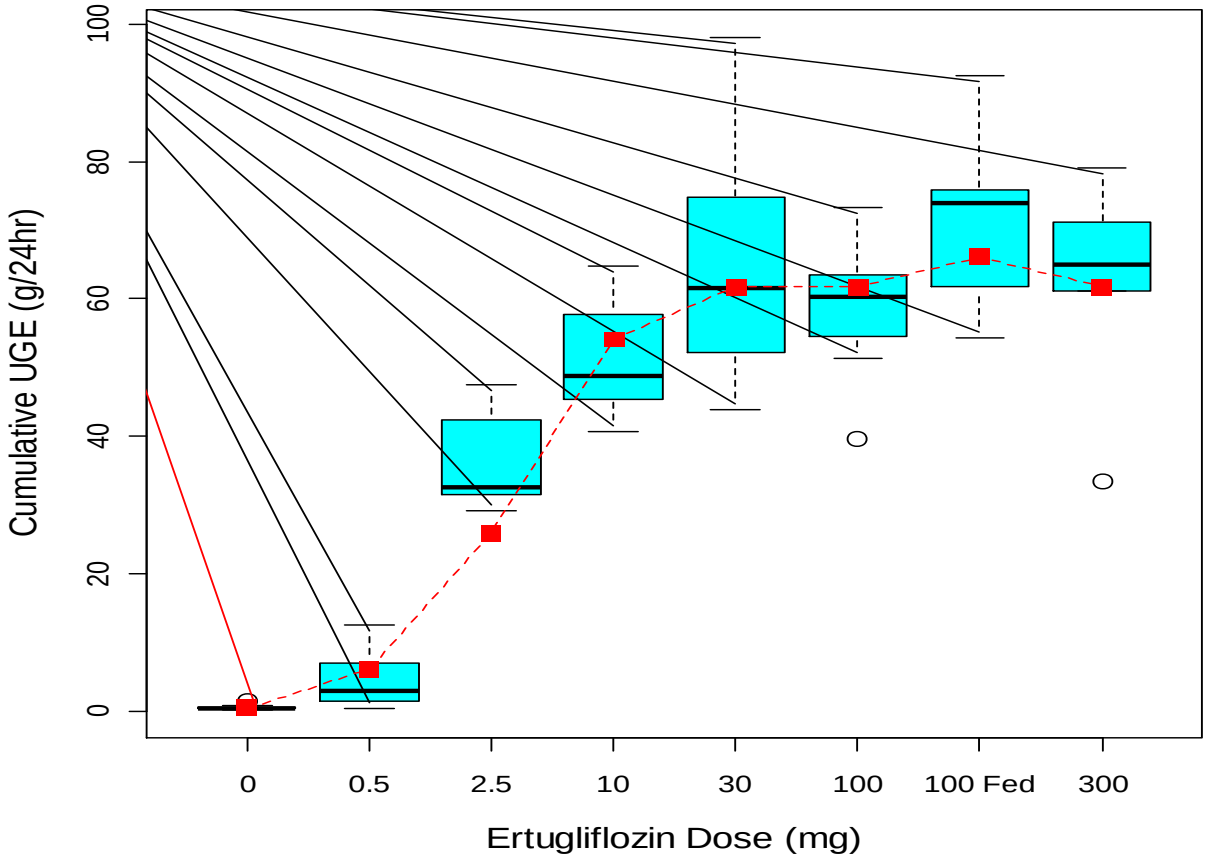
PKPD Model of SGLT2i; predicting clinical Ceff from preclinical PKPD



$$\frac{dUGE}{dt} = \underbrace{PG \times GFR}_{\text{Glucose filtration}} - \underbrace{PG \times GFR \times f_{reabs} \times \left(1 - \frac{I_{max} \bullet C}{C + IC_{50}}\right)}_{\text{Glucose reabsorption}}$$



3. Demonstrate proof of pharmacology during FIH at a well-tolerated dose



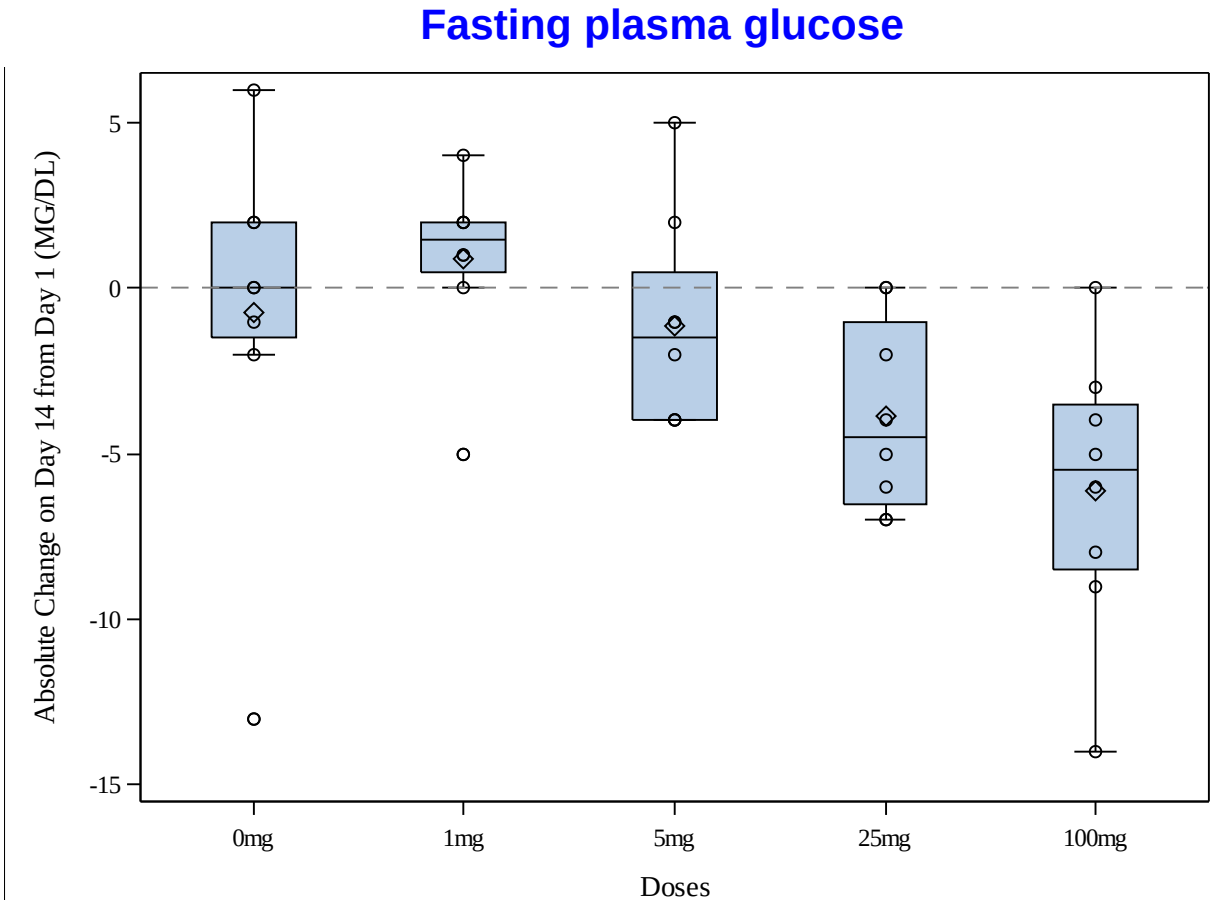
SGLT2i Preclinical PK-PD predicts human PK-PD; ➔ clinical proof of pharmacology

4. Demonstrate clinical proof of mechanism; reduce fasting blood glucose

Healthy Volunteers;

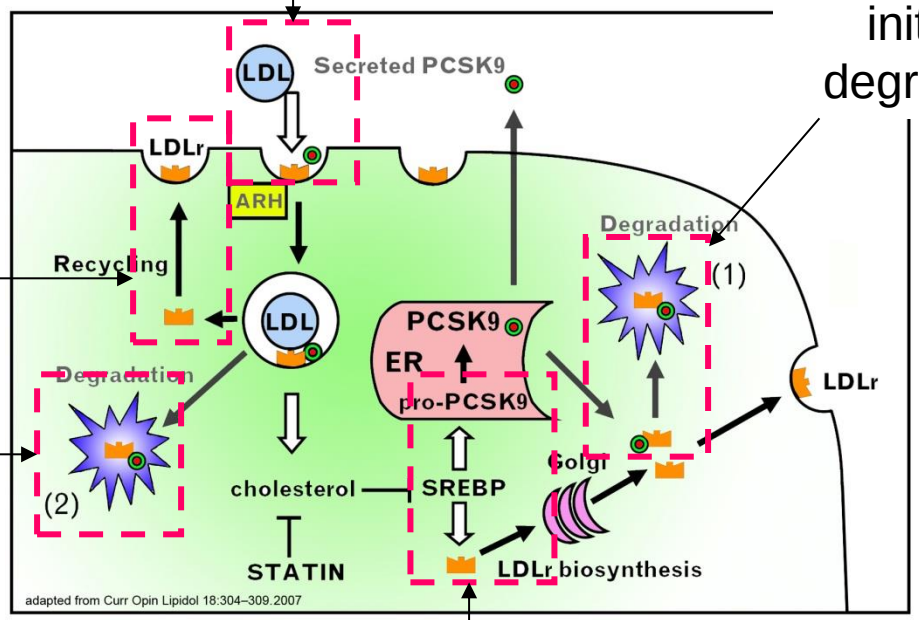
Mean BMI c. 30 Kg/m²

14 days treatment



Knowledge of Human Biology Enables Quantitative Systems Pharmacology (QSP) Modelling; e.g. PCSK9

Binding of LDL +/- PCSK9 to LDLR; internalization



Internally initiated degradation

Efficiency of recycling

Externally initiated degradation

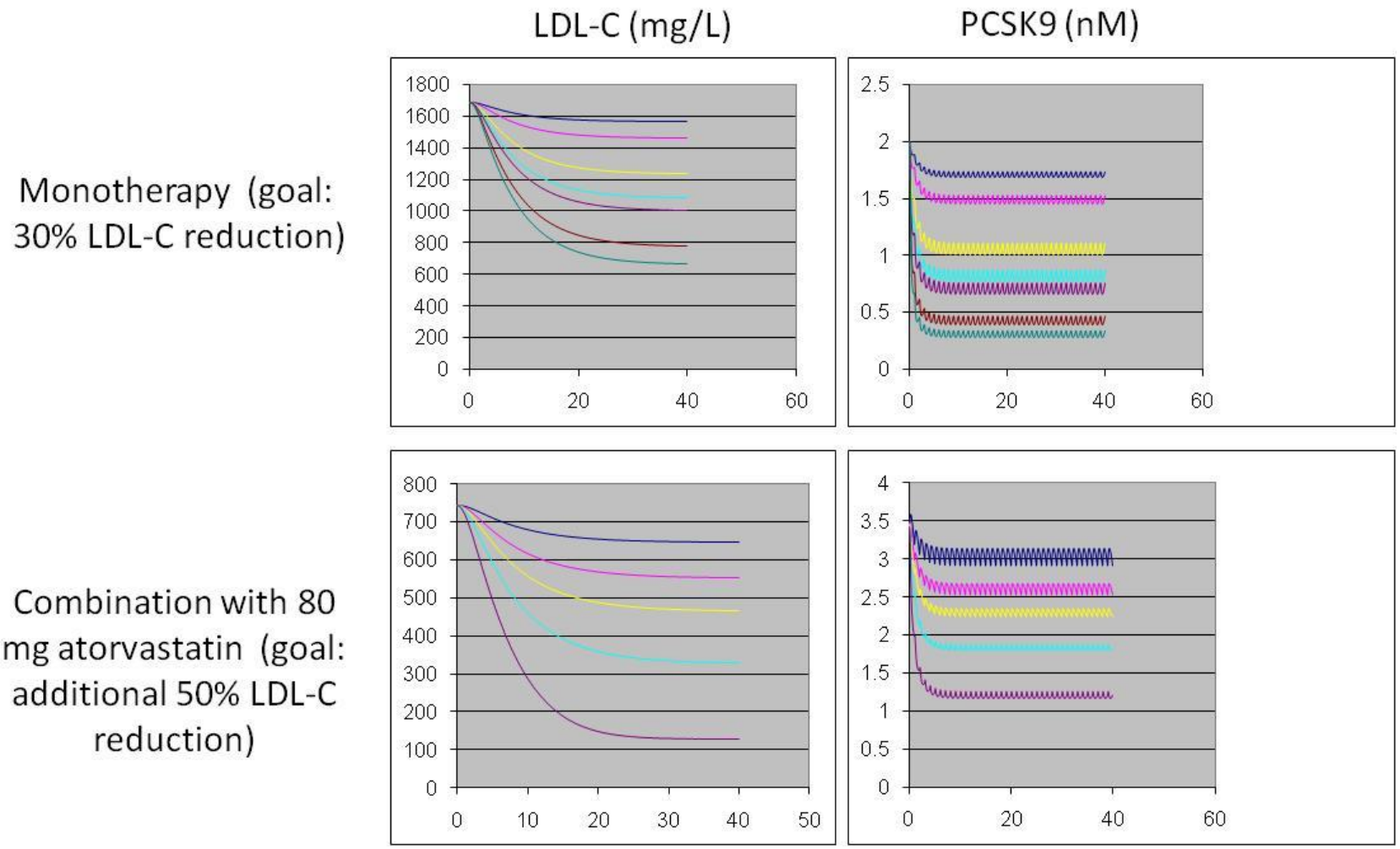
Co-regulated synthesis

Also:

- LDL-C synthesis (*de novo* and dietary)
- Endocytotic clearance of PCSK9
- Non-PCSK9-mediated LDLR clearance
- Non-LDLR-mediated LDL clearance

All parameters informed from literature values/data for human
Incorporates knowledge of statin (standard of care) effects

PCSK9 QSP Model Output



Clear Synergy Expected in Combination with Atorvastatin

Genetic variants causal of, or protective against human disease, but inadequately understood biological consequences to enable drug discovery

Genetic Locus	Variant(s)	Disease	Date causality established
MC4R	4bp insert codon 264 4bp deletion codon 211 both truncated receptor LOF	Obesity	1998
SCN9A Na(v)1.7	I848T, L858H; GOF S459X, I767X, W897X; LOF	Erythermalgia Insensitive to thermal & mechanical stimuli	2004 2006
SLC30A8	R138X 7bpshift a.a. position 34 Both LOF	Type 2 Diabetes	2013
PNPLA3	I148M	Liver Disease	2015

How can development of biological knowledge, including human, around these genes and pathways be expanded rapidly?

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