PCSK9 Inhibition:

From Genetics to Patients

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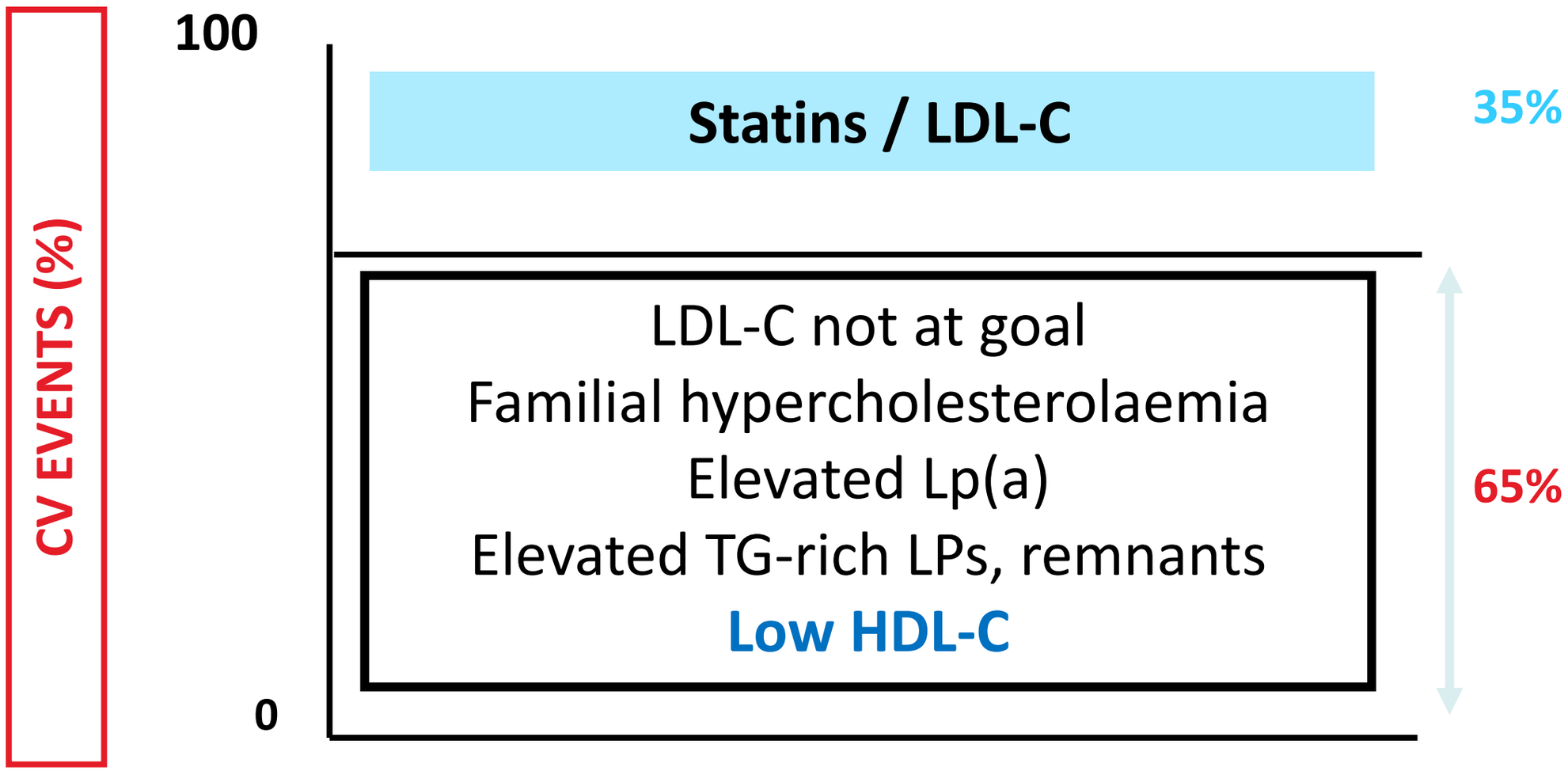
Unmet clinical needs in CVD: Focus on lipids



What are the principal factors which regulate circulating LDL-C levels?

Can such mechanistic understanding identify new therapeutic targets ?

Regulation of plasma LDL-C levels

- Rates of hepatic production of precursor VLDL
- Rates of intravascular remodelling of VLDL and LDL
- Rates of direct hepatic production of LDL
- Rates of hepatic LDL-R-mediated catabolism
- Rates of non-LDL-R-mediated LDL catabolism

VLDL very low-density lipoprotein; LDL low-density lipoprotein; LDL-R, LDL-receptor

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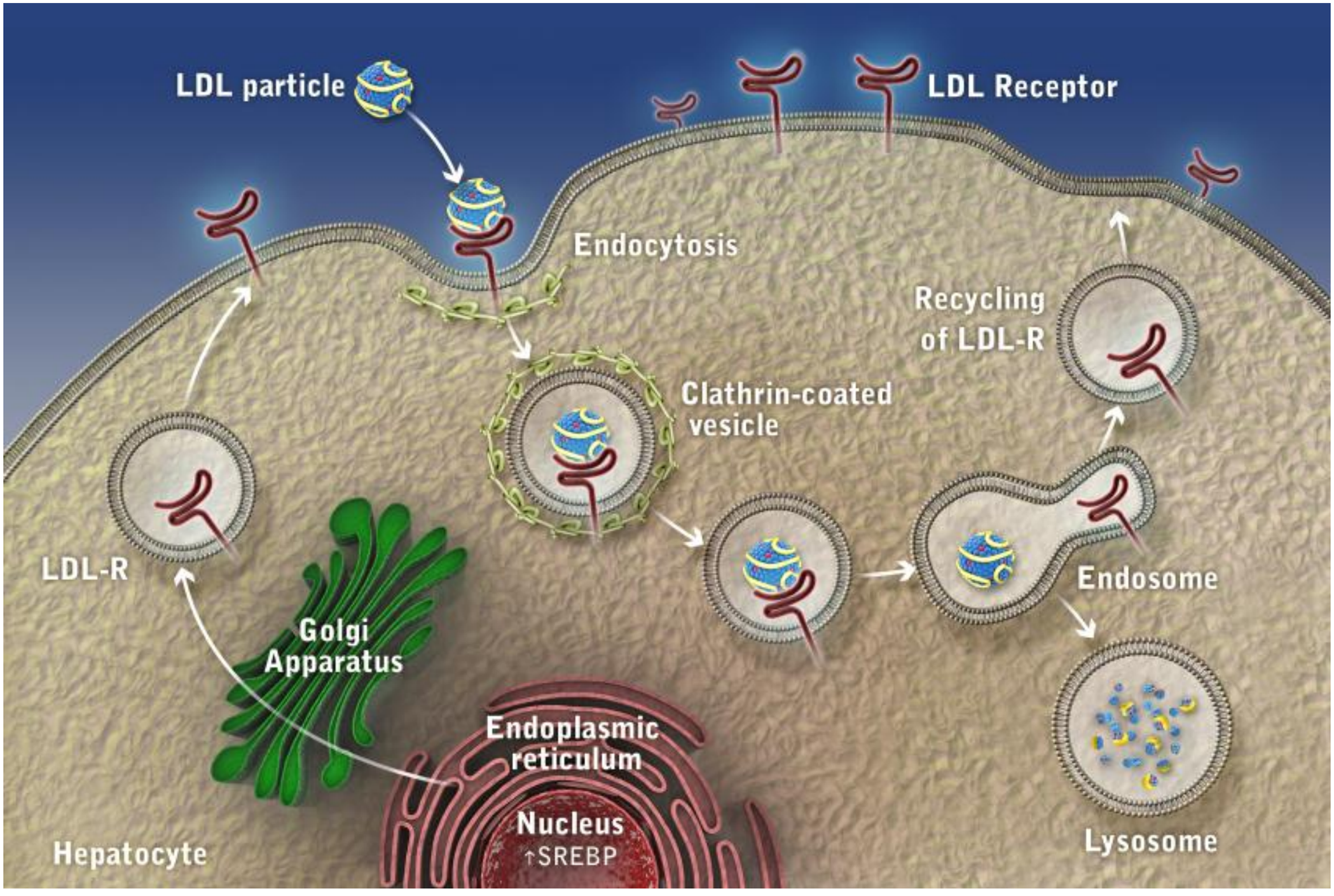
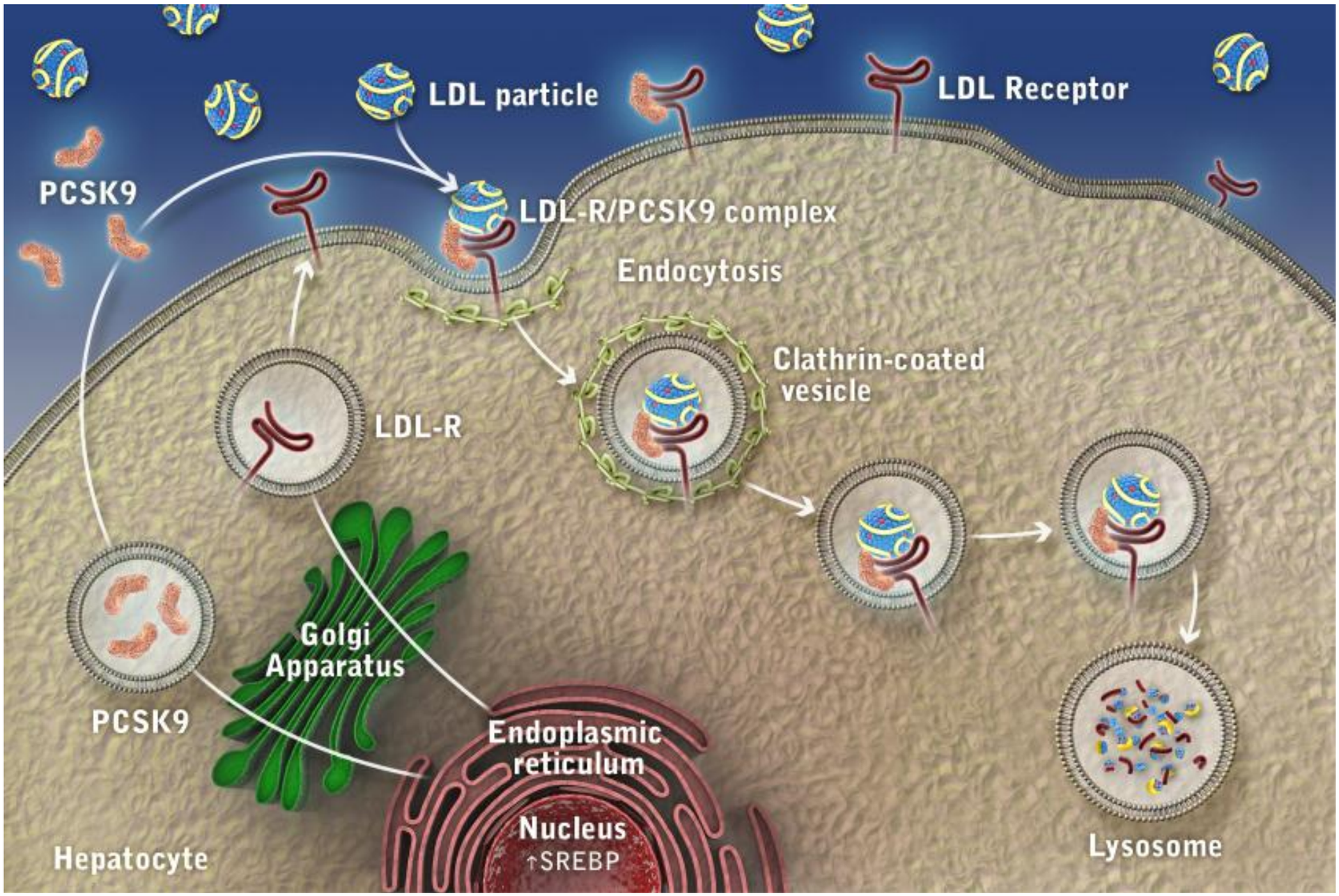
Catabolism of LDL by the hepatic LDL-R



http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_438651.pdf
(Accessed January 2014)

PCSK9: Key regulator of LDL-R expression and LDL degradation



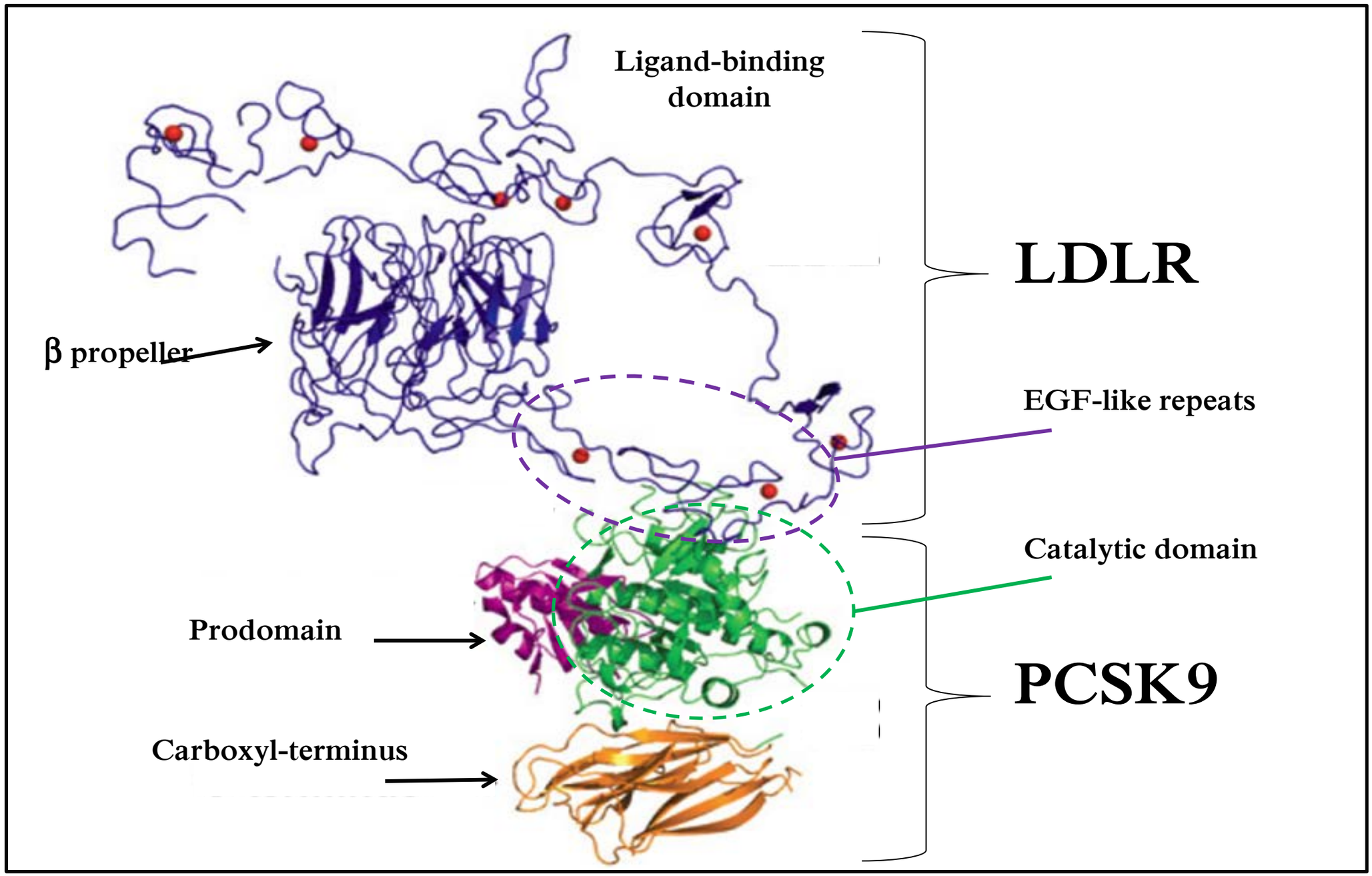
http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_438651.pdf (Accessed January 2014)

What is PCSK9?

Pro-protein convertase subtilisin-like kexin type 9

- A secreted protease which is a 692 amino acid mature protein, consisting of 3 domains: prodomain, catalytic and C-terminal
- Primarily expressed in liver, intestine and kidney
- Rapid turnover in plasma (<10 mins); plasma removal principally via the LDL-R

PCSK9 binding to the LDL-R



Horton JD et al. J Lipid Res 2009; 50: S172–7

Impact of PCSK9 on the hepatic LDL-R

- LDL receptor numbers on the cell surface decrease as a result of enhanced intracellular degradation of the LDL-R
- Plasma LDL levels rise

Does variation in the PCSK9 gene alter its function, with impact on circulating LDL levels?

- **Gain of function (GoF) missense mutations =**
  genetic hypercholesterolaemia (FH phenotype)

- **Loss of function (LoF) nonsense mutations =**
  hypocholesterolaemia with low LDL levels and major reduction in CHD incidence

PCSK9 GoF mutations =

Severe hypercholesterolaemia

Clinical characteristics and fasting lipid values (mmol/l) in patients heterozygous for mutations N157K and D374Y in the PCSK9 gene and close relatives

Family	ID	Sex	Age	Mutatyion	Total serum cholesterol	HDL cholesterol	Triglycerides	LDL cholesterol	Xanthomas	CHD[a]
0034	FH122	Female	42	D374Y	13.6	1.0	1.01	12.1	+	-
0034	FH123	Male	45	-	6.5	Not determined	Not determined	Not determined	-	-
0034	FH121	Female	19	D374Y	13.6	0.8	2.05	11.9	+	-
0034	FH120	Female	21	D274Y	8.9	1.0	0.56	7.4	+	-
0075	FH75a	Male	40	D374Y	11.6	1.4	1.4	9.6	+	-
0075	FH85c	Female	35	-	6.3	Not determined	Not determined	Not determined	-	-
0075	FH75d	Male	7	D374Y	8.8	1.5	0.9	6.6	-	-
0075	FH75b	Female	16	D374Y	8.1	1.0	0.8	6.7	-	-
0305	0481	Female	25	N157K	11.8	Not determined	0.7	Not determined	-	-
				D374Y						

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]CHD, coronary heart disease manifested as angina pectoris and myocardial infarction.

Leren TP. Clin Genet 2004; 65: 419–22

Population studies: PCSK9 LoF mutations

- Subjects with LoF mutations in PCSK9 or total lack of PCSK9
- Have naturally low levels of LDL-C and reduced CHD (→ efficacy)
- These mutations are not associated with other detectable abnormalities (→ safety)

	PCSK9 Mutation	LDL-C Reduction	CHD Reduction	Population
Benn *et al*. JACC 2010	R46L	12%	46%	Copenhagen City Heart Study n=10,032 Copenhagen General Population Study n=26,013 Copenhagen Ischemic Heart Disease Study n=9654
Cohen *et al*. NEJM 2006	R46L Y142X or C679X	14% 28%	47% 88%	Atherosclerosis Risk Community Study (US) (Black patients, n=3363; white patients, n=9524)

Adapted from Cohen JC. N Engl J Med 2006; 354: 1264–72, Benn MJ. Am Coll Cardiol 2010; 55: 2833–42.

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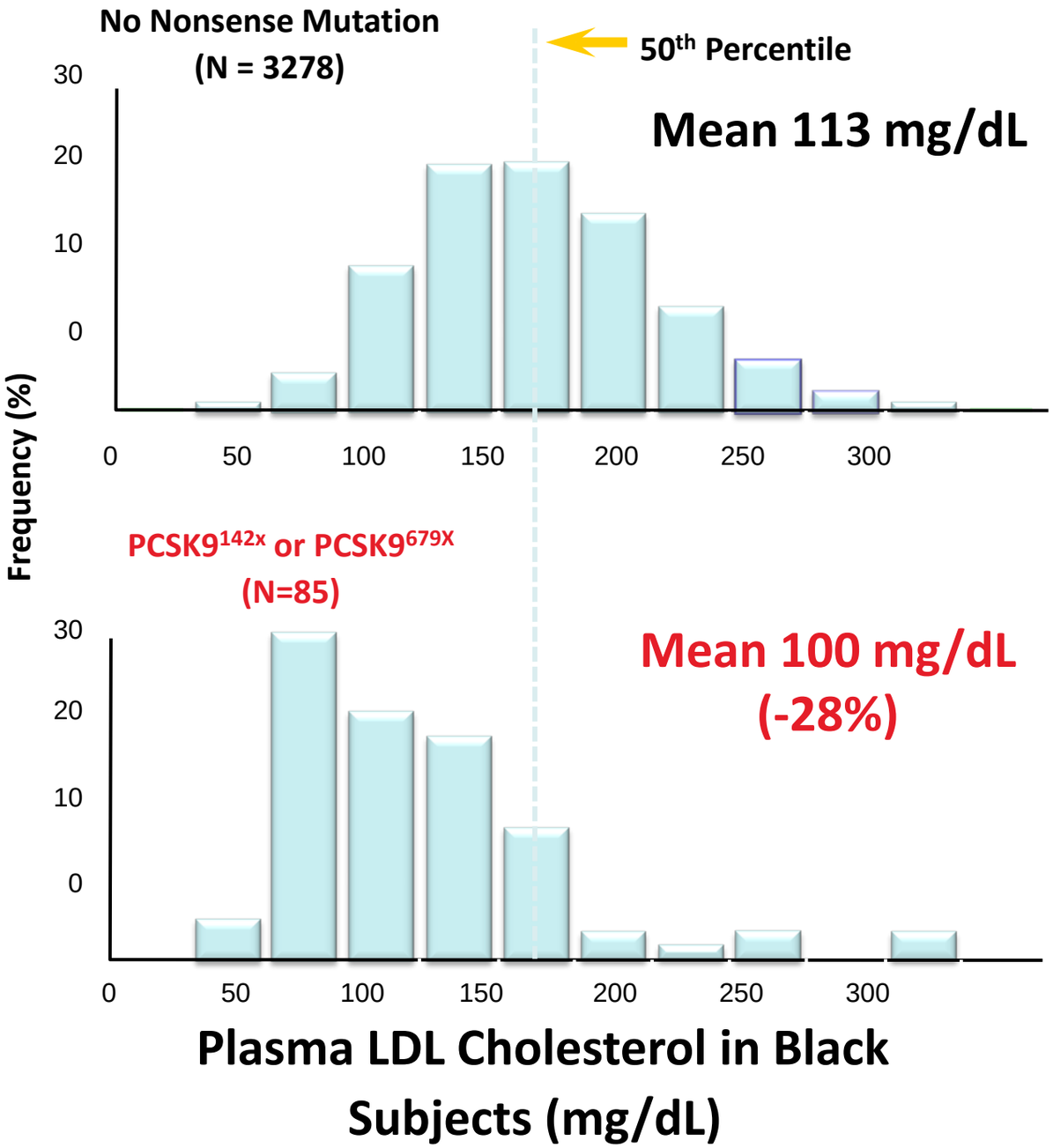
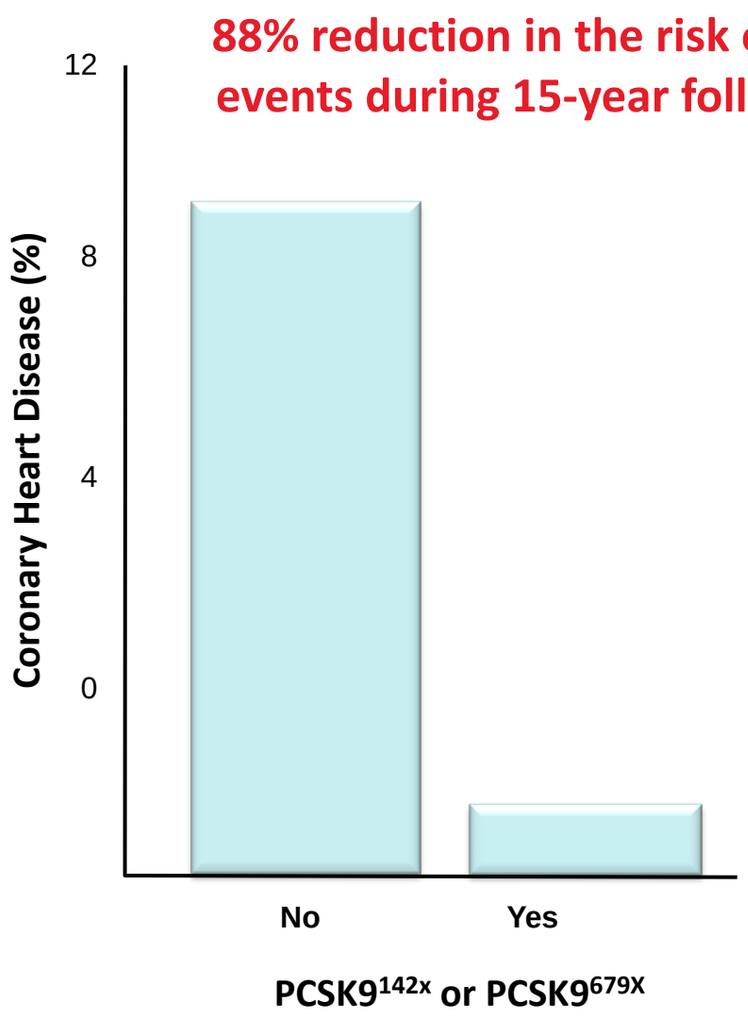
LoF PCSK9 mutations are associated with low LDL-C and low prevalence of CHD events





ARIC=Atherosclerosis Risk in the Community
Adapted from Cohen JC. N Engl J Med 2006; 354: 1264–72.

PCSK9

Emergence as a new therapeutic target in hypercholesterolaemia and related CHD

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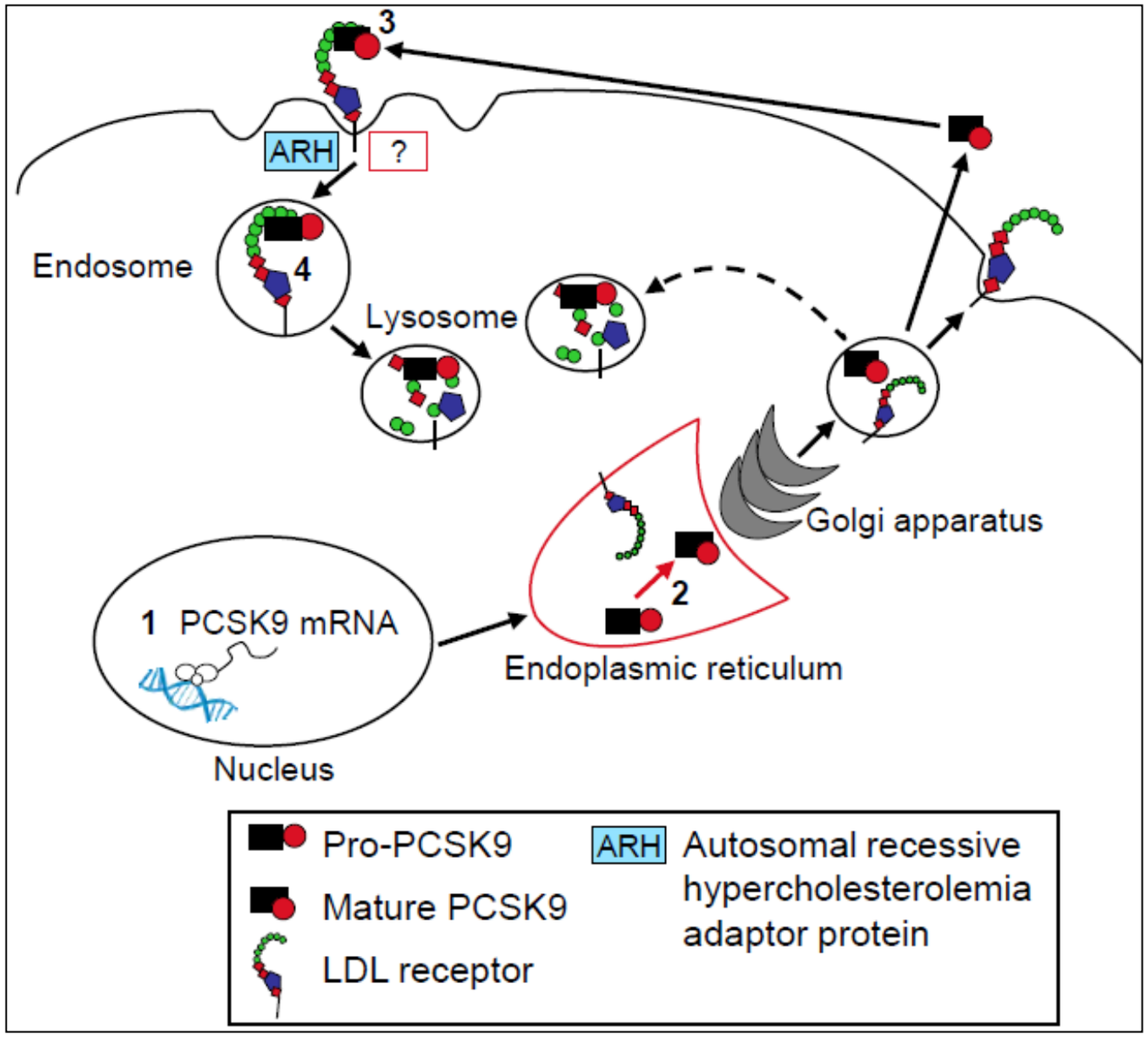
PCSK9

Potential targets in the PCSK9 pathway



Hedrick JA. Curr Opin Investig Drugs 2009, 10: 938–46.

1. **Reduction of PCSK9 protein production**
2. **Reduction of PCSK9 mRNA expression**
3. **Inhibition of PCSK9 binding to the LDL-R**
4. **Inhibition of PCSK9-mediated degradation of the LDL-R**

Therapeutic agents targeting PCSK9

- **Inhibition of the binding of PCSK9 to the LDL-R e.g. MABs, small peptides**
- **Inhibition of PCSK9 synthesis e.g. ASOs, siRNAs**
- **Inhibition of the intracellular processing of PCSK9 to the mature protein (small molecules)**

PCSK9

A new therapeutic target in hypercholesterolaemia

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