Beyond the statin therapy

The importance of HDL cholesterol

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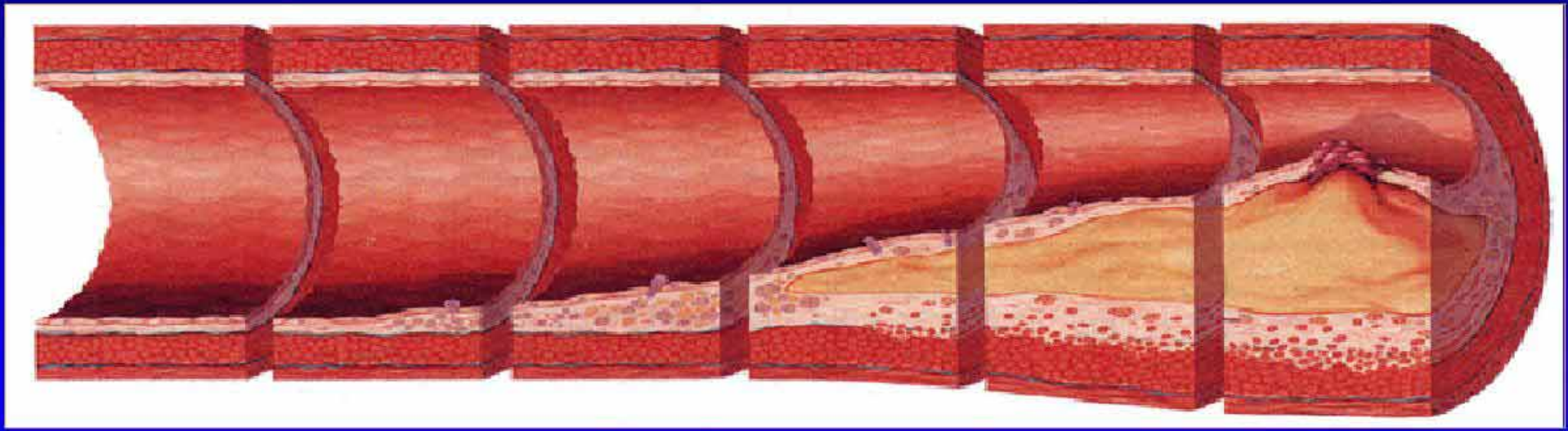
Atherosclerosis Timeline

Endothelial Dysfunction

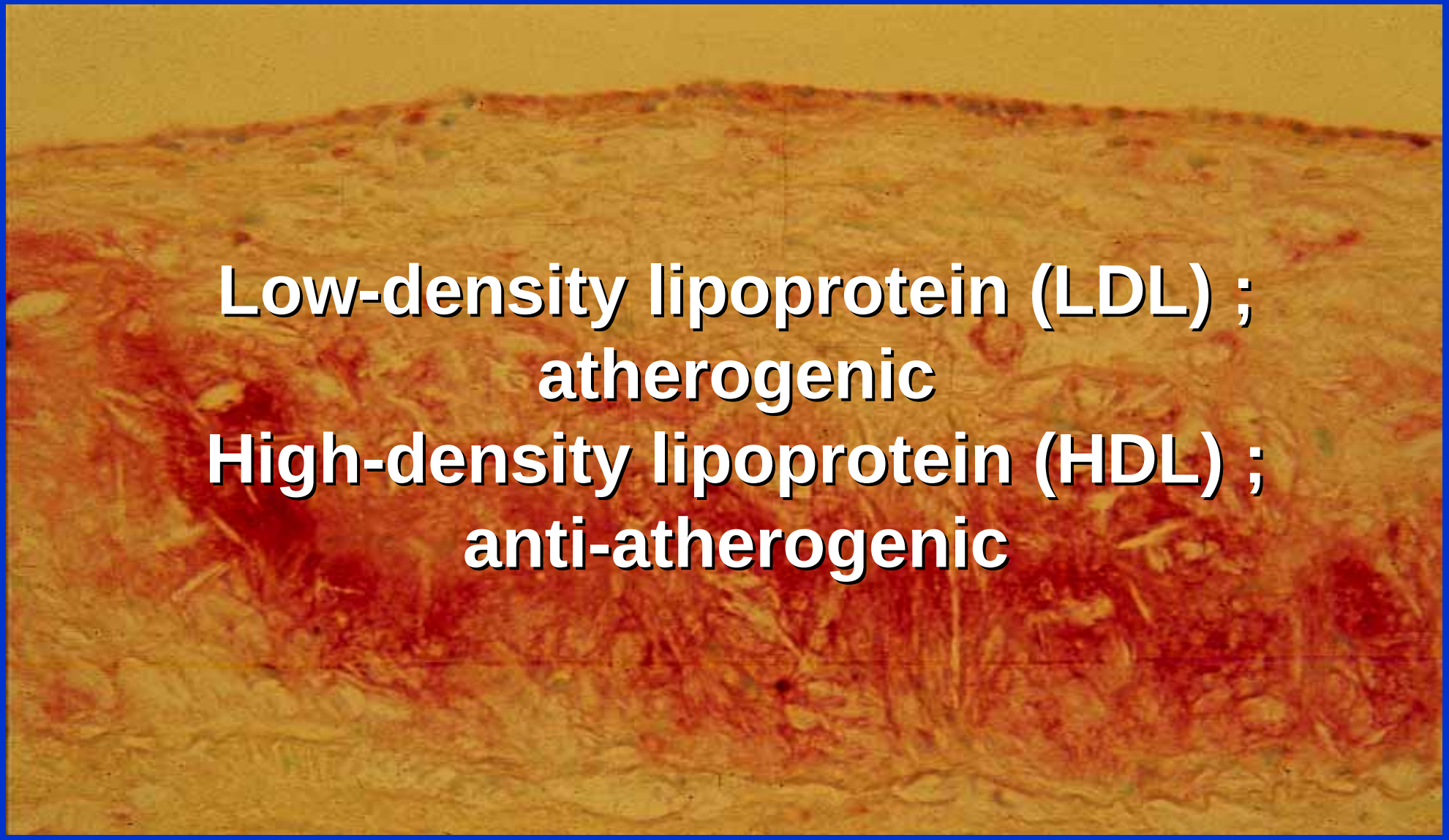
Foam Cells	Fatty Streak	Intermediate Lesion	Atheroma	Fibrous Plaque	Complicated Lesion/Rupture



From first decade	From third decade	From fourth decade

Growth mainly by lipid accumulation	Smooth muscle and collagen	Thrombosis, hematoma

Stary et al. *Circulation*. 1995;92:1355-1374.

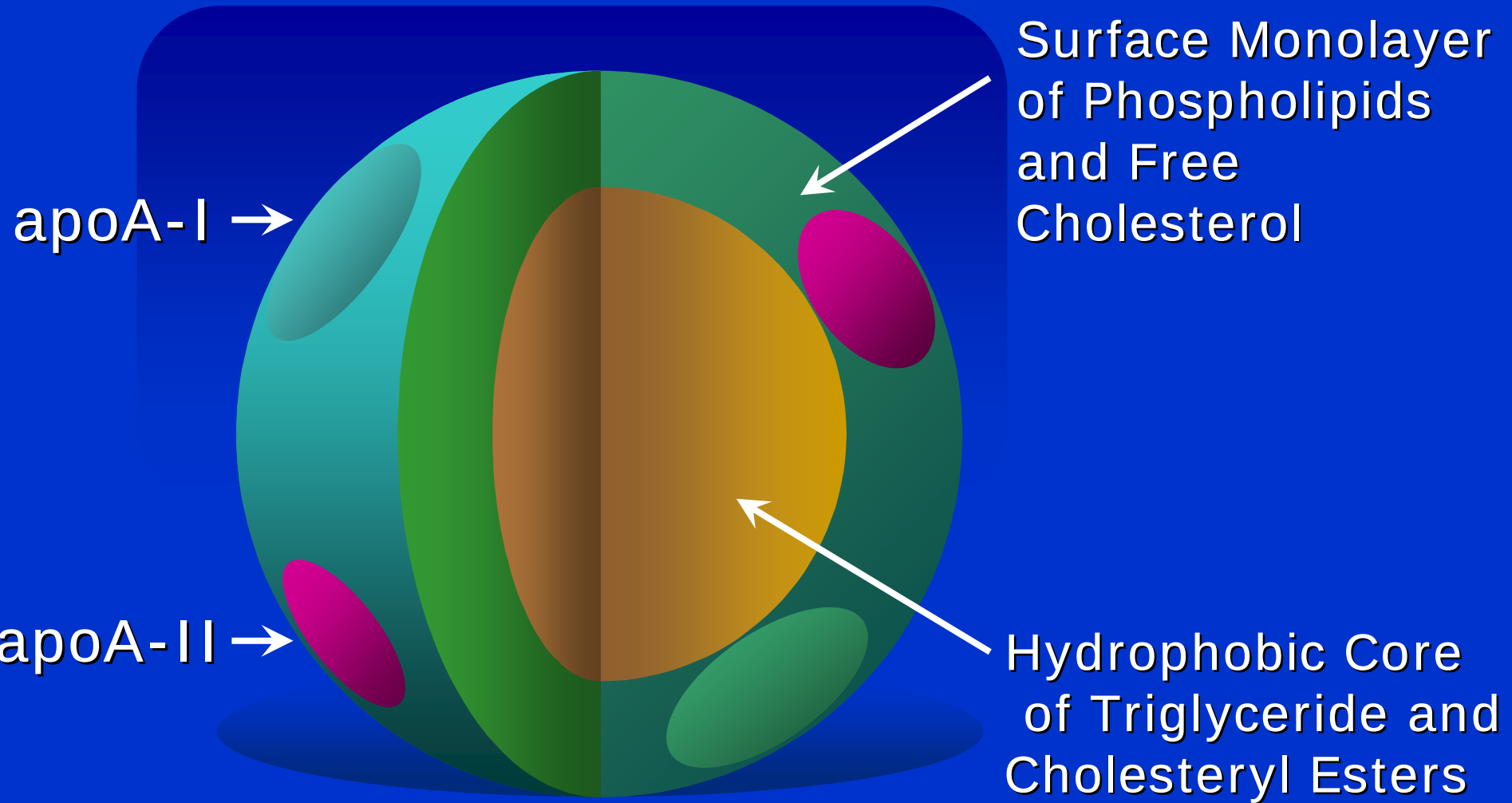

Low-density lipoprotein (LDL) ;
atherogenic
High-density lipoprotein (HDL) ;
anti-atherogenic

HDL and atherosclerosis

- 2-4 % reduction of cardiovascular disease (CVD) in every 1 mg/dl elevation ; more powerful than LDL reduction

- Low serum HDL-C level (<40mg/dl) is recognized as an major risk factor of CVD (NCEP-III guideline, 2001)

Structure of HDL



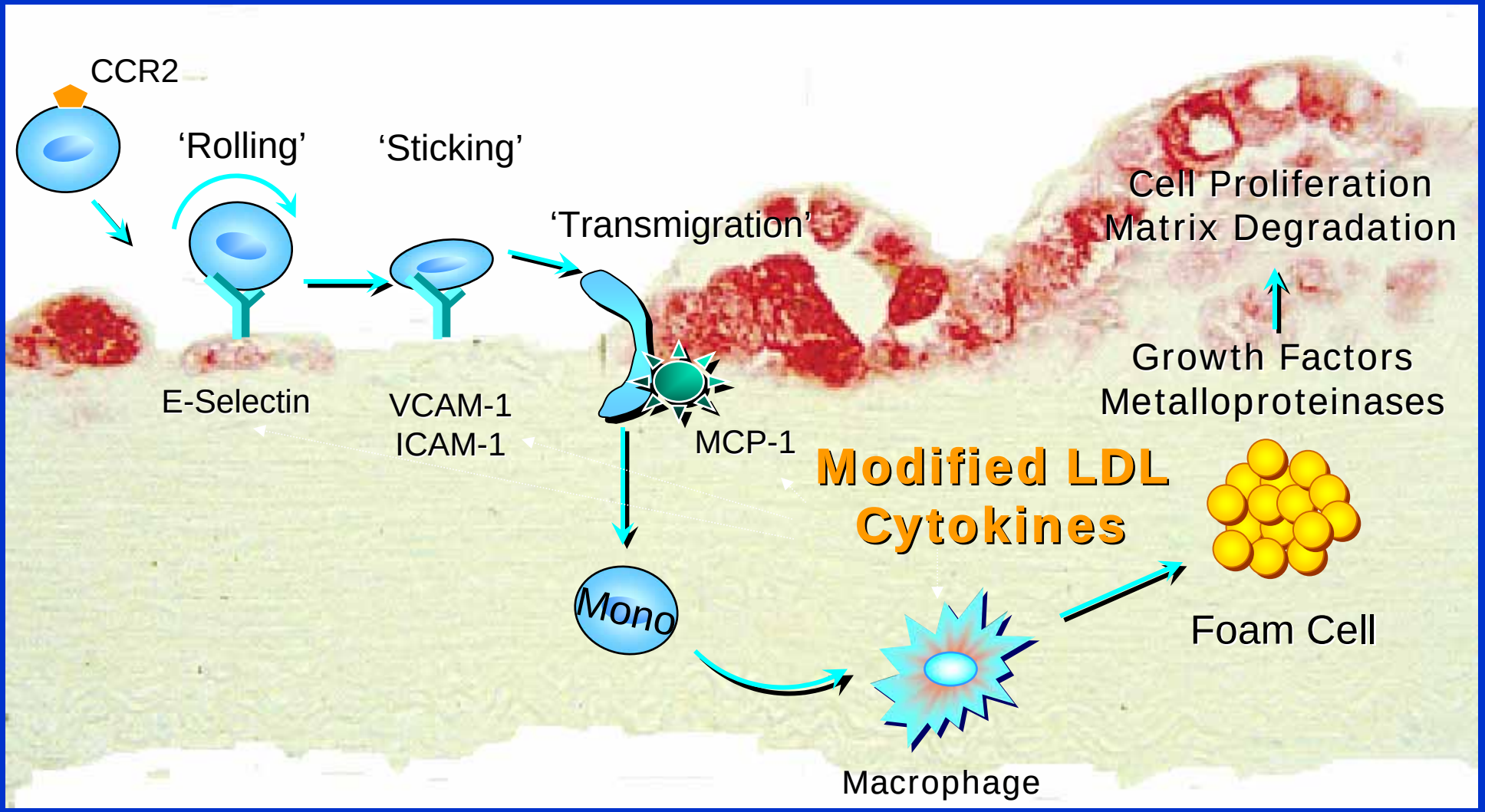
Rye KA et al. *Atherosclerosis* 1999;145:227-238.

Anti-atherogenic Role of HDL

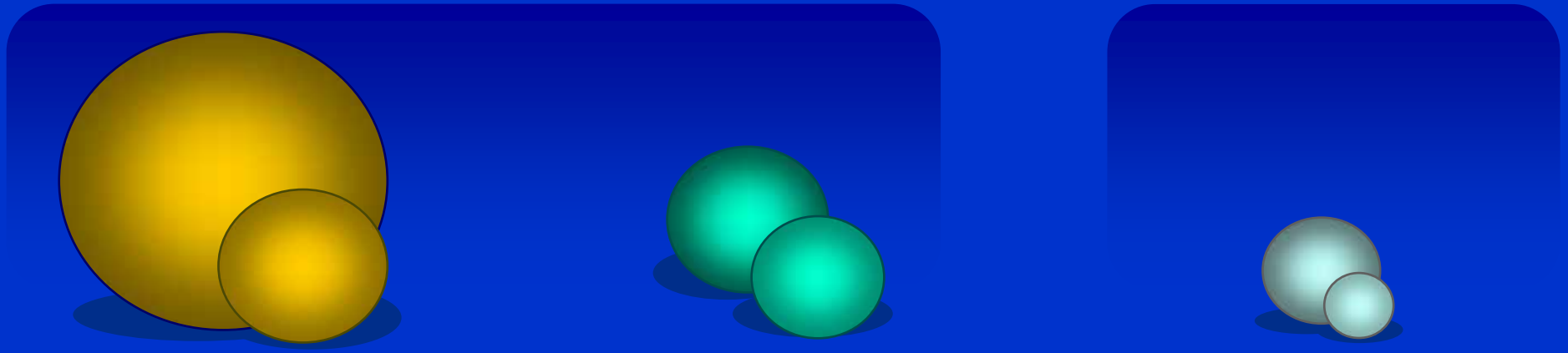
- Anti-inflammatory
- Anti-oxidative
- Reverse Cholesterol Transport

HDL is anti-inflammatory

The Process of Atherosclerosis



Lipoprotein Classes and Inflammation



Chylomicrons, VLDL, and their catabolic remnants

LDL

HDL

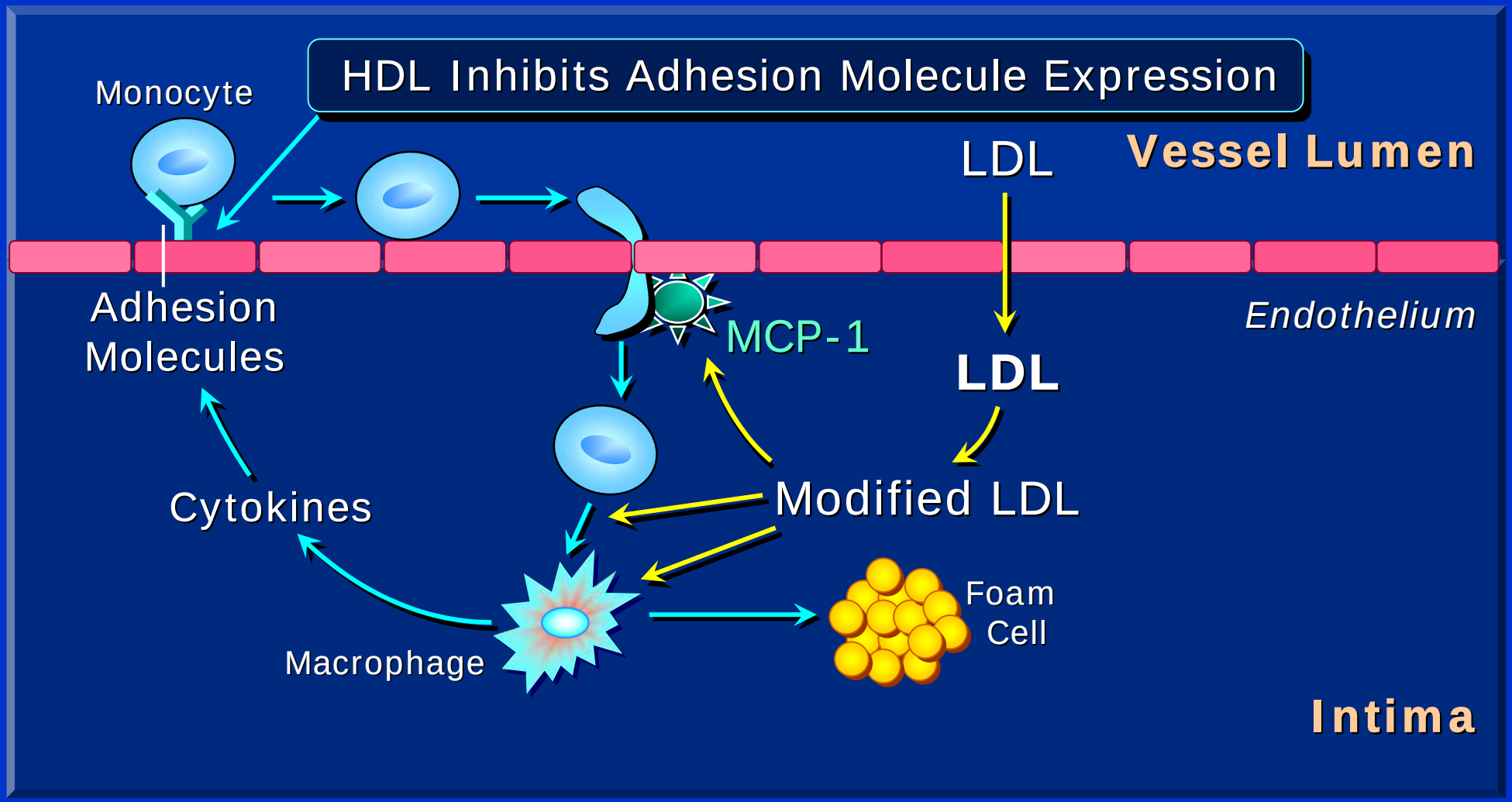
> 30 nm *20–22 nm* *9–15 nm*

Potentially proinflammatory

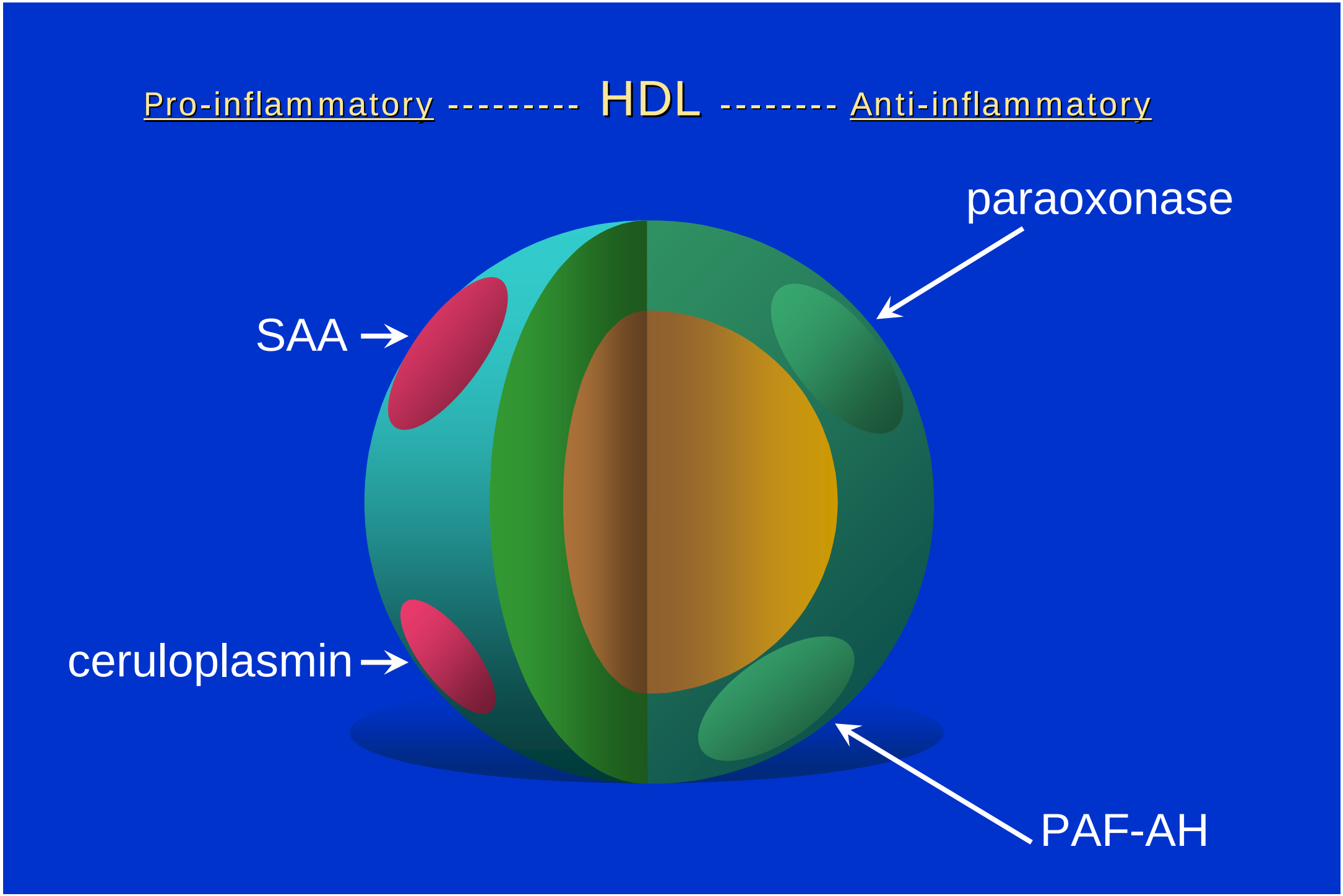
Potentially anti-inflammatory

Doi H et al. *Circulation* 2000;102:670-676; Colome C et al. *Atherosclerosis* 2000; 149:295-302; Cockerill GW et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-1994.

HDL inhibits the Expression of Adhesion Molecules

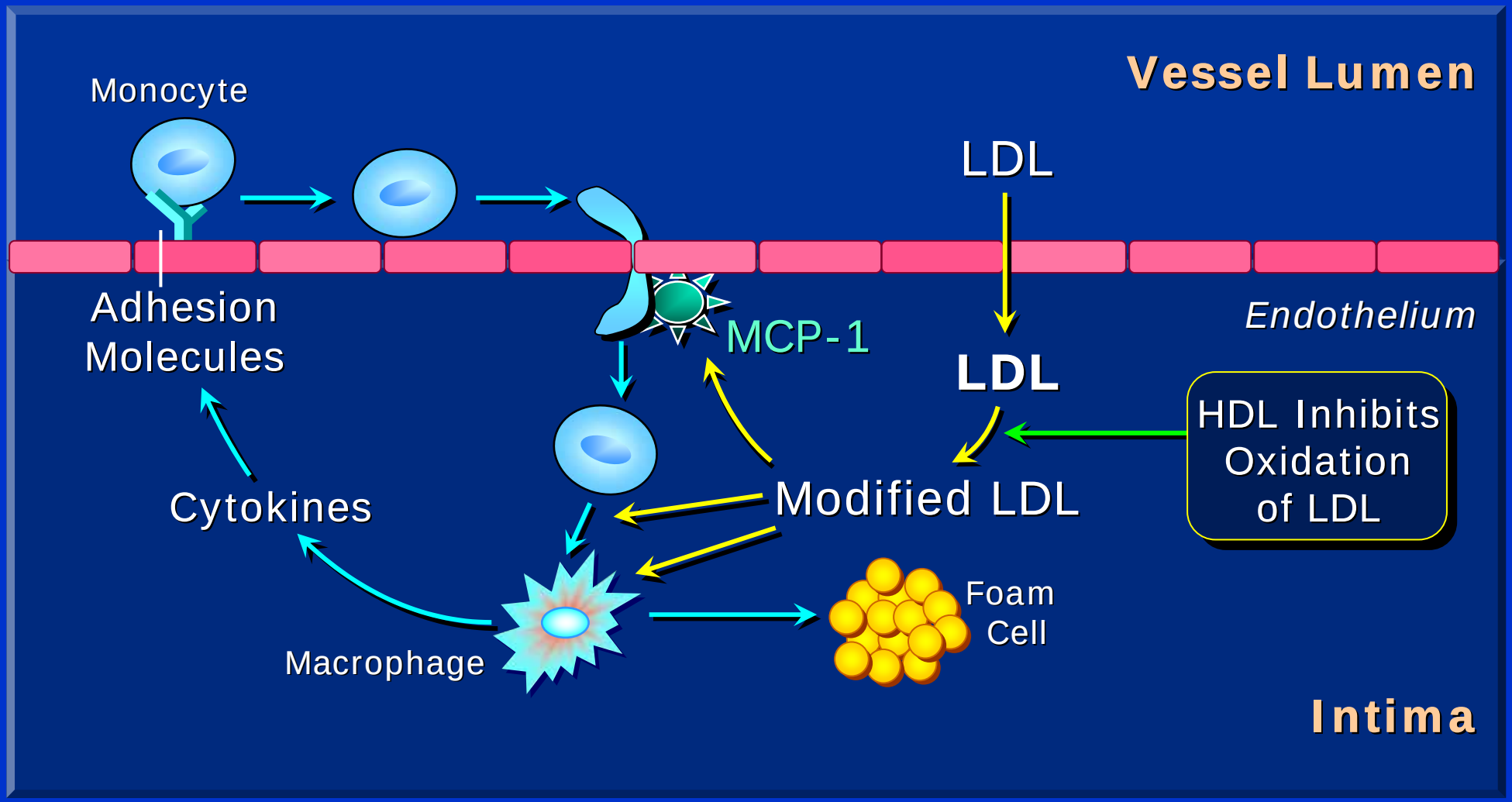


Cockerill GW et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-1994.


Pro-inflammatory --------- HDL -------- Anti-inflammatory
paraoxonase
SAA
ceruloplasmin
PAF-AH

HDL is anti-oxidative

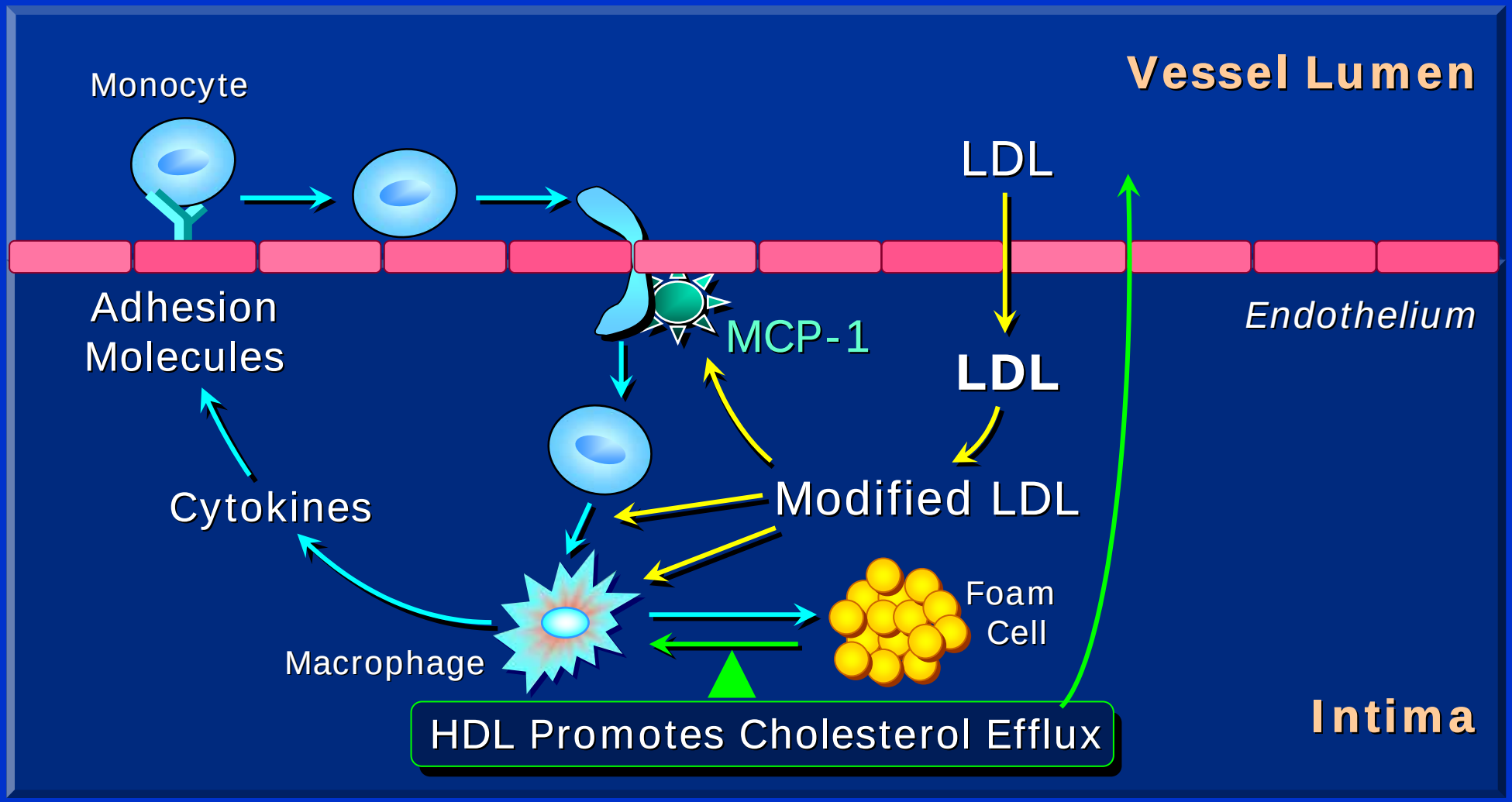
HDL Inhibits the Oxidative Modification of LDL



Mackness MI et al. *Biochem J* 1993;294:829-834.

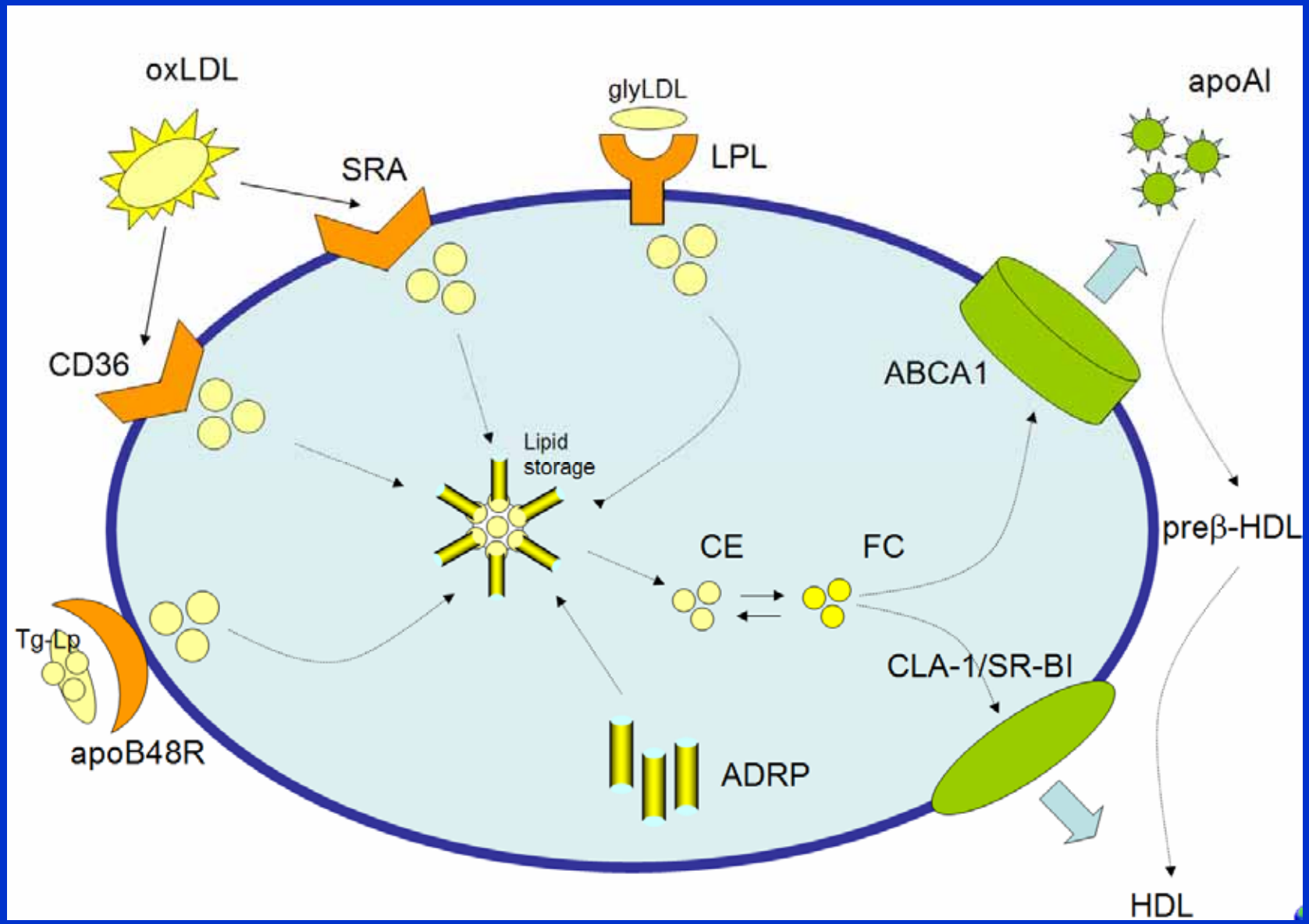
HDL promotes cholesterol efflux

HDL Prevents Formation of Foam Cells



Miyazaki A et al. *Biochim Biophys Acta* 1992;1126:73-80.

Cholesterol Flux in Macrophages



Therapeutic modalities to enhance cholesterol efflux from atheroma

- Agents that increase functionally active HDL

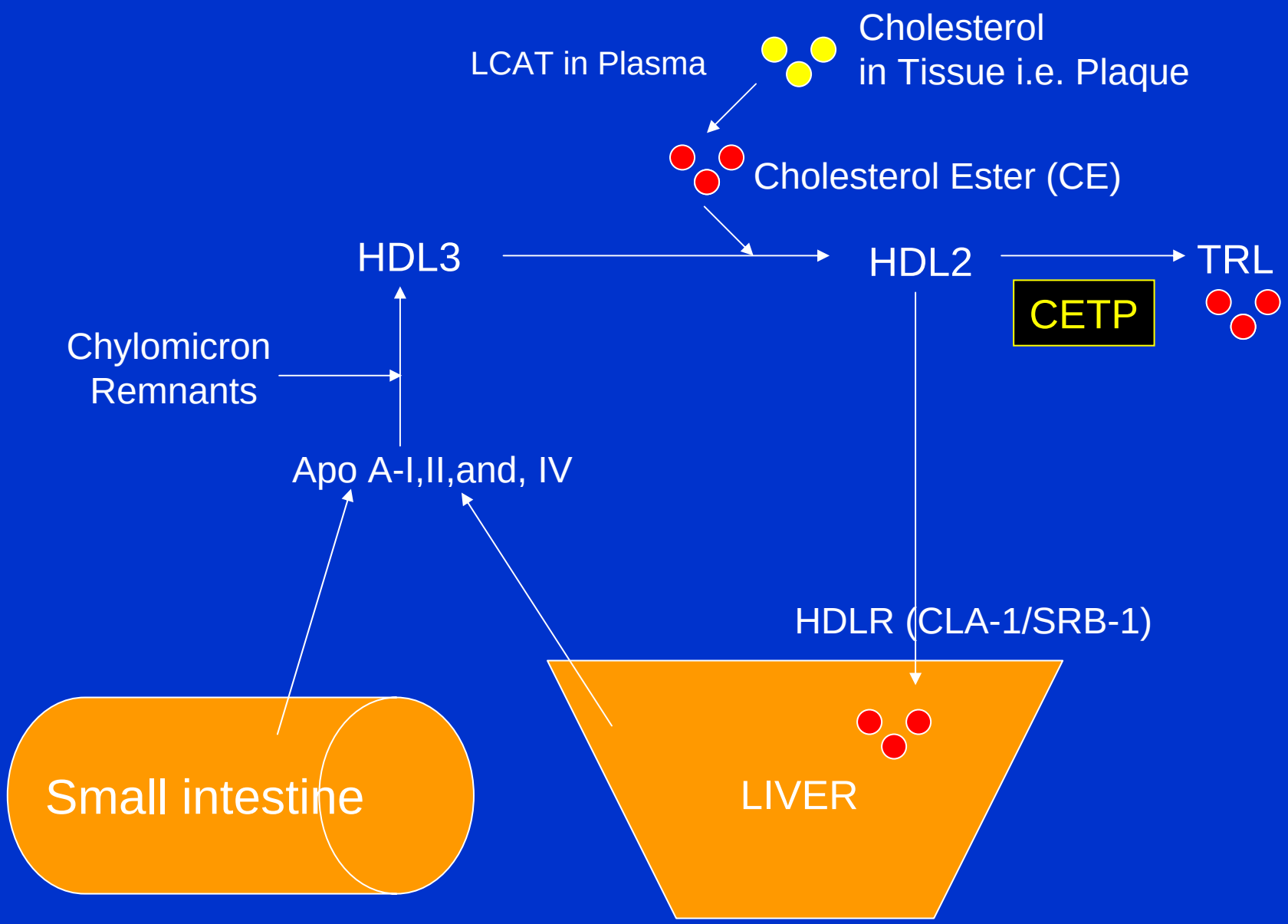
  - Niasin, Statins, Fibrates

- Apo A-1 recombinant protein or agents that upregulate Apo A-1
- Agents that upregulate ABCA1 ; PPARs agonists
- Mutants of Apo A-1 ; Apo A-1 milano or paris

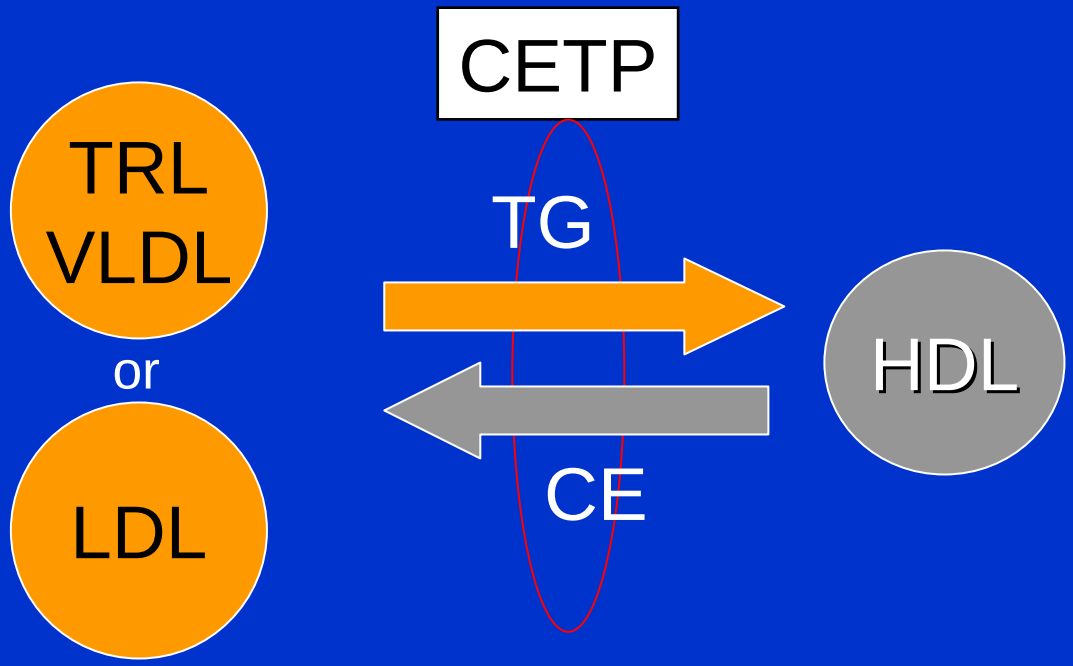
Apo A-1 milano

- Arginine to cysteine substitution at a.a. position 173 of apo A-1
- Subjects with apoA-1 milano does not develop atherosclerosis despite low HDL levels
- Intermittent Apo A-1 milano/phospholipid complex infusion to patients with ACS resulted in significant 4.2 % reduction in plaque volume (JAMA 2003:292)

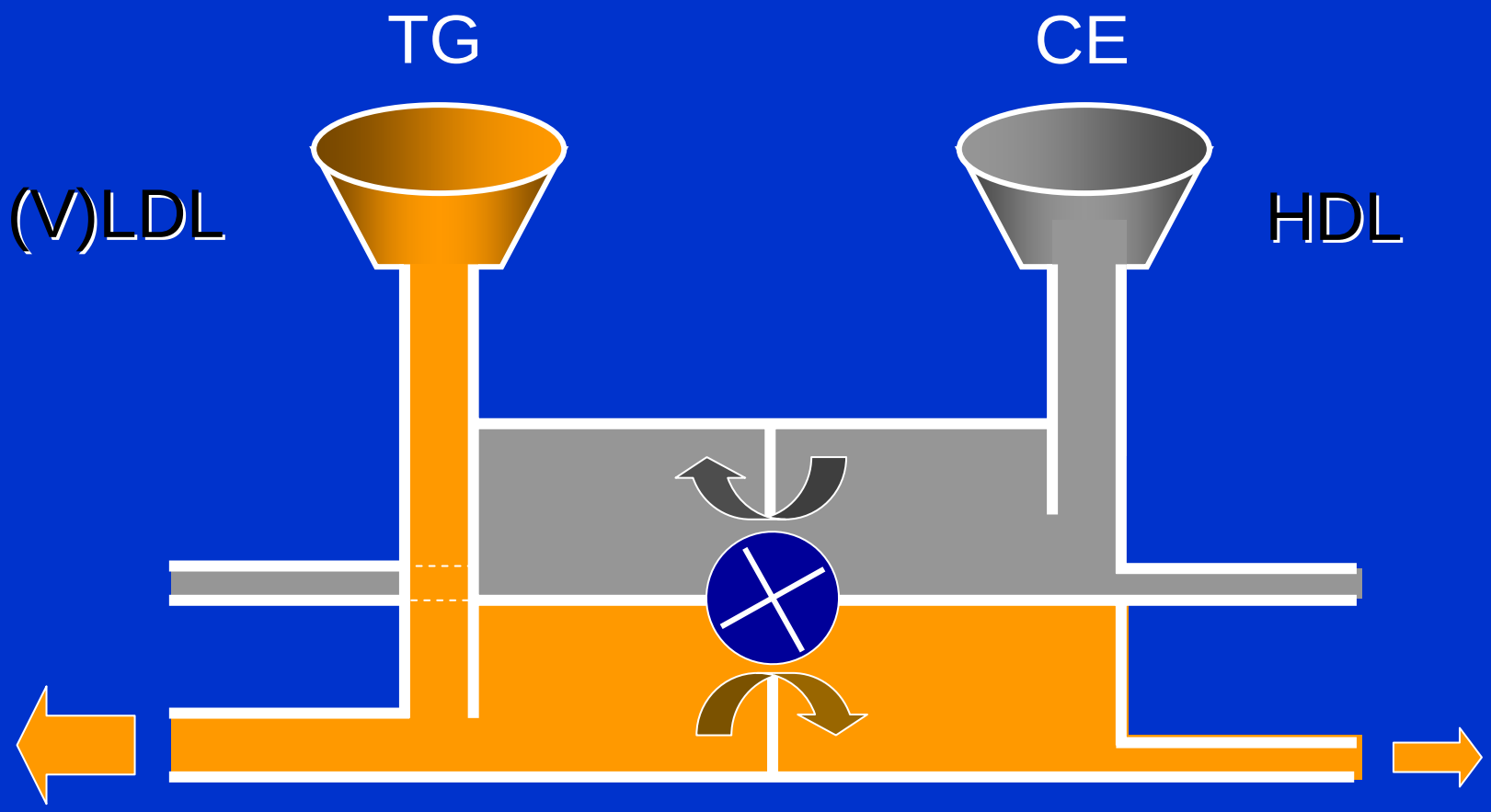
“ HDL in reverse cholesterol transport “



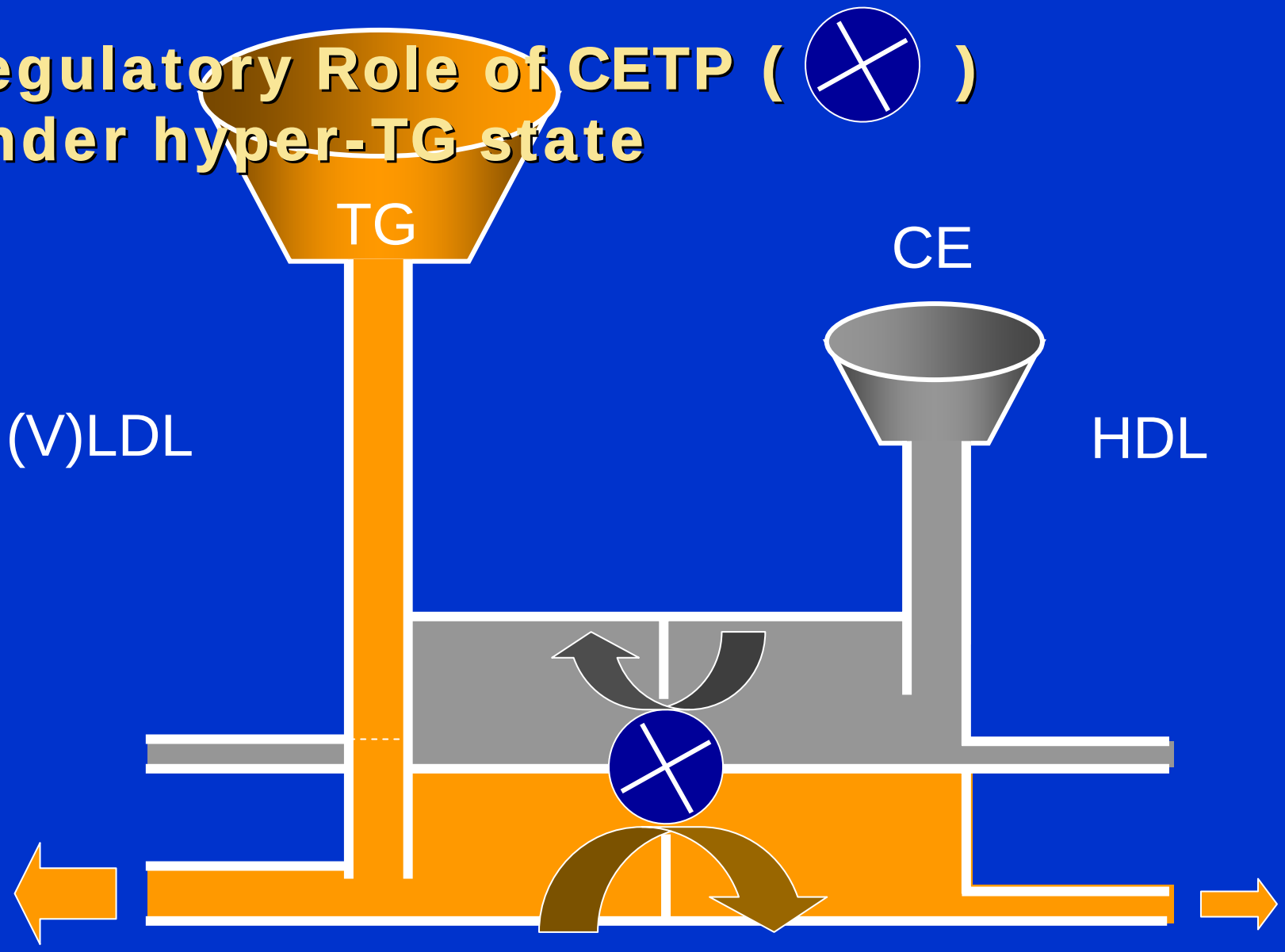
Cholesterol Ester Transport Protein (CETP)



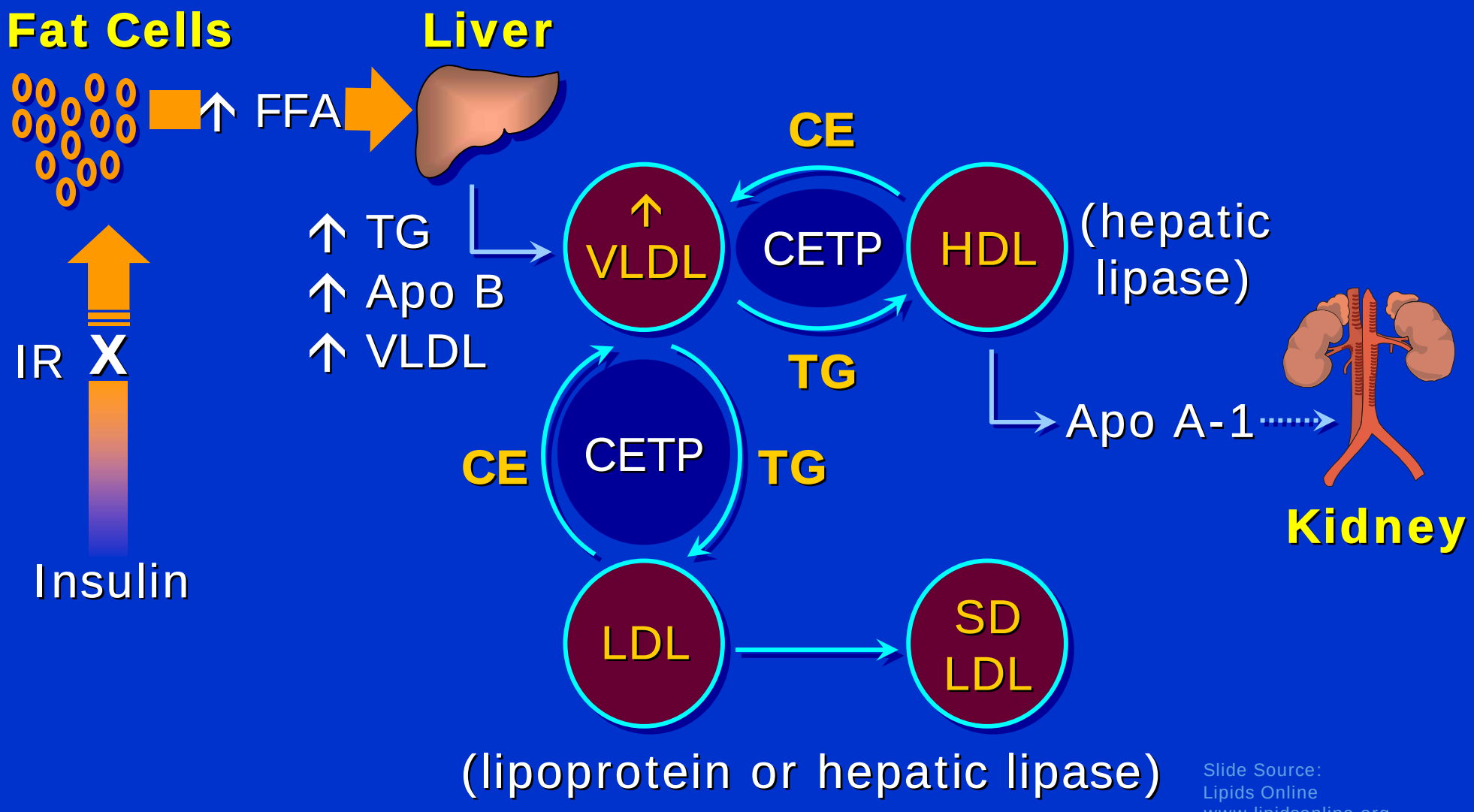
Regulatory Role of CETP ( )
Under usual state



Regulatory Role of CETP (⊗)
Under hyper-TG state



CETP in Dyslipidemia



Potential Benefits of CETP inhibition

- May elevate HDL
- May reduce small dense LDL

Learning from genetic CETP-deficiency

- Japan (probably Korea, too) is an endemic area of genetic CETP deficiency.
- G-to A mutation of +1 position of int 14 and D442G mutation are prevalent in Japan.
- They show elevated HDL-C, apoA-1, A-II, and E levels.
- LDLR expression levels are also upregulated due to CETP-deficiency.

Honolulu Heart Study

- Prevalence of CHD in immigrant Japanese with D442G mutation ; not significantly different from wild-type phenotypes. – at least not atherogenic.

PM in CETP genes (Taq IB)

- Presence of B2 allele (low CETP levels) showed higher HDL levels and lower incidence of CHD.

Animal experiments

- Consistently show that CETP is atherogenic.

Development of CETP inhibitor ; Torcetrapib (NEJM 2004 350;1505)

- Increases HDL
- Decreases small dense LDL
- Further decreases LDL when combined with atorvastatin

Table 2. Plasma HDL Cholesterol and Apolipoprotein A-I and A-II Levels at the End of the Placebo and Drug Phases.*

Variable and Study Phase	Atorvastatin plus Torcetrapib (120 mg/day) (N=9)	Torcetrapib Alone (120 mg/day) (N=10)	Torcetrapib Alone (120 mg twice/day) (N=6)
HDL cholesterol			
Study phase (mg/dl)			
Placebo	29±4	32±7	34±5
Torcetrapib	47±10†	46±14‡	70±15†
Percentage change	61	46	106
HDL_2 cholesterol			
Study phase (mg/dl)			
Placebo	2.9±2.6	6.4±3.8	7.6±3.2
Torcetrapib	11.0±4.3†	11.1±7.8§	29.3±13.6¶
Percentage change	323	87	283
HDL_3 cholesterol			
Study phase (mg/dl)			
Placebo	26.2±4.8	25.2±3.6	26.2±2.5
Torcetrapib	35.9±9.9‖	32.6±6.5**	40.7±6.1‖
Percentage change	36	29	56
Ratio of total cholesterol to HDL cholesterol			
Study phase			
Placebo	5.3±1.4	6.4±1.6	6.0±1.4
Torcetrapib	3.1±0.6† ††	4.4±1.5†	3.0±1.0†
Percentage change	−40	−31	−51
Apolipoprotein A-I			
Study phase (mg/dl)			
Placebo	106±14	110±11	112±13
Torcetrapib	120±23**	127±15†	151±6†
Percentage change	13	16	36
Apolipoprotein A-II			
Study phase (mg/dl)			
Placebo	30±4	29±2	30±1
Torcetrapib	33±4†	33±5‡‡	36±3†
Percentage change	10	12	21

* Plus–minus values are means ±SD. Minus signs denote a decrease. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein.
† P<0.001 for the comparison with placebo.
‡ P=0.001 for the comparison with placebo.
§ P=0.02 for the comparison with placebo.
¶ P=0.004 for the comparison with placebo.
‖ P=0.002 for the comparison with placebo.
** P=0.003 for the comparison with placebo.
†† P=0.02 for the comparison with 120 mg of torcetrapib daily among the subjects who did not receive atorvastatin.
‡‡ P=0.01 for the comparison with placebo.

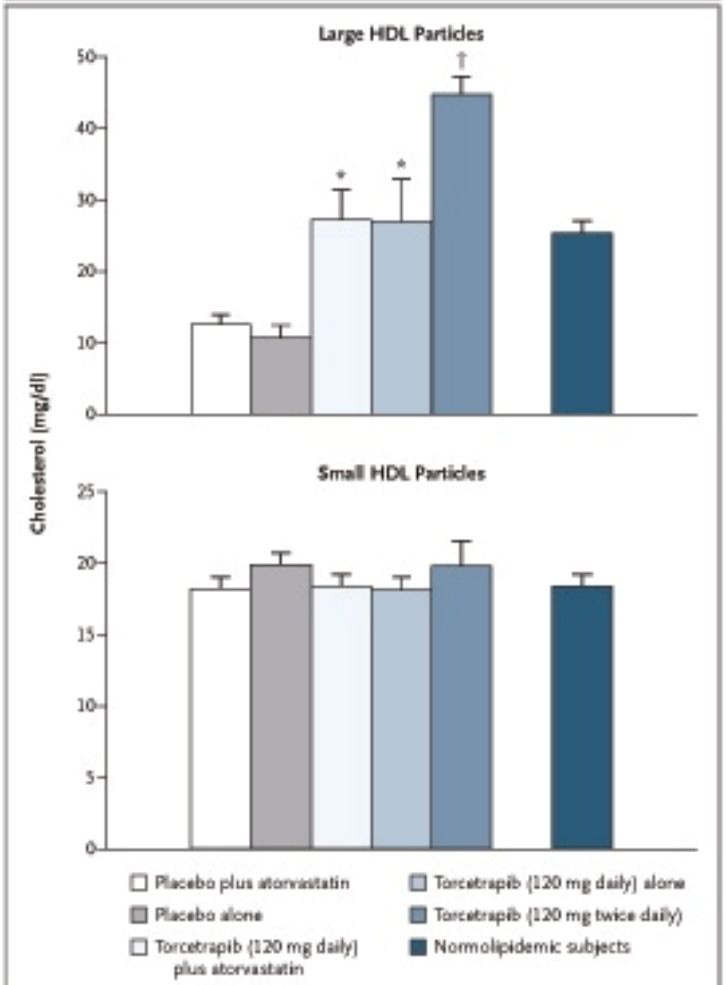


Figure 1. Mean (±SE) Levels of High-Density Lipoprotein (HDL) Subclasses in Each Group of Subjects during the Placebo and Torcetrapib Phases of the Study.

All the subjects had low HDL cholesterol levels at base line. Data for a group of 38 age- and sex-matched subjects with normolipidemia are also provided.[27] As compared with placebo, torcetrapib significantly increased the levels of large HDL particles in each group (top panel); the dose of 120 mg daily normalized the levels of these particles. The asterisks (P=0.001) and dagger (P<0.001) indicate a significant difference from placebo. Torcetrapib did not significantly affect the levels of small HDL particles (bottom panel). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Table 3. Plasma Levels of Lipids, LDL Cholesterol, and Apolipoprotein B at the End of the Placebo and Drug Phases.*

Variable and Study Phase	Atorvastatin plus Torcetrapib (120 mg/day) (N=9)	Torcetrapib Alone (120 mg/day) (N=10)	Torcetrapib Alone (120 mg twice/day) (N=6)
Total cholesterol			
Study phase (mg/dl)			
Placebo	150±33†	192±28	199±26
Torcetrapib	141±21‡	193±42	200±36
Percentage change	−5	<1	<1
Unesterified cholesterol			
Study phase (mg/dl)			
Placebo	40±8‡	51±7	53±8
Torcetrapib	38±5§	52±11	53±9
Percentage change	−3	<1	−1
Esterified cholesterol			
Study phase (mg/dl)			
Placebo	111±26†	141±23	145±19
Torcetrapib	103±16‡	141±31	148±28
Percentage change	−5	0	2
Triglycerides			
Study phase (mg/dl)			
Placebo	122±47	161±58	154±56
Torcetrapib	98±42¶‖	154±67	109±51¶
Percentage change	−18‖	1	−26
Phospholipids			
Study phase (mg/dl)			
Placebo	169±20§	204±23	212±24
Torcetrapib	172±21**	215±38	226±26¶
Percentage change	2	4	7
LDL cholesterol			
Study phase (mg/dl)			
Placebo	94±30**	129±25	136±24
Torcetrapib	76±19†† ‡‡	119±36	114±40
Percentage change	−17	−8	−17
Apolipoprotein B			
Study phase (mg/dl)			
Placebo	86±15**	102±11	104±13
Torcetrapib	73±11§ §§	92±13¶¶	87±17††
Percentage change	−14	−10	−17

* Plus–minus values are means ±SD. Minus signs denote a decrease. Because many secondary end points were analyzed, a P value of 0.045 may not be definitive. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. LDL denotes low-density lipoprotein.

† P=0.008 for the comparison with 120 mg of torcetrapib daily among the subjects who did not receive atorvastatin.
‡ P=0.004 for the comparison with 120 mg of torcetrapib daily among the subjects who did not receive atorvastatin.
§ P=0.003 for the comparison with 120 mg of torcetrapib daily among the subjects who did not receive atorvastatin.
¶ P=0.05 for the comparison with placebo.
‖ P=0.05 for the comparison with 120 mg of torcetrapib daily among the subjects who did not receive atorvastatin.
** P=0.02 for the comparison with 120 mg of torcetrapib daily among the subjects who did not receive atorvastatin.
†† P=0.02 for the comparison with placebo.
‡‡ P=0.006 for the comparison with 120 mg of torcetrapib daily among the subjects who did not receive atorvastatin.
§§ P=0.002 for the comparison with placebo.
¶¶ P=0.004 for the comparison with placebo.

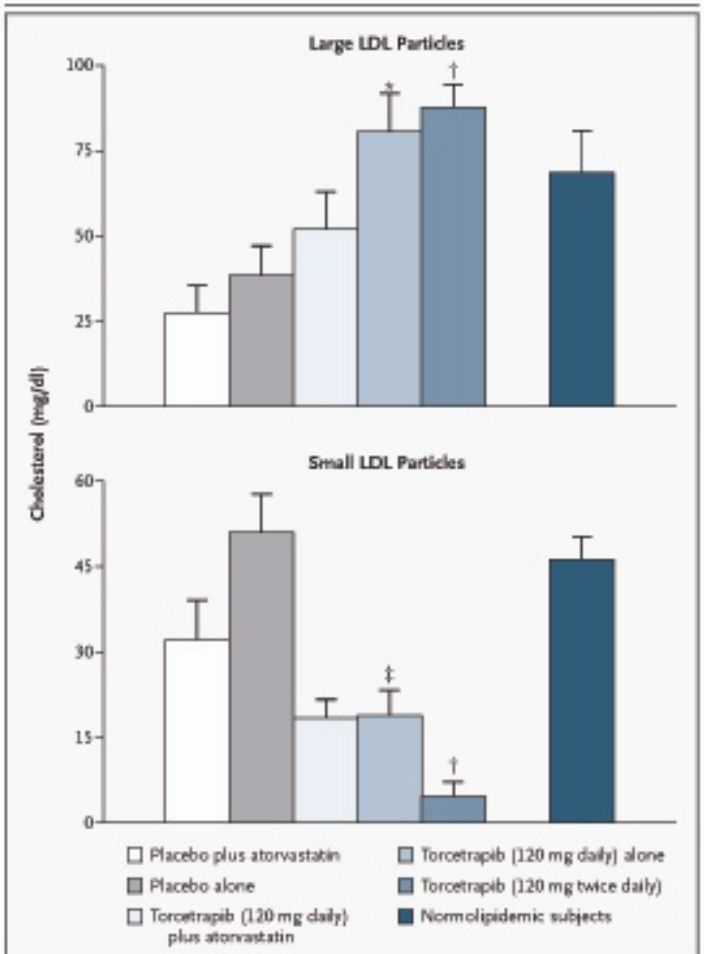


Figure 2. Mean (±SE) Levels of Low-Density Lipoprotein (LDL) Subclasses in Each Group of Subjects during the Placebo and Torcetrapib Phases of the Study.

All the subjects had low HDL cholesterol levels at base line. Data for a group of 38 age- and sex-matched subjects with normolipidemia are also provided.[27] As compared with placebo, torcetrapib increased the levels of large LDL particles in each group (top panel). Conversely, the levels of small LDL particles were reduced by torcetrapib (bottom panel), with each of the study groups having a level lower than that in the group of subjects with normolipidemia (46±49 mg per deciliter [1.3±1.3 mmol per liter]). The asterisk (P=0.005), daggers (P=0.03), and double dagger (P=0.04) indicate a significant difference from placebo. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Wrap-up ; HDL and CETP inhibition

Summary

- Low serum HDL level is a major risk factor.
- The anti-atherogenic function of HDL is attributed to
  - Anti-inflammatory
  - Anti-oxidative
  - Reverse cholesterol transport
- Cholesterol efflux directly from atheroma can be induced by Apo A-1 milano.
- Raising serum HDL cholesterol level can be achieved by a CETP inhibitor, i.e. Torcetrapib.

CETP inhibitors to be proved in the future..

- Can raise HDL cholesterol levels (in subjects with dyslipidemia).
- HDL particles that appear after (partial) CETP inhibition seem to be functionally intact.
  - Is that so in hypercholesterolemic patients ?
  - Is it functional enough to prevent atherogenesis ?