UPDATES ON

HYPERCHOLESTEROLEMIA

WITH EMPHASIS ON PCSK9 INHIBITORS

July, 2018
Chicago

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Board Certified in Cardiology
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Happy
4th
Of
July!

Thank you!

CENTER FOR DISEASE CONTROL AND PREVENTION – U. S. statistics

- 71 millions have high level of LDL
- Only 1/3 of adults with high LDL receiving treatment
- 1 in 5 patients on statin cannot adequately lower LDL (or 11 million patients)
- 1.3 millions with ACS have LDL over 100 despite statin
- Over 50% stop taking after 6 months. Compliance, adherence, side effects?

Statins

HMG CoA Reductase inhibitors

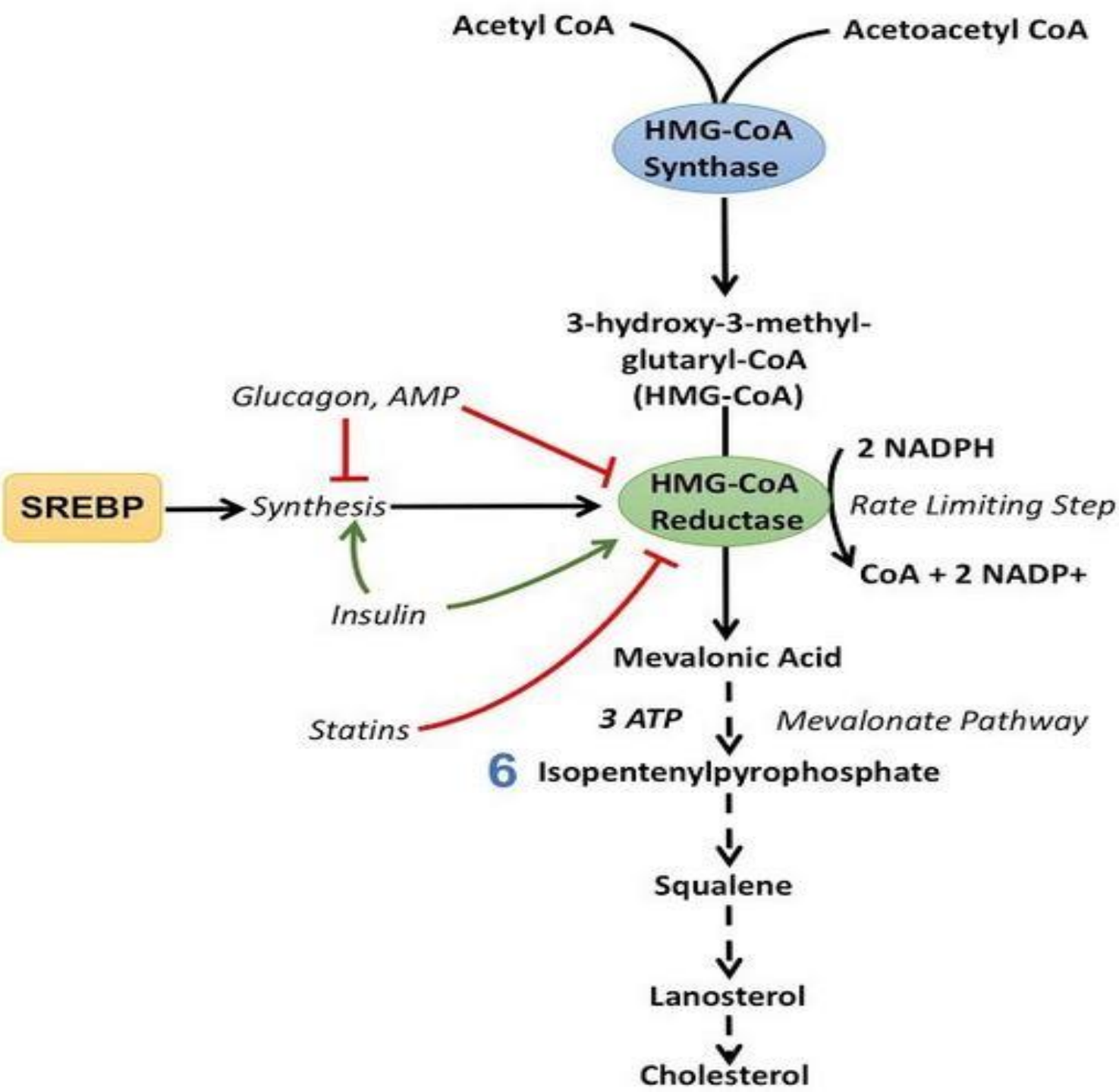
Cornerstone of Rx to lower LDL

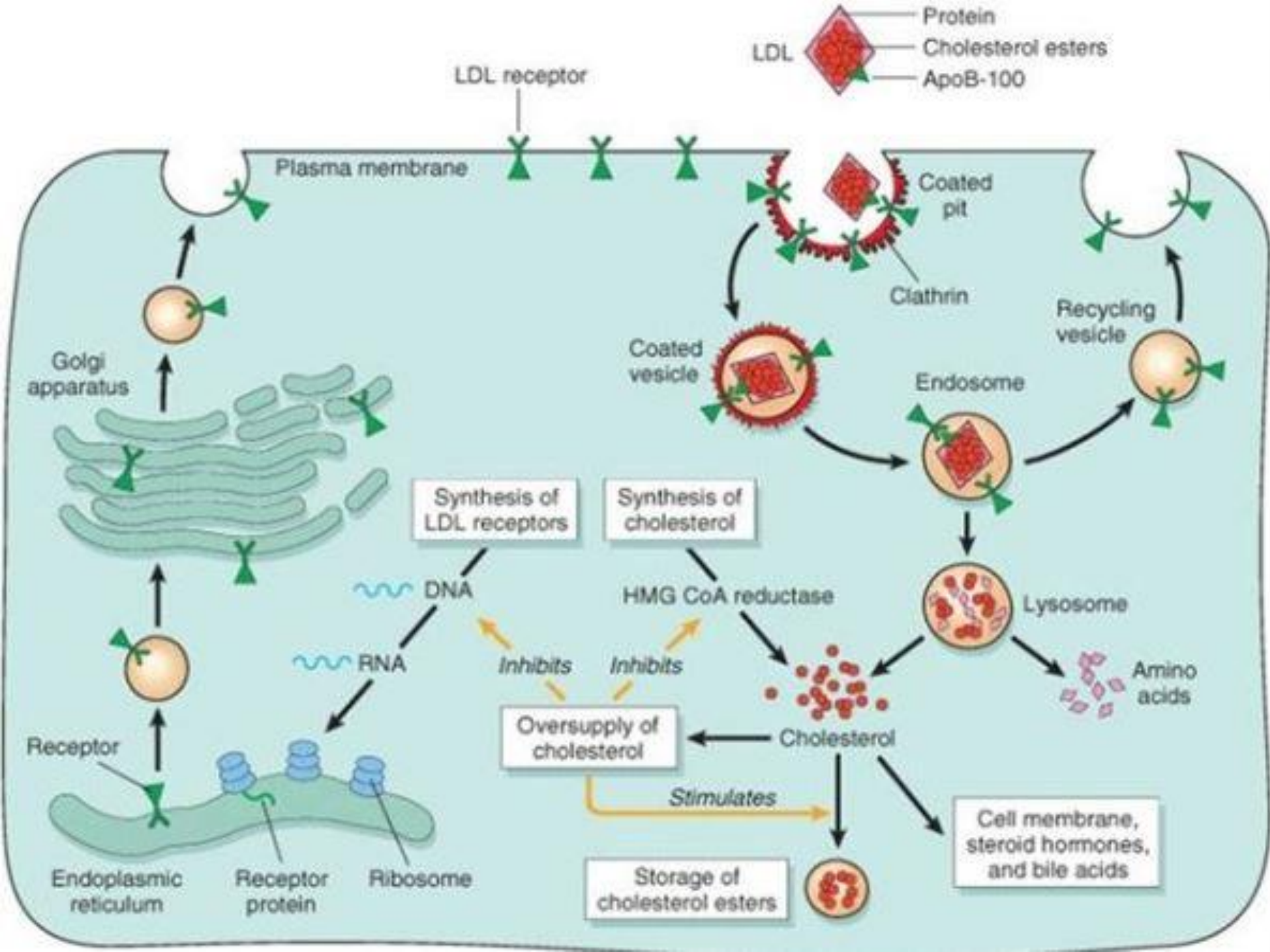
Available since 1980's

Ezetimibe

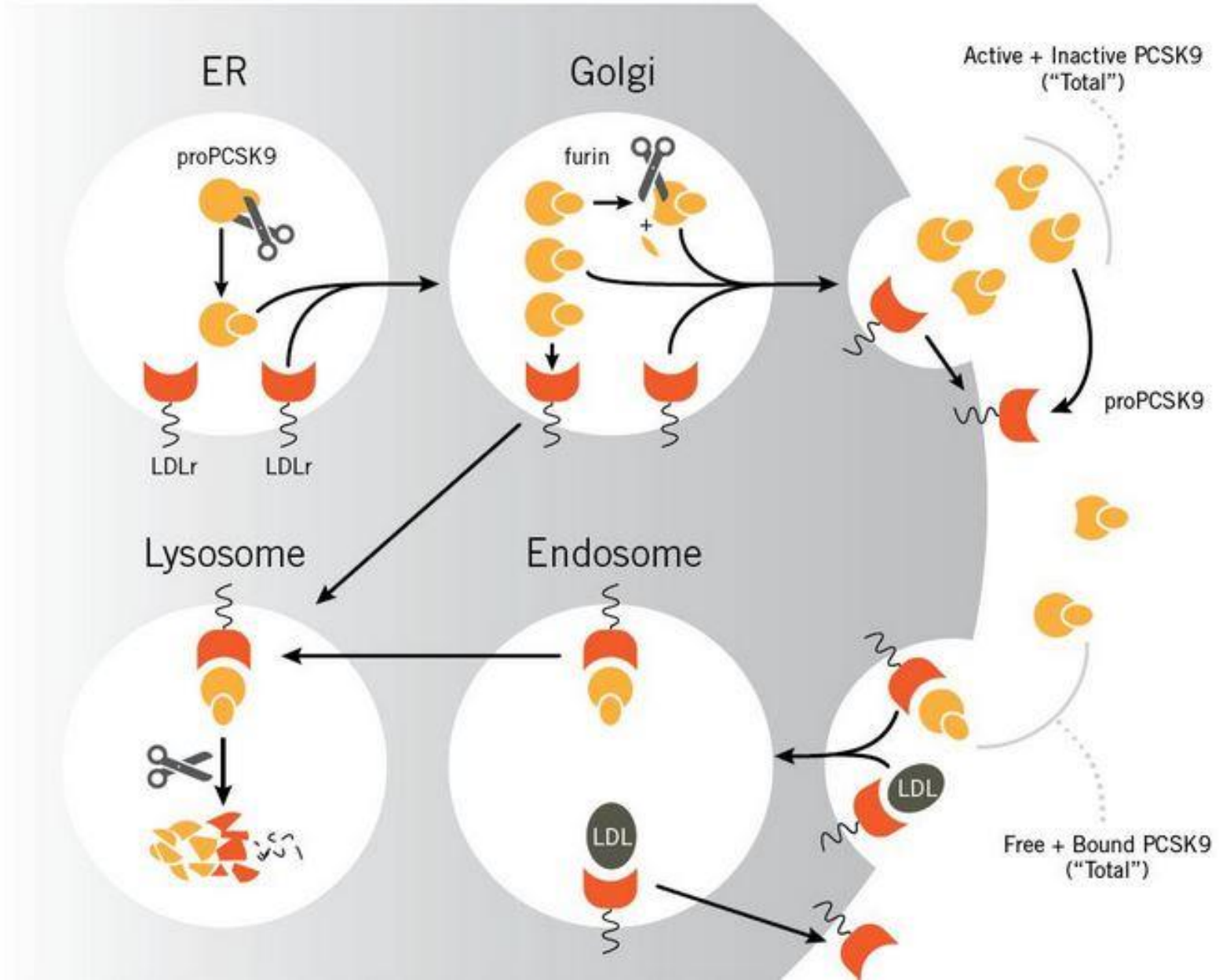
Blocks absorption

Less potent than statin

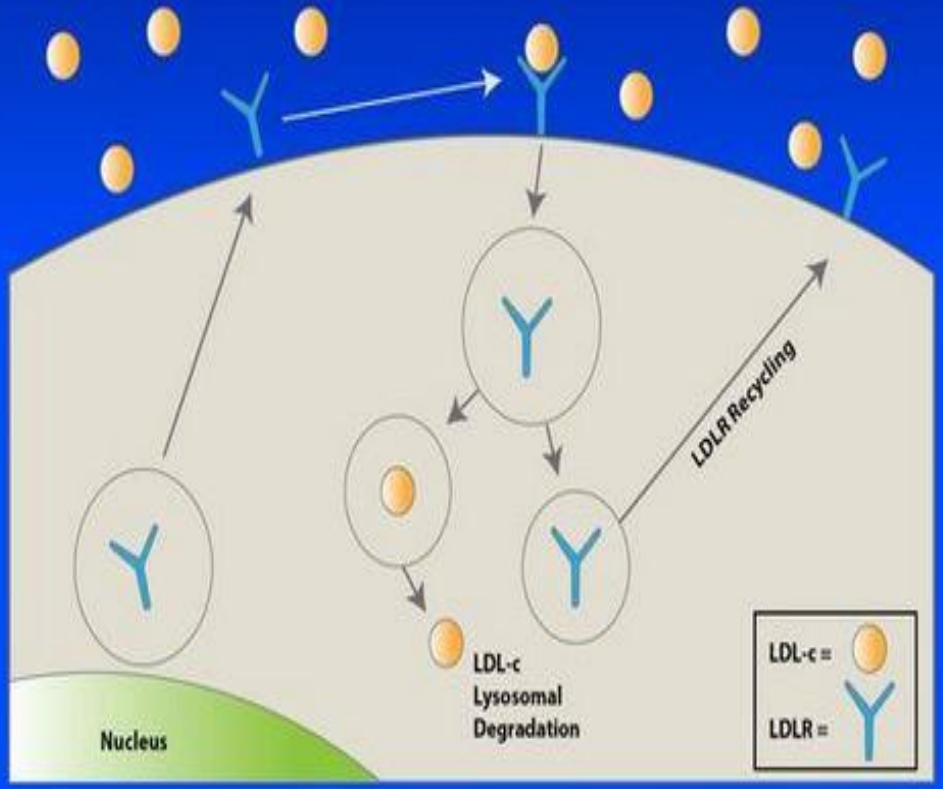

Acetyl CoA
Acetoacetyl CoA
HMG-CoA Synthase
3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA)
Glucagon, AMP
SREBP
Synthesis
HMG-CoA Reductase
2 NADPH
Rate Limiting Step
CoA + 2 NADP+
Insulin
Mevalonic Acid
Statins
3 ATP
Mevalonate Pathway
6 Isopentenylpyrophosphate
Squalene
Lanosterol
Cholesterol

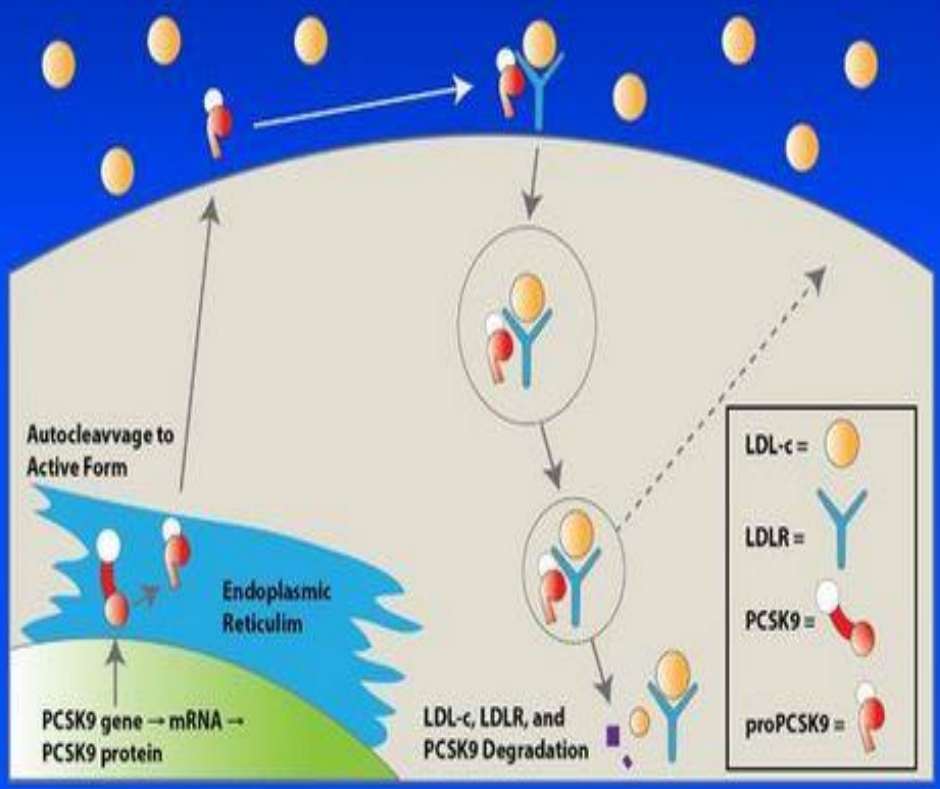

Protein
LDL
Cholesterol esters
ApoB-100
LDL receptor
Plasma membrane
Coated pit
Clathrin
Recycling vesicle
Golgi apparatus
Coated vesicle
Endosome
Synthesis of LDL receptors
Synthesis of cholesterol
DNA
HMG CoA reductase
Lysosome
RNA
Inhibits
Inhibits
Amino acids
Receptor
Oversupply of cholesterol
Cholesterol
Stimulates
Cell membrane, steroid hormones, and bile acids
Endoplasmic reticulum
Receptor protein
Ribosome
Storage of cholesterol esters

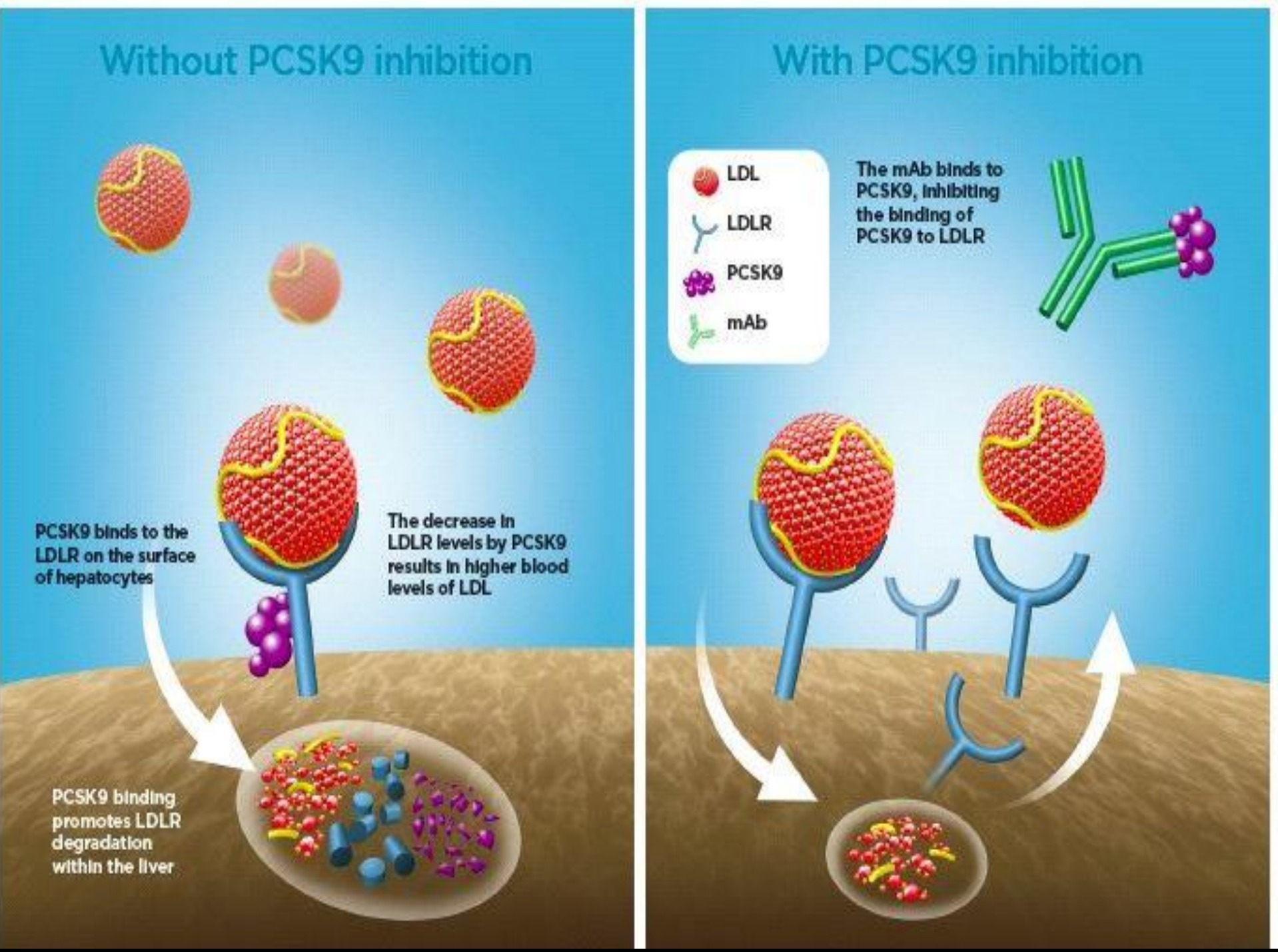
PCSK9 "Life" Cycle

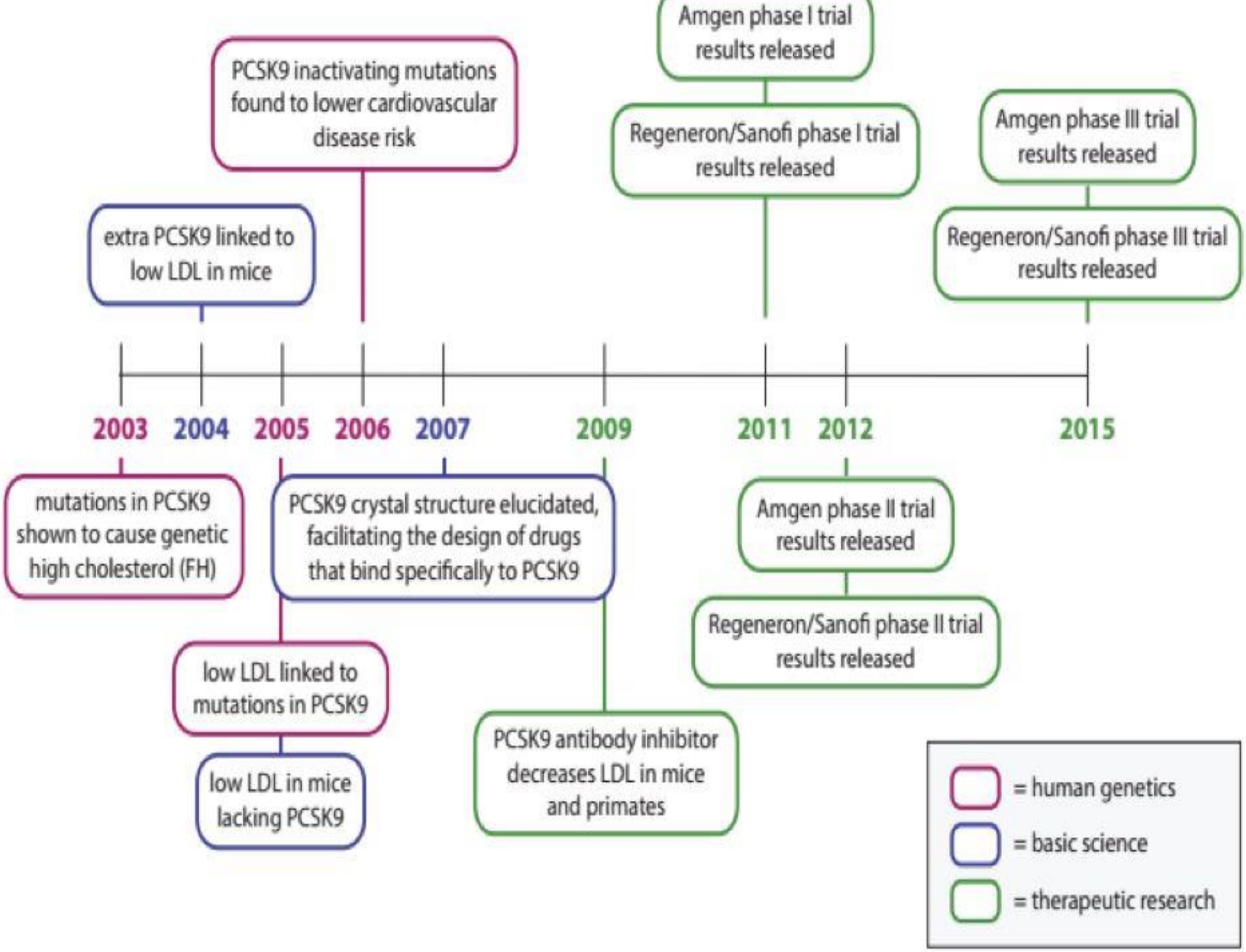


Physiology – Regulation of LDL Receptors






Without PCSK9 inhibition
PCSK9 binds to the LDLR on the surface of hepatocytes
The decrease in LDLR levels by PCSK9 results in higher blood levels of LDL
PCSK9 binding promotes LDLR degradation within the liver
With PCSK9 inhibition
LDL
LDLR
PCSK9
mAb
The mAb binds to PCSK9, inhibiting the binding of PCSK9 to LDLR


Amgen phase I trial results released
PCSK9 inactivating mutations found to lower cardiovascular disease risk
Regeneron/Sanofi phase I trial results released
Amgen phase III trial results released
extra PCSK9 linked to low LDL in mice
Regeneron/Sanofi phase III trial results released
2003
2004
2005
2006
2007
2009
2011
2012
2015
mutations in PCSK9 shown to cause genetic high cholesterol (FH)
PCSK9 crystal structure elucidated, facilitating the design of drugs that bind specifically to PCSK9
Amgen phase II trial results released
Regeneron/Sanofi phase II trial results released
low LDL linked to mutations in PCSK9
low LDL in mice lacking PCSK9
PCSK9 antibody inhibitor decreases LDL in mice and primates
= human genetics
= basic science
= therapeutic research

PCSK9 INHIBITORS

- PCSK9 (proprotein convertase sutilisin kexin 9) inactivates LDL receptors in the liver cell surface that transport LDL into the liver for breakdown
- Inhibitors are MABs which inactivate PCSK9 by binding
- Alirocumab (Praluent) and Evolocumab (Repatha) approved by FDA in 2015
- Subcutaneous injection once to twice a month, over 60% decrease in LDL

CV Outcome Trials of PCSK9 inhibitors

	Alirocumab	Evolocumab	RN316	
Soponsor	Sanofi / Regeneron	Amgen	Pfizer	
Trial	**ODYSSEY** outcomes	**Fourier**	**Spire** I	**Spire** II
Sample size	18.000	22.500	12.000	6.300
Patients	4-16w post ACS	MI, stroke, PAD	High CV risk	
Statin	Evidence based med	Atorva > 20	Lipid Lowering	
LDL-C mg/dl	>70	> 79	70-99	> 100
PCSK9 dosing	2w	2w – 4w	2w	
Endpoint	CHD death, MI, isch stroke, Hospt for UA	CV death, MI, stroke, H for UA, coro revasc	CV death, MI, stroke urg revasc	
Completion	3 / 2018	12 / 2017	8 / 2017	

Clinical Characteristic	Repatha (evolocumab)	Praluent (alirocumab)
Mechanism	PCSK9 is an endogenous protein that degrades LDLRs on liver cells, diminishing the ability of LDLRs to capture LDL-C from the blood. By inhibiting PCSK9 activity, medications like alirocumab and evolocumab increase LDLR levels on the surface of liver cells, thereby increasing the intensity of LDLR-mediated LDL-C clearance.	
Efficacy	Reduced average LDL-C levels 55%-75%[a]	Reduce average LDL-C levels 46%-60%[a]
MACE Reduction Data	In post hoc data analysis, evolocumab reduced the rate of cardiovascular events over 1 year of treatment (0.95% with evolocumab vs 2.18% with standard therapy; $P = .003$).	A post hoc analysis of a 24-week trial showed that MACEs occurred at a lower rate in patients receiving alirocumab than patients receiving placebo (1.7% vs 3.3%; $P = .02$).
Proposed Dosing	140 mg administered subcutaneously every 2 weeks or 420 mg administered subcutaneously each month	75 mg administered subcutaneously every 2 weeks or 150 mg administered every 2 weeks if greater LDL-C reduction is necessary
Common AEs[b]	Injection-site reactions, pruritus, myalgia, upper respiratory tract infection, nasopharyngitis	
Drug-neutralizing Antibodies	No recorded cases of drug-neutralizing antibodies	Drug-neutralizing antibodies appear in 1.2% of patients
Rare but Concerning AEs	5 cases of angioedema have been reported	Hypersensitivity, hypersensitivity vasculitis, and nummular eczema
Injection-site Reactions	3.3%-5.7% of patients, depending on trial duration and design	6.1% of all patients (pooled data from all clinical trials)

AE = adverse event; LDL-C = low-density lipoprotein cholesterol; LDLRs = low-density lipoprotein receptors; MACE = major adverse cardiovascular event; PCSK9 = proprotein convertase subtilisin/kexin type 9.

[a]A meta-analysis of PCSK9 inhibitor trials estimated that patients may expect LDL-C lowering of more than 50% with PCSK9 inhibitors as monotherapy and more than 70% when PCSK9 inhibitors are used with background lipid-lowering treatment.[23]

[b]The rate of serious treatment-emergent AEs or the rate of discontinuation due to such events in patients taking PCSK9 inhibitors is not statistically different from AE rates in placebo groups (risk ratio = 1.01; 95% CI, 0.98 to 1.04).[24]

ODDESSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab)

Over 18,000 patients, 2341 high risk, with high cholesterol on statin, 75mg. Alirocumab subcutaneously every 2 weeks, or 400mg every 4 weeks

18 months phase 3 trial

LDL over 60% drop after 24 weeks and remained low over 78 weeks

MI and stroke 1.7% compared with 3.3% in placebo group

July, 2015 approved by FDA with caveat that effect on CV and total mortalities not known, would be out 2017 or 2018

Side effects: common cold, injection site reactions, flu

FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)

27.564 patients, 2976 high risk, on statin and or ezetimibe, LDL apheresis. Evolocumab 140 mg. subcutaneously every 2 weeks or 420 mg. every month

2.2 years phase 3 trial

LDL over 60% drop

MI decreased by 27%, stroke by 21% and revascularization by 22%

August, 2015 approved by FDA

Side effects: arthralgia, injection site reaction, headache, limb pain

GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound)

- 968 patients with angiographic CAD, mean age of 59.8, all on statin, addition of 420 mg. monthly Evolocumab for 18 months, reported 2016
- Achieved average LDL of 36.6 mg./dL. compared with 93 mg. /dL. with statin alone
- Produced regression, mean change in PAV of -0.95% for evolocumab-statin group compared with +0.05 in statin only patients (P<0.001)
- Produced regression in 64% of evolocumab-statin patients vs. 47% of statin only patients (P<0.001)

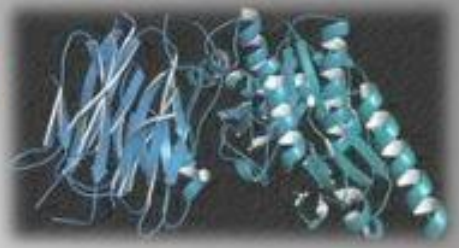
Metaanalysis (Dec. 2017):

- 35 randomized trials, PCSK9 inhibitors
- 45,539 patients
- Mean follow up of 85.5 weeks
- Mean baseline LDL=116
- MI 2.3% vs. 3.6%, P<0.001
- Stroke 1% vs. 1.4%, P<0.02
- Coronary revascularization 1% vs. 1.42%, P<0.001
- All cause mortality, P<0.12
- Cardiovascular mortality, P<0.95

ODDYSSEY – ACC, March 2018

- 18,924 patients, recent MI or unstable angina, phase 3
- Primary endpoints: (combined MI, stroke, death from CAD or unstable angina requiring hospitalization) decreased by 15%
- 2-5 years, median follow up of 2.8 years
- Nonfatal MI=6.6%/7.6%, p=0.006
- Ischemic stroke=1.2%/1.6%, p=0.01
- Unstable angina=0.4%/0.6%, p=0.02
- All cause mortality and CHD mortality =no significant difference, p=0.38
- Subgroup analysis: subjects with baseline LDL of 100 or higher, primary end point decreased by 24%, CHD by 28%, CV death by 31% and all cause mortality by 29%

PCSK9-I Patient Population and Potential[1]



- FDA-approved for relatively small patient group w/ uncontrolled LDL despite max therapy and at high risk for CVD
  - Familial hypercholesterolemia: ~620,000 in US
  - Severe hypercholesterolemia uncontrolled with statins: ~1 million in US
- BUT patient pool could expand quickly if PCSK9-Is are deemed appropriate to treat:
  - 1-3 million Americans who are "statin intolerant"
  - ~ 15 million Americans with established CAD

Potential Long-term Outcomes

- Long term effects of very low LDL are unknown
- Studies to date have not been powered to look at mortality or CVD adverse events
- Meta-analysis by Navarese et al suggested[5]:
  - 50% statistically significant reduction in all-cause mortality
  - 50%, nonsignificant reduction in cardiovascular mortality
- **But**: Low total number of events, wide confidence intervals

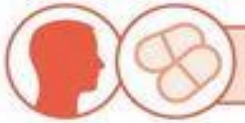
Statin drugs (atorvastatin [Lipitor] and Crestor)

- Generics/Brands cost $600 per year
- Oral tablets
- Effective in lowering cholesterol (high dose ~ 50% reduction in LDL)
- Side effects include myalgia and liver function test increases
- Proven cardiovascular event reduction in outcomes data

PCSK9 inhibitors (Praluent® and Repatha™)

- Cost $4,000 to $12,000 per patient per year
- Self-injected antibody
- 60% to 65% reduction in LDL
- No identified drug interactions and fewer side effects
- Initial approval for familial hypercholesterolemia and clinical atherosclerotic disease
- No cardiovascular event reduction outcomes data expected until 2017

CENTRAL ILLUSTRATION: Determining When to Add Nonstatin Therapy



Patient at ASCVD risk on maximum statin therapy

LDL-C thresholds for considering additional LDL-C lowering treatment with:

PCSK9 mAB for ~50% LDL-C reduction

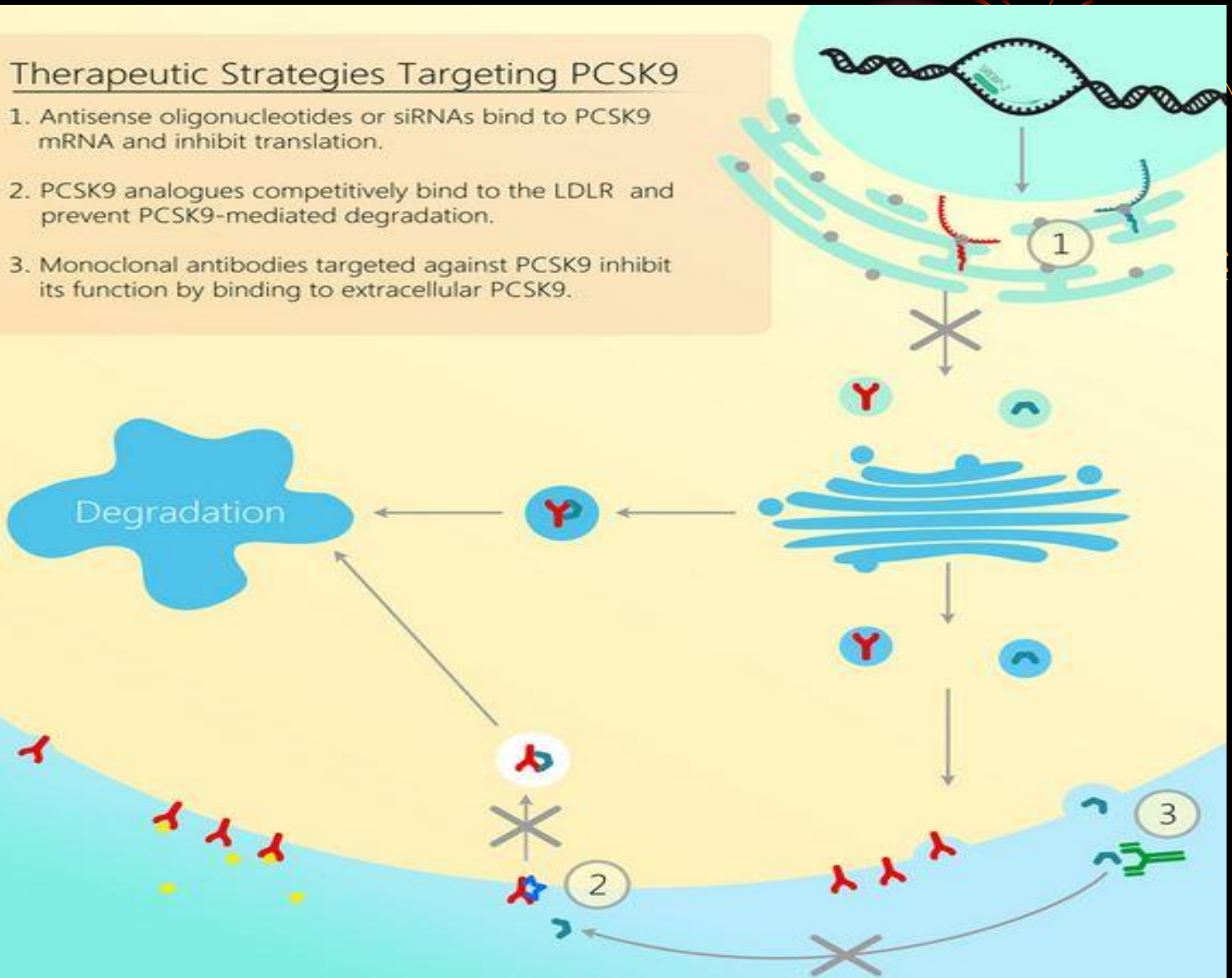
or

Ezetimibe for ~20% LDL-C reduction

Patient LDL-C (mg/dl)	Very high-risk patient (≥30 10-year ASCVD risk)	High-risk (20–29% 10-year ASCVD risk)	Moderate-risk (10–19% 10-year ASCVD risk)
≥190	PCSK9 mAb (NNT ≤21-28); Ezetimibe (NNT <30)	PCSK9 mAb (NNT ≤21-28); Ezetimibe (NNT <50)	PCSK9 mAb (NNT <50)
≥160			
≥130	Ezetimibe (NNT <50)		
≥100		PCSK9 mAb (NNT <50)	
≥70	PCSK9 mAb (NNT <50)		

Therapeutic Strategies Targeting PCSK9

1. Antisense oligonucleotides or siRNAs bind to PCSK9 mRNA and inhibit translation.
2. PCSK9 analogues competitively bind to the LDLR and prevent PCSK9-mediated degradation.
3. Monoclonal antibodies targeted against PCSK9 inhibit its function by binding to extracellular PCSK9.

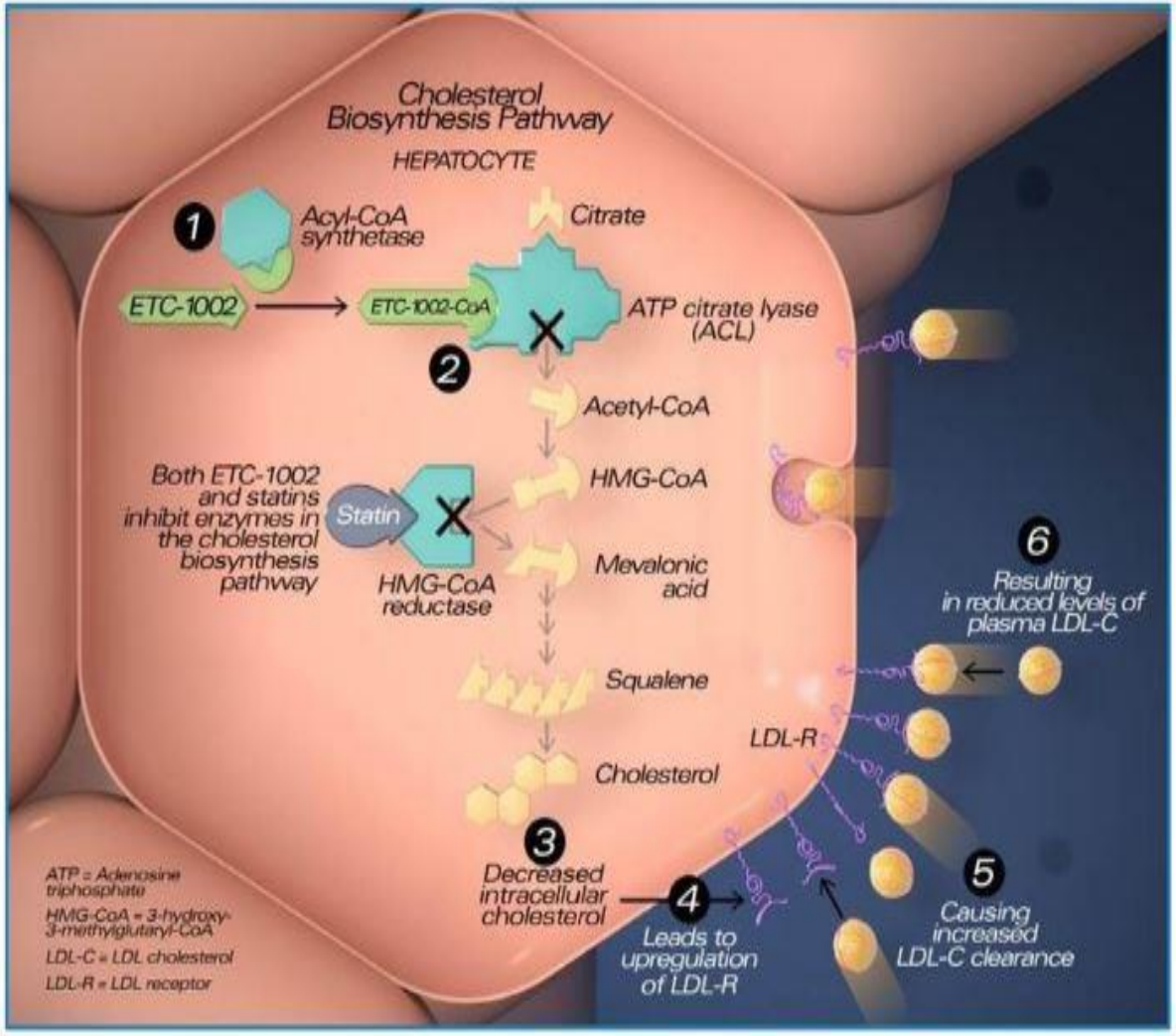


Inclisiran (iRNA)

- RNAi (siRNA), natural cellular process of gene silencing.
- Four phase 3 studies: ORION 5 – 60 pts. With HoFH, ORION 9 – 400 patients with HeFH, ORION 10-1500 patients, ORION 11-1500
- Orion 11 Trial: 1500 pts. with ASCVD or ASCVD risk equivalent (DM, FHLP, elevated LDL despite Rx and high risk score, LDL of 70 or higher), Inclisiran vs. Placebo, finished recruiting Nov. 1, 2017, 18 months, 300mg. Subcutaneously on day 1, day 90, day 270 and day 450. Measurements of LDL, HDL, nonHDL, PCSK9 and CRP

Bempedoic Acid Mechanism of Action – ACLi

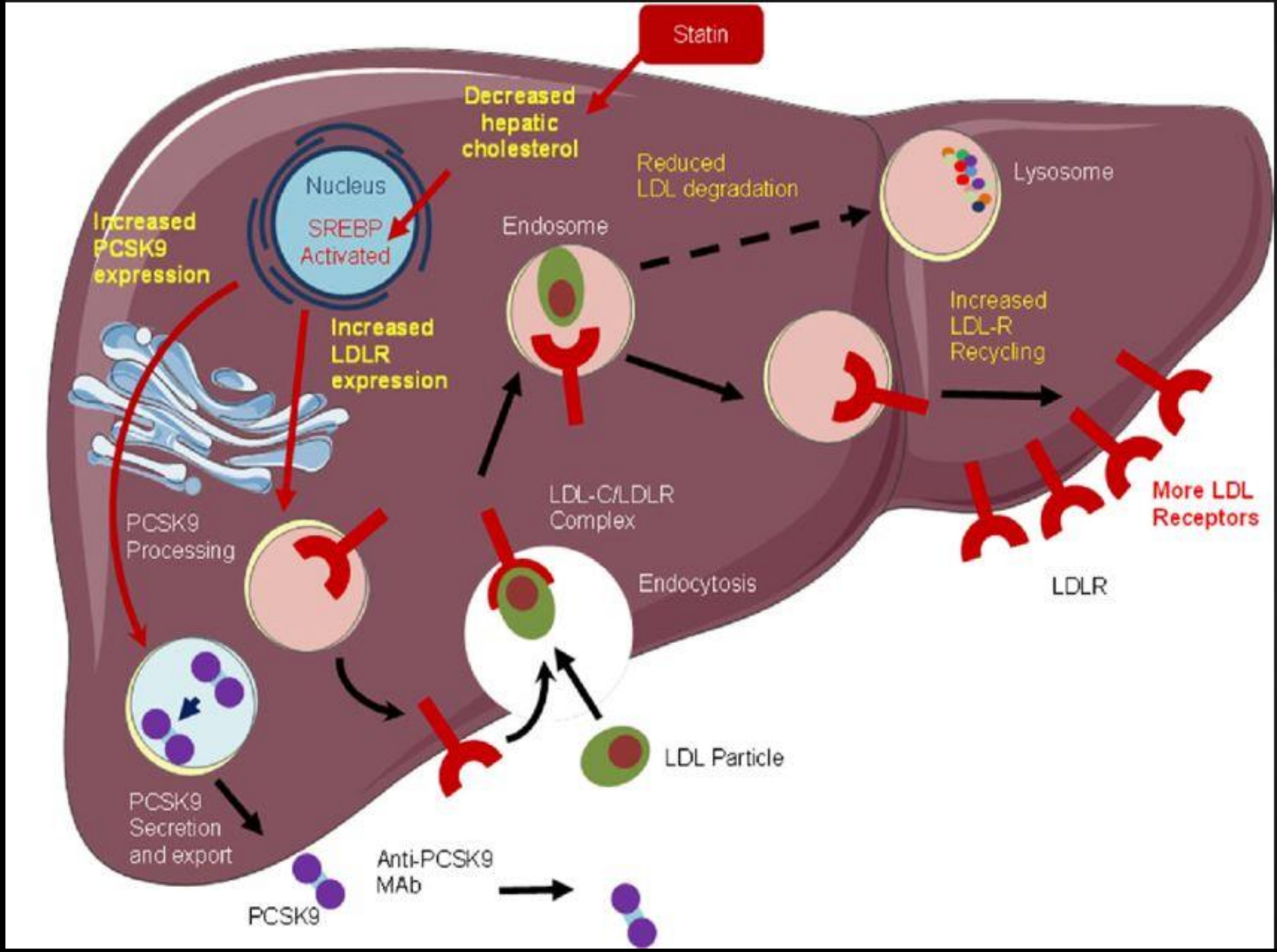
Liver Targeted, Muscle-Sparing Drug

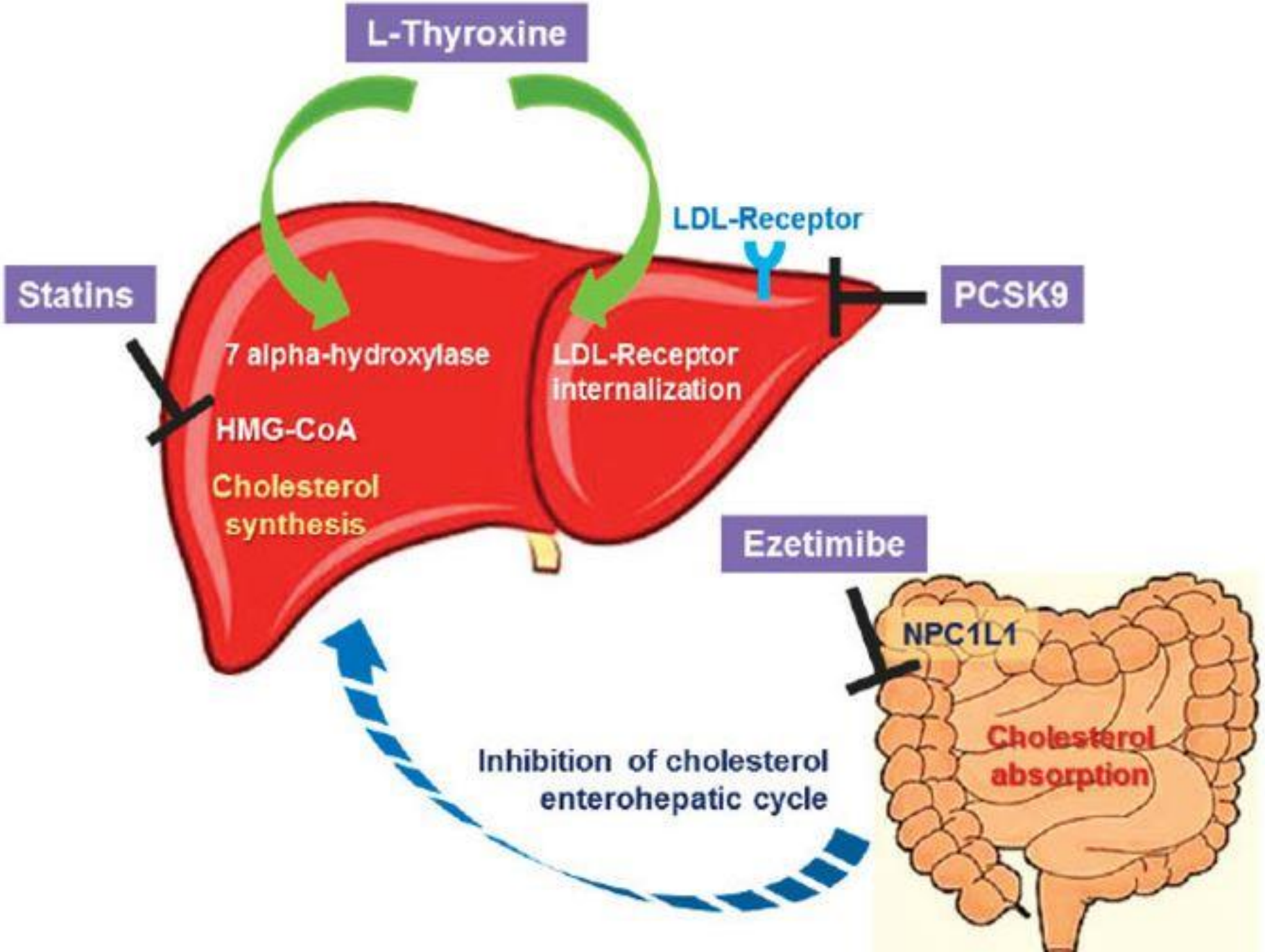


- Bempedoic acid is a "prodrug*" that requires activation by a liver-specific enzyme, acyl-CoA synthetase (***ACS Enzyme***), to form the active ETC-1002-coenzyme A (***ETC-1002-CoA***)
- ***ETC-1002-CoA*** inhibits cholesterol synthesis, ***promotes LDL receptor up-regulation***, and lowers plasma LDL-C
- The ***ACS Enzyme*** is not present in skeletal muscle resulting in lower potential for muscle-related side effects

BEMPEDOIC ACID (ETC 1002)

- Targets ATP Citrate Lyase enzyme earlier in the pathway of cholesterol synthesis
- In the liver, it is converted to CoA derivative or ETC 1002, directly inhibits ACL, resulting in decreased cholesterol synthesis and upregulation of LDL receptor activity in the liver
- Inactive until it gets to the liver where it is converted to active form by enzyme ACSV1 (not found in skeletal muscle)
- Phases 1 and 2 = 1300 patients
- Phase 3-Study 4, 3600 patients, 180 mg. p.o. daily, after 12 weeks= 28% decrease in LDL ($p=<0.001$), 33% decrease in CRP ($p<0.001$). Other phase 3 studies: on statin intolerant ASCHD patients; in combination with Ezetemibe


Statin
Decreased hepatic cholesterol
Nucleus
SREBP Activated
Increased PCSK9 expression
Increased LDLR expression
Reduced LDL degradation
Endosome
Lysosome
Increased LDL-R Recycling
More LDL Receptors
LDLR
PCSK9 Processing
LDL-C/LDLR Complex
Endocytosis
LDL Particle
PCSK9 Secretion and export
PCSK9
Anti-PCSK9 MAb


L-Thyroxine
LDL-Receptor
Statins
PCSK9
7 alpha-hydroxylase
LDL-Receptor internalization
HMG-CoA
Cholesterol synthesis
Ezetimibe
NPC1L1
Cholesterol absorption
Inhibition of cholesterol enterohepatic cycle

LIFE STYLE CHANGES

- Million Hearts Project – 2012-2016, CV events decreased by 500,000. ABCS – aspirin when appropriate, blood pressure control, cholesterol control, smoking cessation. 2017-2022, add low sodium diet and increased physical activity

  Potential to prevent 200,000 deaths from heart disease and stroke each year in the U.S.
- Diet – PREDIMED, DASH
- PURE and STABILITY studies – increased physical activity, 15,486 subjects, 39 countries, 3.7 years
- Recent study from China on 487,334 subjects, 10 to 30 min. of exercise/day
- Tsimane population in Bolivia, highly active, fishermen, farmers, hunters. 85%, ages 45-90, no coronary calcium on CT, 15% with score of <100, TC= 155, LDL=91, HDL = 40, TG= 110. slightly elevated CRP

LIFE STYLE CHANGES
most effective, safest and least expensive

- Smoking cessation
- Low fat, low salt diet
- Exercise 30-40 minutes a day most days of the week
- Stress control - ABC
- Compliance and adherence

CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study)

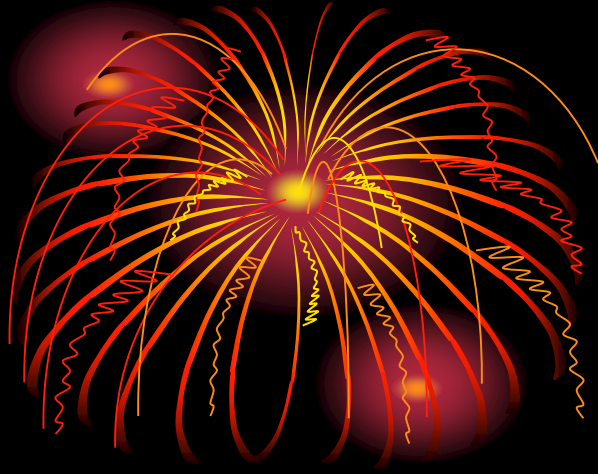
- MAB – anti-interleukin B
- 150-300 mg. subcutaneosly every 3 months
- 10,000 patients with history of MI
- 3.7 years
- No change in LDL, average of 82
- HSCRP > 2mg/L to <2
- Decreased MI, stroke and CV death with P=<0.0001

SGLT2 (sodium glucose transport 2) Inhibitors) and GLP1 (glucagon like peptide 1) agonist or incretin mimetic)


OPTIMISM BLVD


Reunion Dr
2449

The End



Congratulations and thanks from the 4 chambers of my heart...
elc