PCSK9 for LDL Cholesterol Reduction: What have we learned from clinical trials?

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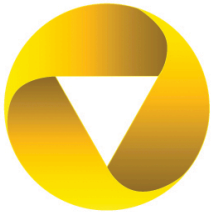

PCSK9FORUM

Part I: The rationale for PCSK9 inhibition

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Why do we need more LDL reducing drugs?

- Growing number of statin adverse patients with limited alternatives
- Special populations (e.g. FH and severe hypercholesterolemia) do not achieve optimal LDL-C levels
- Numerous cardiovascular end point trials have confirmed more LDLc reduction results in more CVD reduction
- European, Canadian, NCEP-ATP III guidelines continue to lower LDLc goal in high risk and even lower risk CVD patients

Proprotein convertase subtilisin/kexin 9 (PCSK9)

- Background: function , genetics and role in LDL-C control
- Potential mechanisms to reduce PCSK9 activity
- Clinical trials

Hypercholesterolemia and early CAD Associated With PCSK9 GOF Mutations

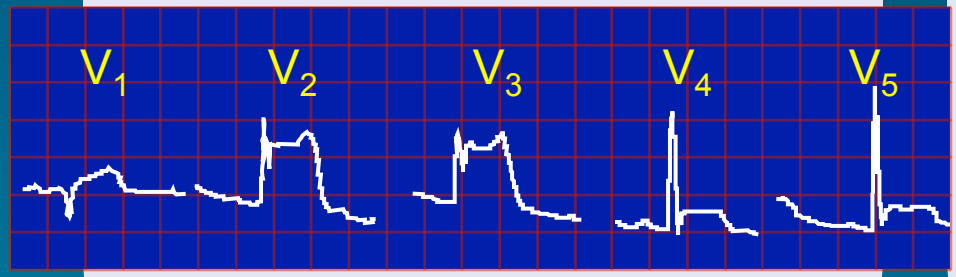
F216L mutation[1]

French proband died from MI

Age: 49 years

TC: 441 mg/dL

LDL-C: 356 mg/dL



Acute Myocardial Infarction[4]

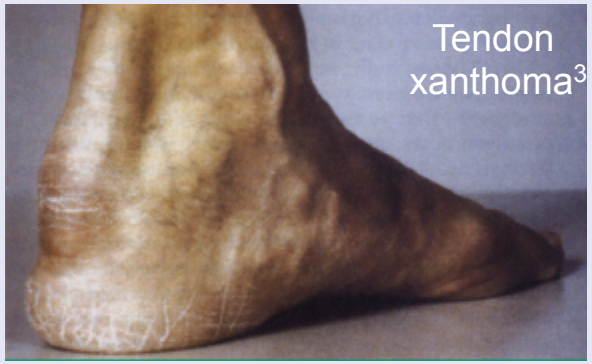
R218S mutation[2]

French proband presented with tendinous xanthoma and arcus corneae

Age: 45 years

TC: 402 mg/dL

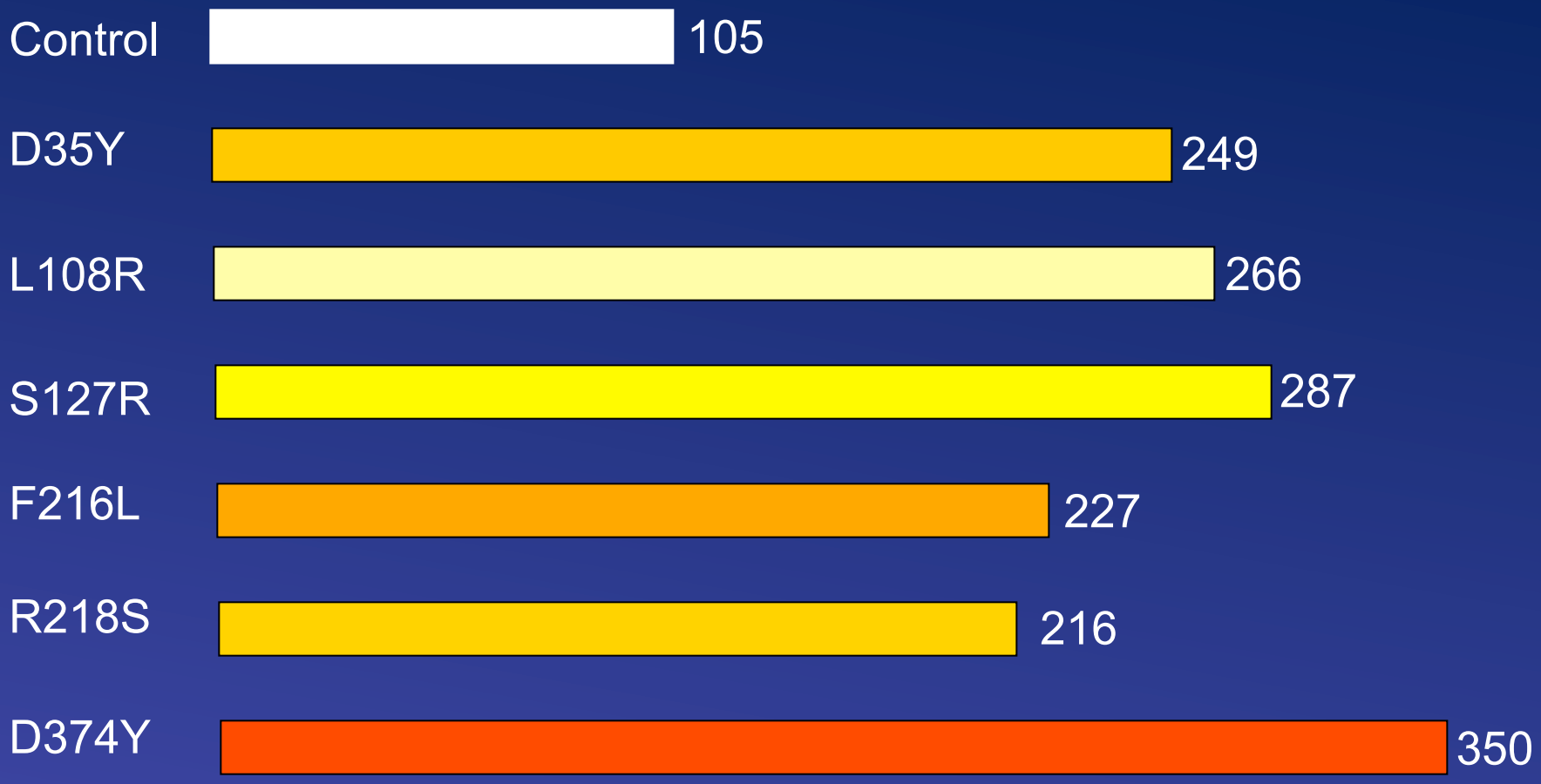
LDL-C: 293 mg/dL



TC = total cholesterol.

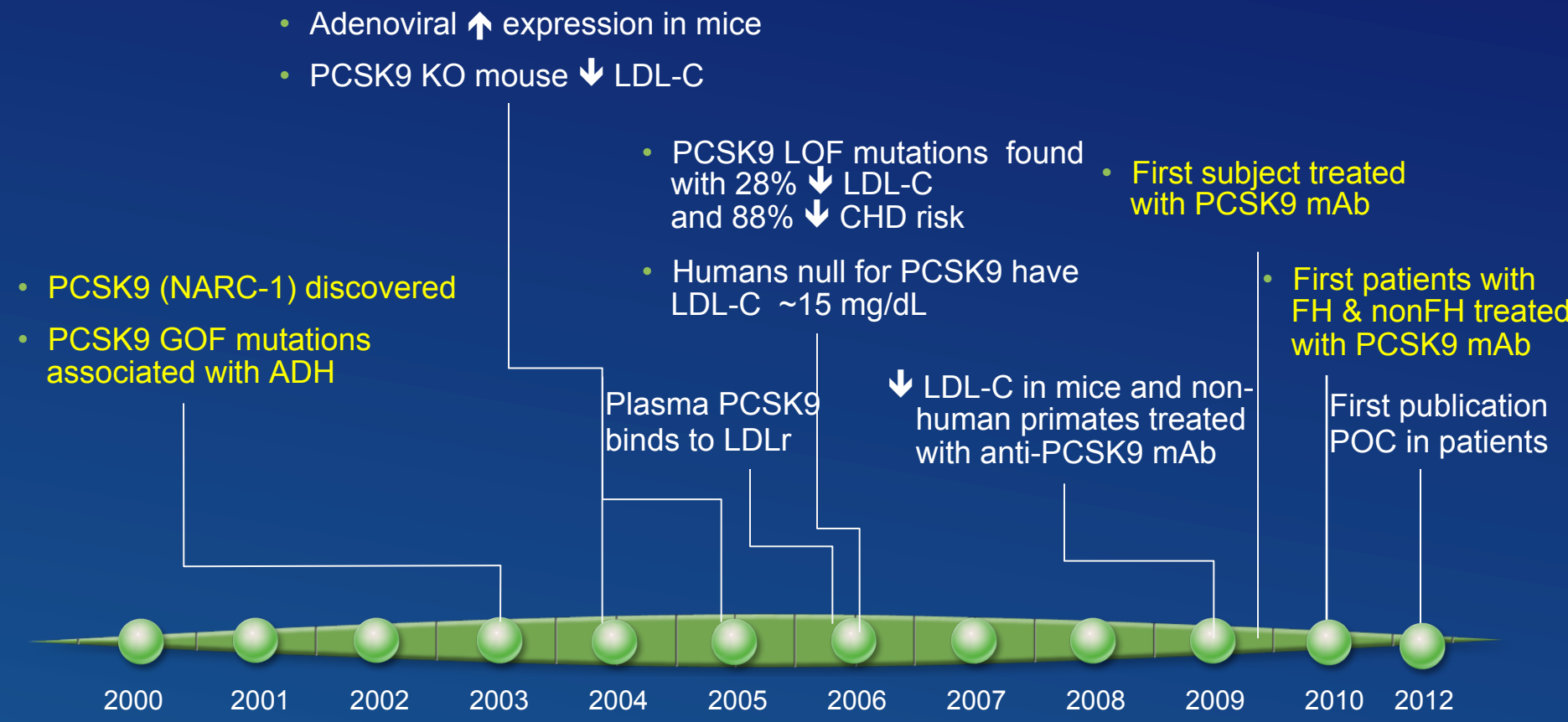
1. Abifadel M, et al. *Nat Genet.* 2003;34:154-156. 2. Abifadel M, et al. *Hum Mutat.* 2009;30:520-529.
3. Durrington P. *Lancet.* 2003;362:717-731. 4. Podrid PJ. UpToDate; March 1, 2012.

Mean LDL-C Levels in Patients with GOF PCSK9 Mutations



Poirier, Mayer. Drug Des Devel Ther 2013; 7: 1135-48

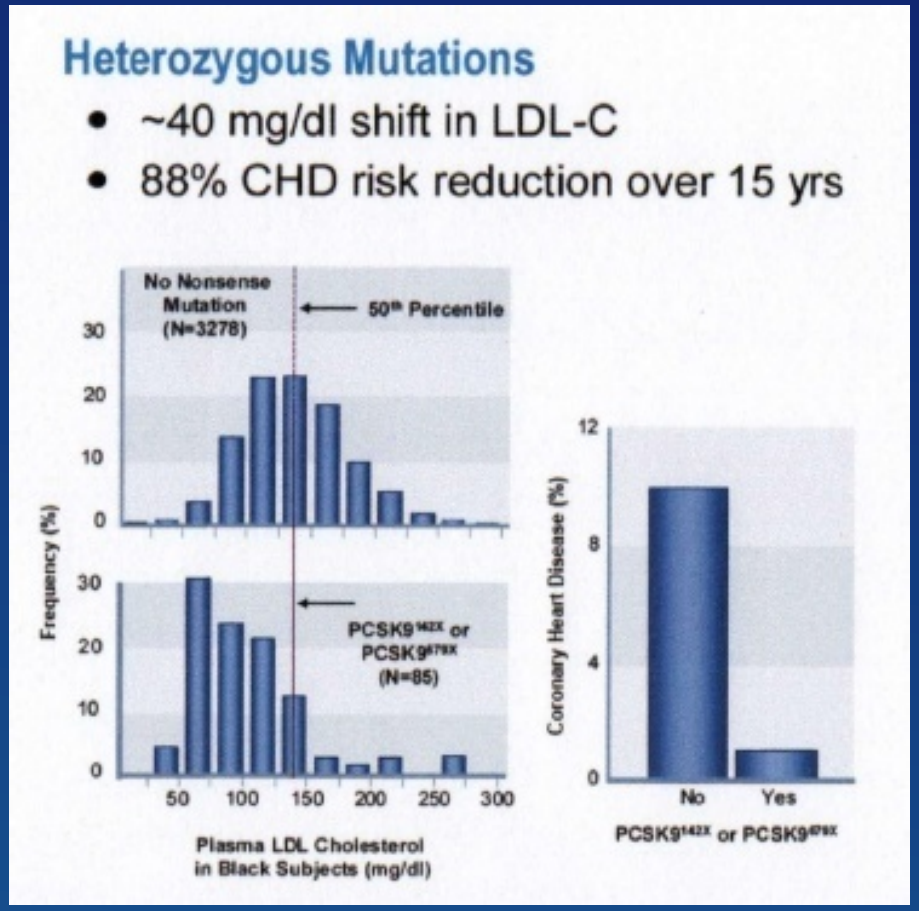
PCSK9:
Rapid Progress From Discovery to Clinic



Seidah NG. *Proc Natl Acad Sci USA* 2003;100(3):928-33, Abifadel M. *Nat Genet* 2003;34(2):154-6, Maxwell KN. *Proc Natl Acad Sci USA* 2004;101(18):7100-5, Rashid S. Proc Natl Acad Sci USA 2005;102(15):5374-79, Lagace TA et al. JCI 2006;116:2995-3005 Cohen JC. *N Engl J Med* 2006;354(12):1264-72, Zhao Z. *Am J Hum Genet* 2006;79(3):514-23, Hooper AJ. *Atherosclerosis* 2007;193(2):445-8, Chan JC. *Proc Natl Acad Sci USA* 2009;106(24):9820-5; Stein et al *N Engl J Med* 2012;366:1108-18

Stein modified from Swergold, Regeneron

Low LDL-C and decreased CAD associated with PCSK9 loss of function mutations



Cohen et al. N Engl J Med 2006. 354;1264-72

Case Reports of Patients Double Loss-of-Function PCSK9 Mutations

- 32 year-old Caucasian woman had no measurable PCSK9 and a LDL-C of 14.
  (*Am J Hum Genet*. 2006;79: 514-523).

Homozygous Mutations

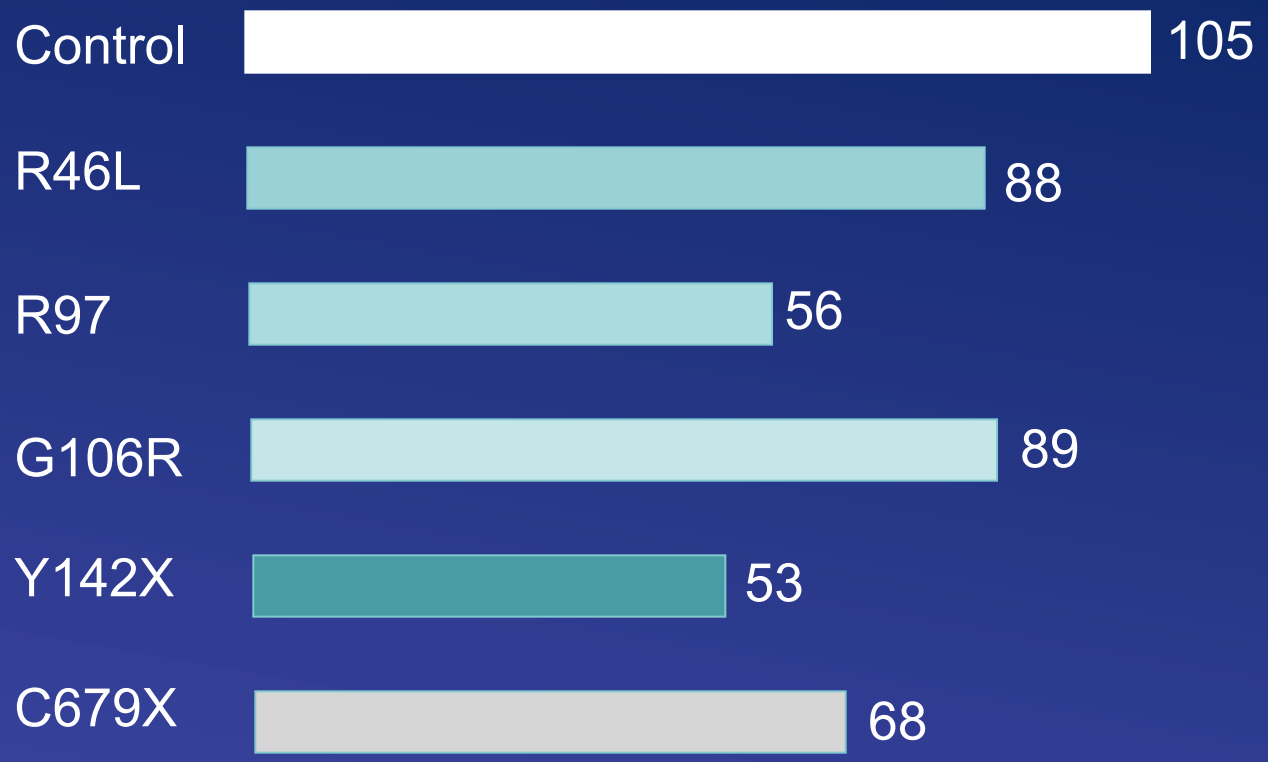
- 32 Year-old woman
- Healthy, fertile
- No detectable PCSK9 levels

PCSK9 null person	Number mg/dL
HDL Cholesterol	65
Triglycerides	119
LDL Cholesterol	14
Total Cholesterol	96

- 21 year-old Zimbabwean woman had no measurable PCSK9 and a LDL-C of 15.
  (*Atherosclerosis*. 2007;193: 445-448)

- 49 year-old French male had no detectable PCSK9 levels and a LDL-C of 16.
  (*Arterioscler Thromb Vasc Biol.* 2009;29:2192-2197)

Mean LDL-C Levels in Patients with LOF PCSK9 Mutations



Poirier, Mayer. Drug Des Devel Ther 2013; 7: 1135-48

Association of PCSK9 Mis-sense/LOF Variant R46L with Early-Onset Myocardial Infarction

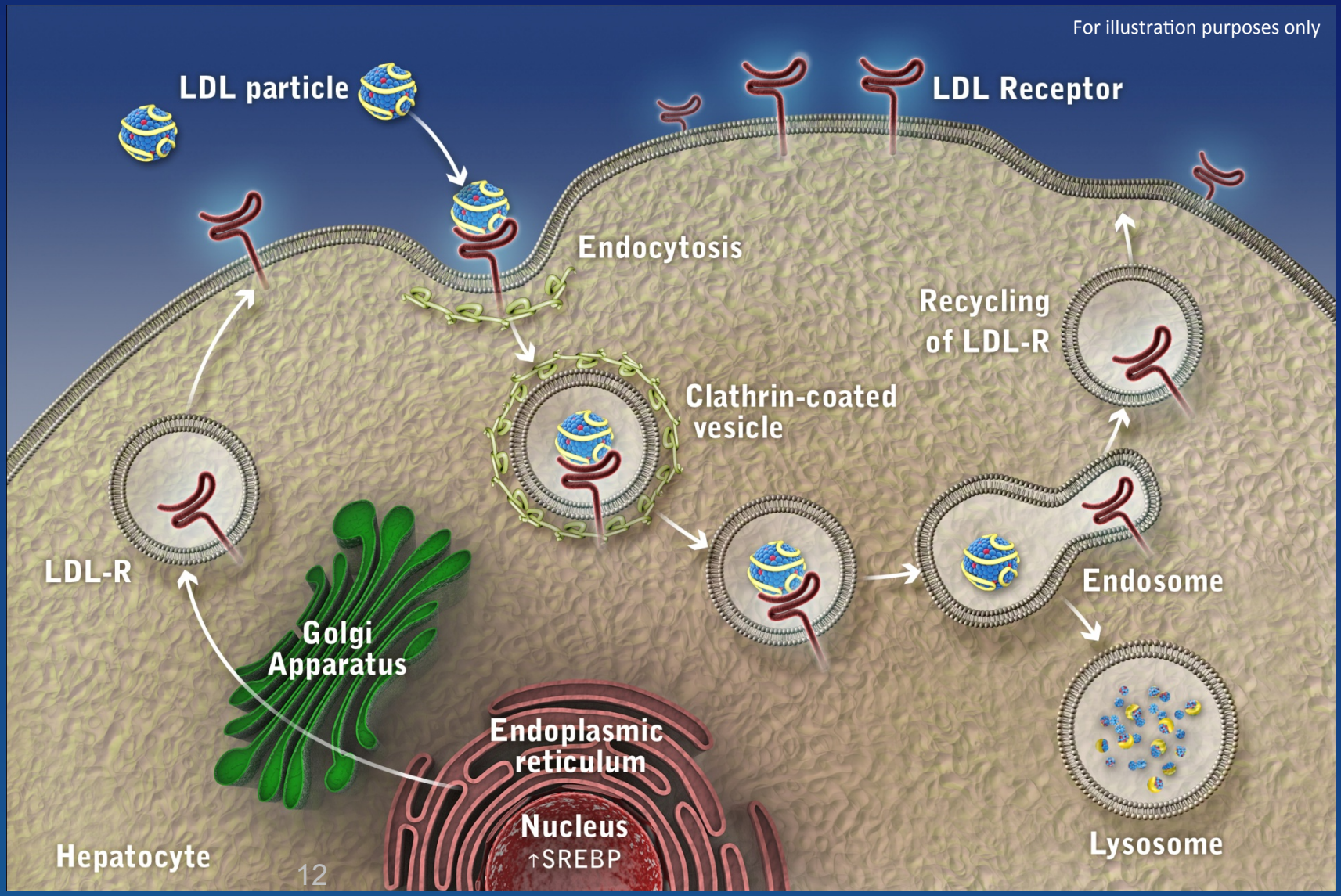
Table 1. Association of *PCSK9* Missense Variant R46L with Early-Onset Myocardial Infarction.

Site	Study	No. of Case Patients	No. of Controls	Frequency of Minor L Allele		Odds Ratio for Early-Onset Myocardial Infarction (95% CI)*	P Value
				Case Patients	Controls		
				%			
Finland	FINRISK	209	210	1.3	4.1	0.30 (0.11–0.84)	0.02
Sweden	Malmö Diet and Cancer Study — cardiovascular cohort	150	149	0.7	2.0	0.32 (0.07–1.61)	0.17
Spain	Registre Gironi del Cor (REGICOR)	361	361	1.0	2.8	0.35 (0.15–0.82)	0.02
Seattle	Heart Attack Risk in Puget Sound	542	631	0.9	1.9	0.45 (0.21–0.98)	0.049
Boston	Massachusetts General Hospital Premature Coronary Artery Disease Study	192	266	1.4	2.3	0.59 (0.21–1.69)	0.46
Combined analysis		1454	1617	0.99	2.4	0.40 (0.26–0.61)	0.00002

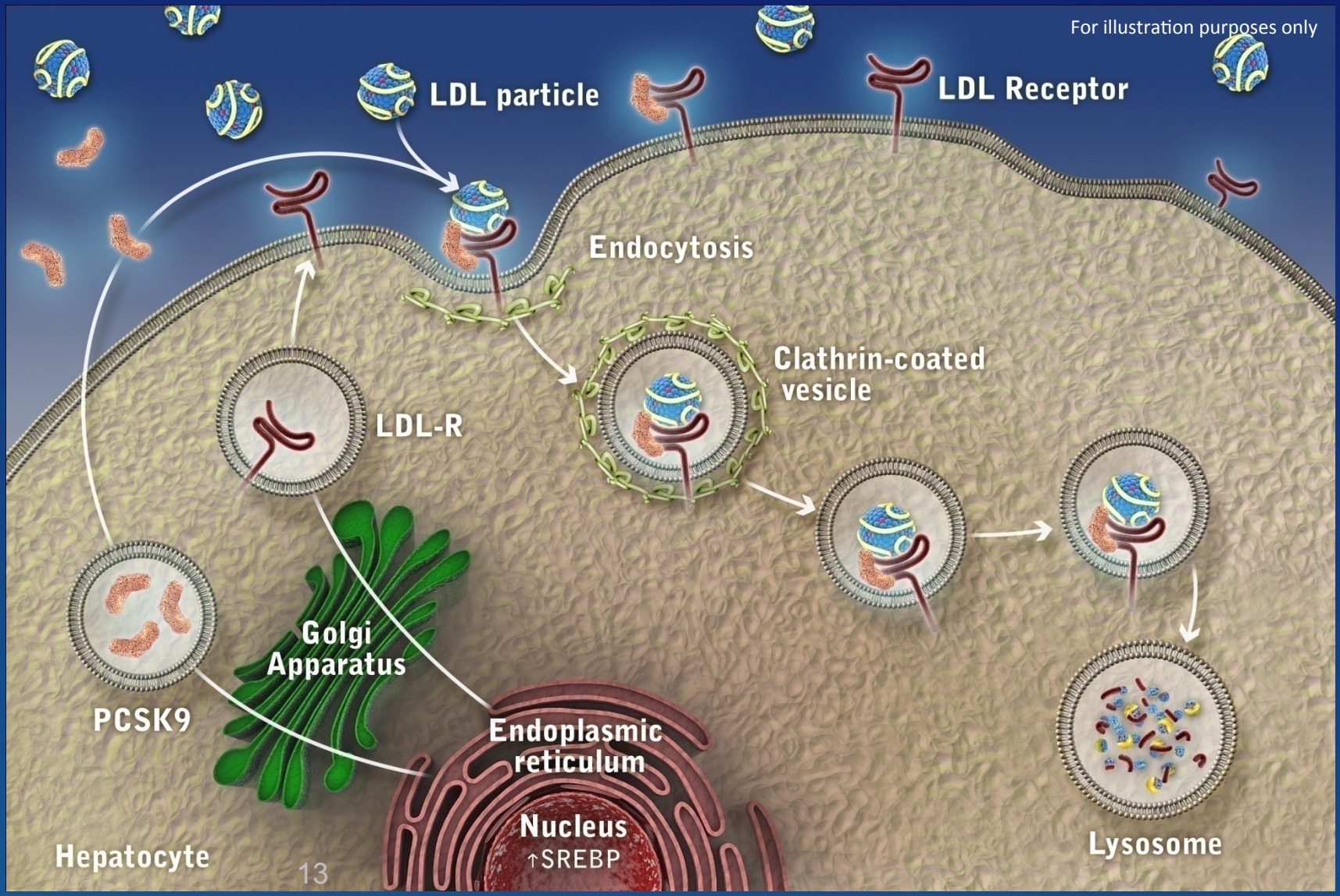
* CI denotes confidence interval.

Kathiresan S and the Myocardial Infarction Genetics Consortium. N Engl J Med 2008;358:2299-2300

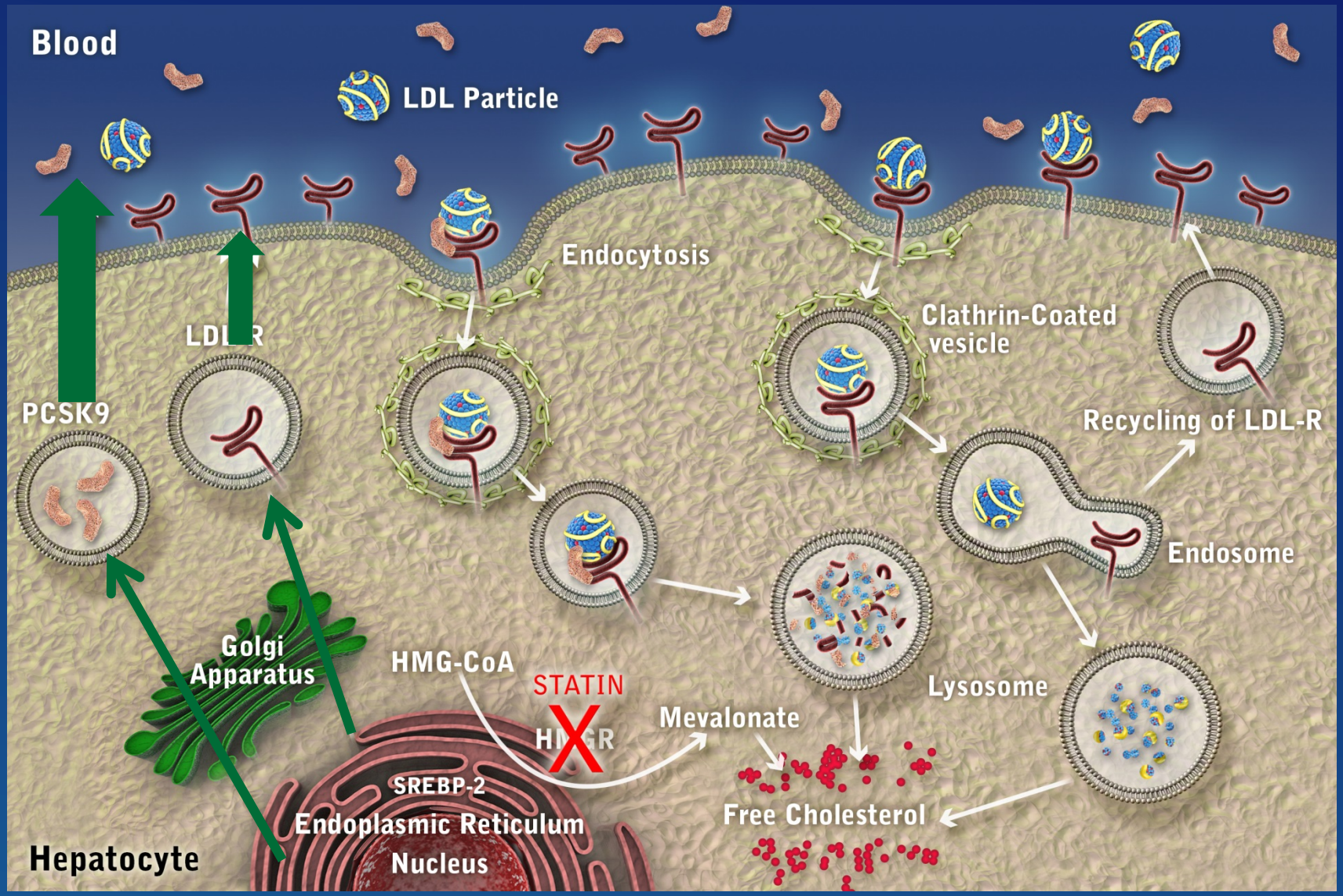
LDL Receptor Function and Life Cycle



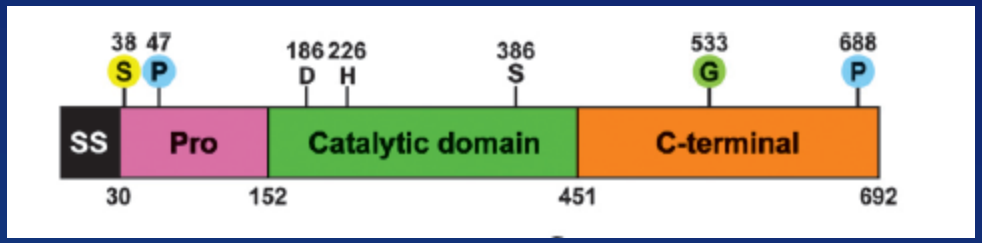
The Role of PCSK9 in the Regulation of LDL Receptor Expression



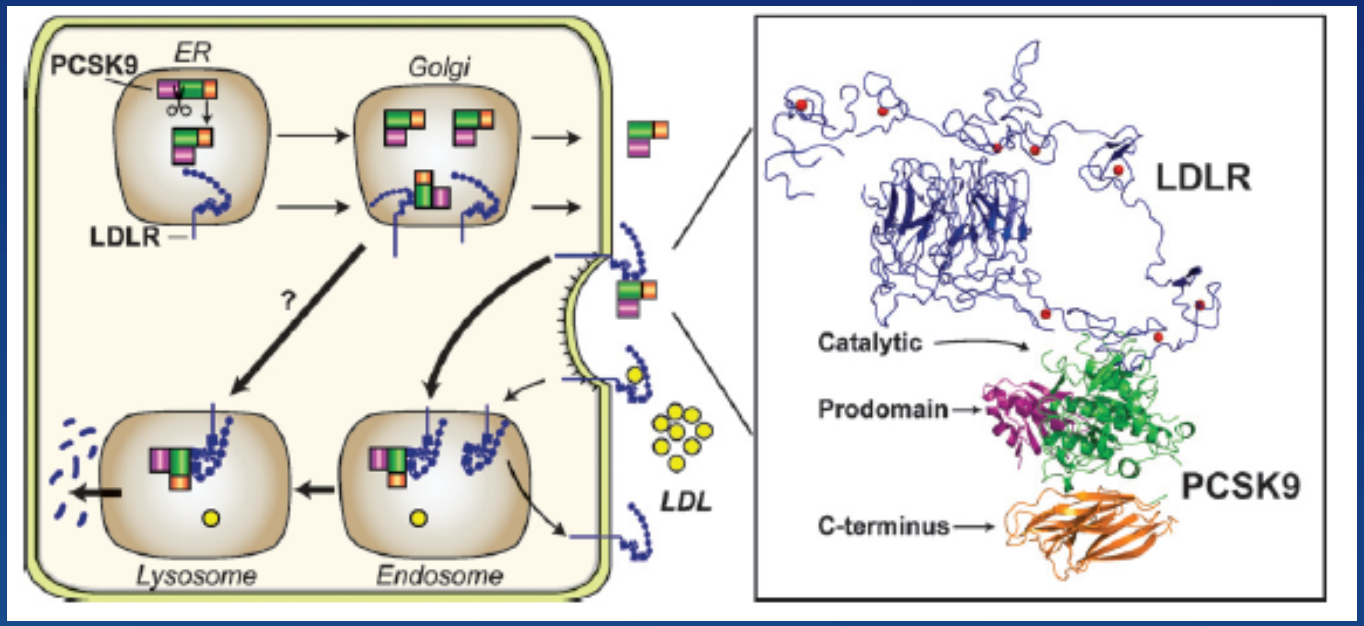
Statin Effect on PCSK9 & LDL receptor



PCSK9 and LDL Receptor Interaction



For illustration purposes only



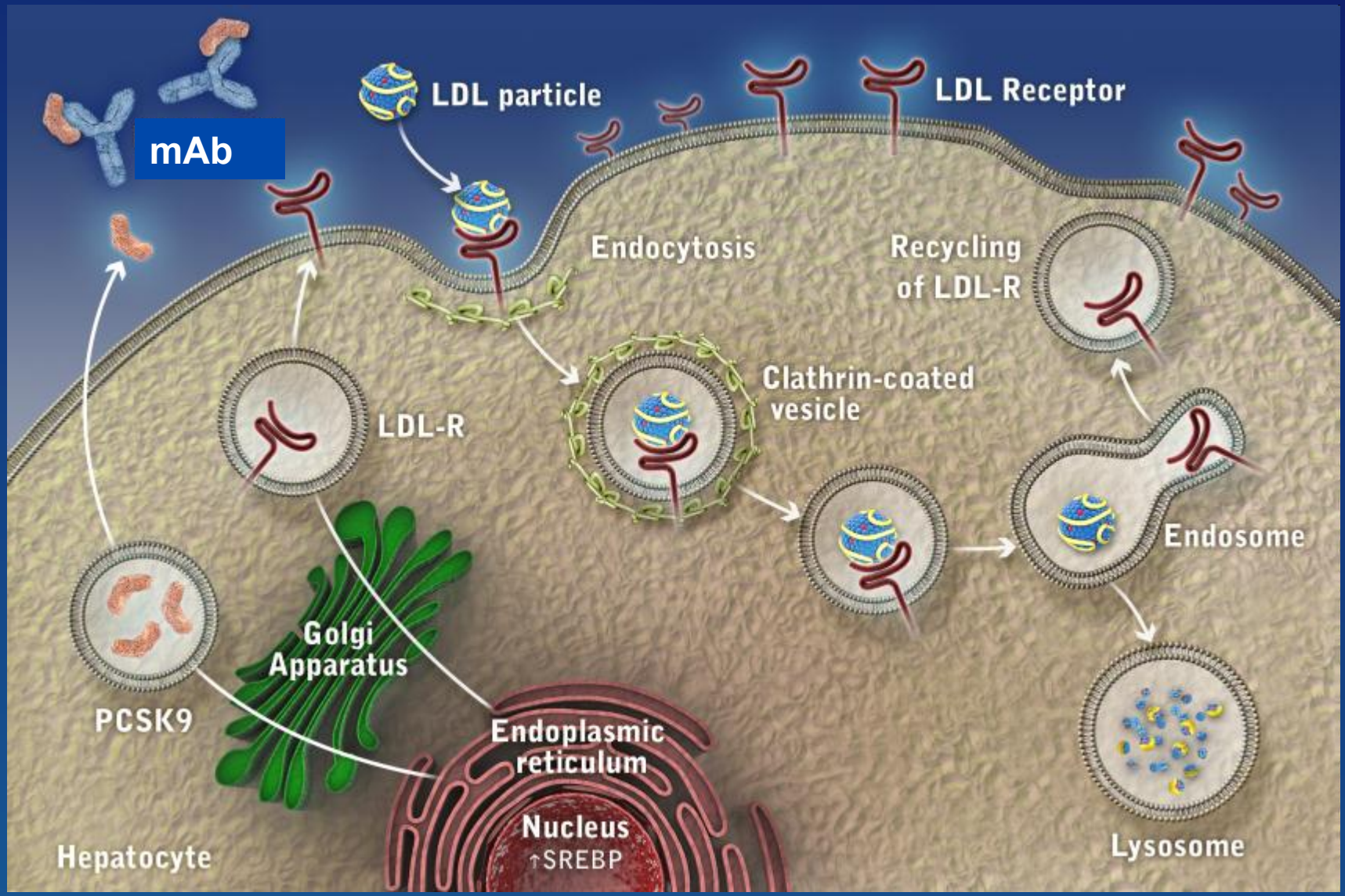
Secreted PCSK9 forms a complex with the EGF-A domain of the LDLR extracellular domain (ECD), leading to endocytosis of the PCSK9-LDLR complex and subsequent degradation of the LDLR

Horton JD, Cohen JC, and Hobbs HH. J Lipid Research 2009;50:S172-177

Approaches to Reducing PCSK9 interaction with LDL receptor

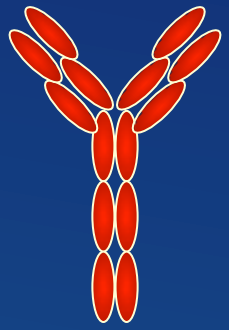
- **Bind plasma PCSK9**
  - **Monoclonal antibodies** (Regeneron/Sanofi, Amgen, Genentech, Novartis, Pfizer)
  - **Adnectins** (Adnexis/BMS)
- **Reduce PCSK9 synthesis**
  - **siRNA** (Alnylam)

Impact of an PCSK9 mAb on LDL Receptor Expression



Evolution of Therapeutic Monoclonal Antibodies

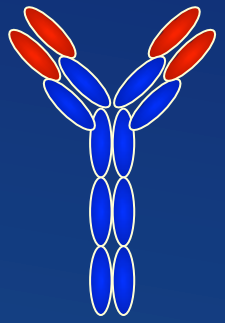
mouse mAb



- mouse variable
- mouse constant
- no repeated dosing

chimeric

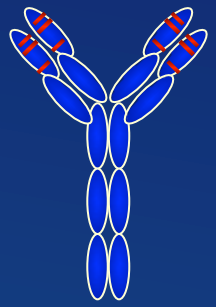
mAbs: rituximab, cetuximab



- all mouse variable
- human constant
- time-consuming to create

humanized

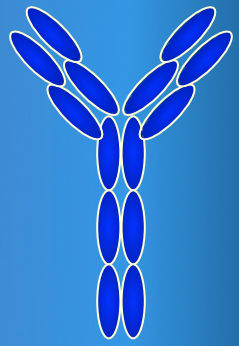
mAbs: trastuzumab/ bevacizumab



- part mouse variable
- human constant
- time-consuming to create

human mAb

mAbs: adalimumab/ panitumumab



- human variable
- human constant
- repeated dosing possible

Potential immune response to therapeutic antibody