Lipoprotein Metabolism

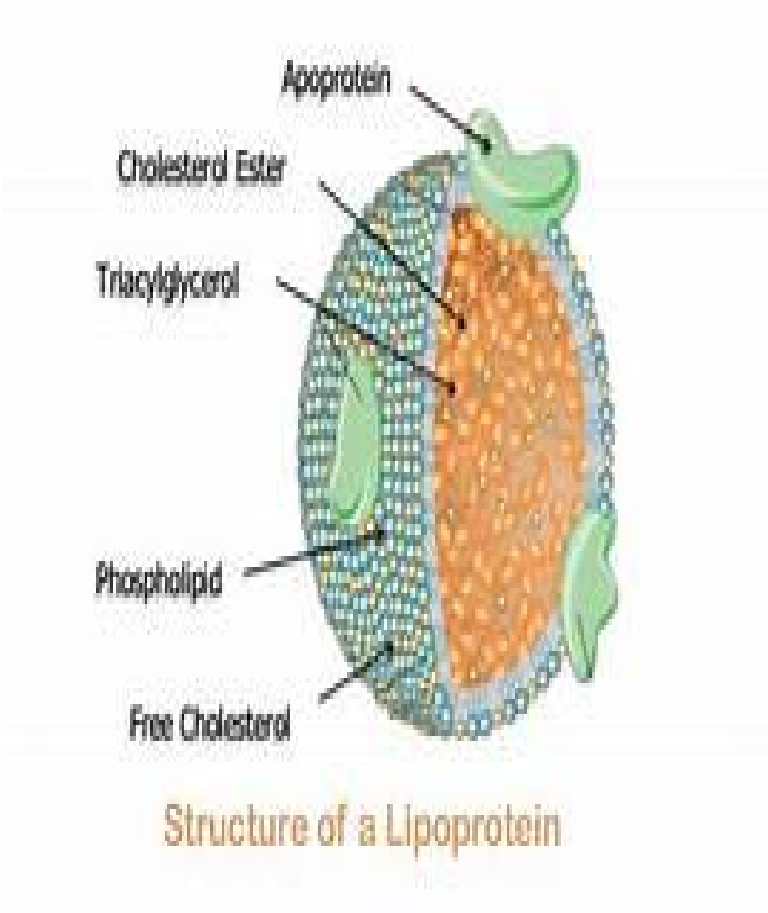
Generation,Operation,Destruction
Formation,Functions,Utilization
Of
Lipoproteins
In
Health And Disease

In Human Body
How Transportation Of Lipids Occur
Through Aqueous Media ?

What are Lipoproteins ?

- Lipoproteins are **complex macromolecules**

- Biosynthesized by **aggregation of Lipids and Apoproteins.**



Structure of a Lipoprotein

- **Lipoproteins** are **compound Lipids/Conjugated Proteins.**

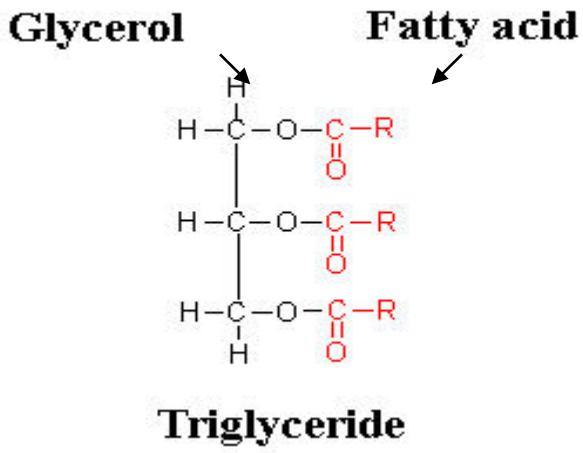
- Lipoproteins **acquire charge** and **made soluble** in aqueous phase.

Why Lipoproteins are Biosynthesized?

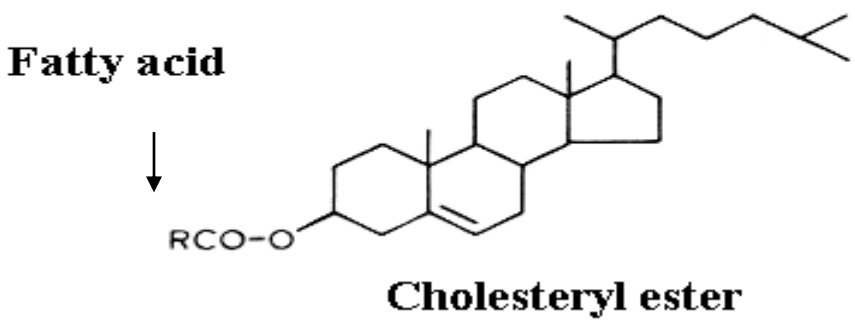
All types of Lipoproteins are Biosynthesized In Human body

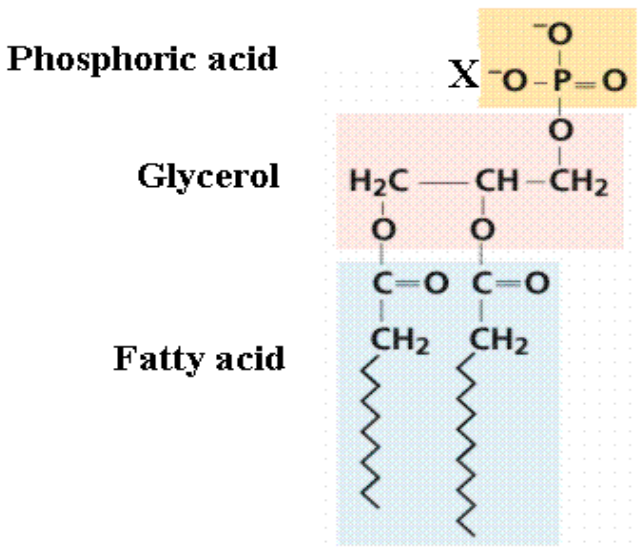
❖**Neutral Lipid (Nonpolar)Biomolecules: Relatively insoluble in water**

❖**Therefore, Lipids are transported in plasma and Lymph (aqueous phase) as Lipoproteins**

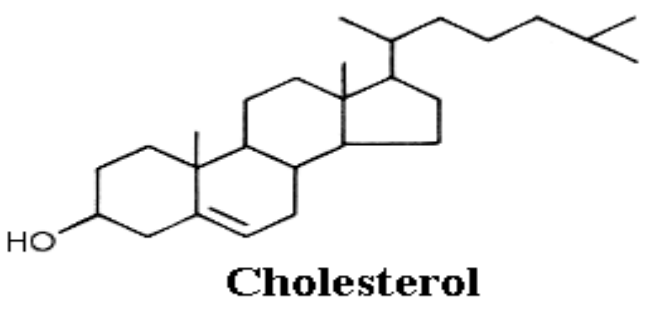


Hydrophobic lipids





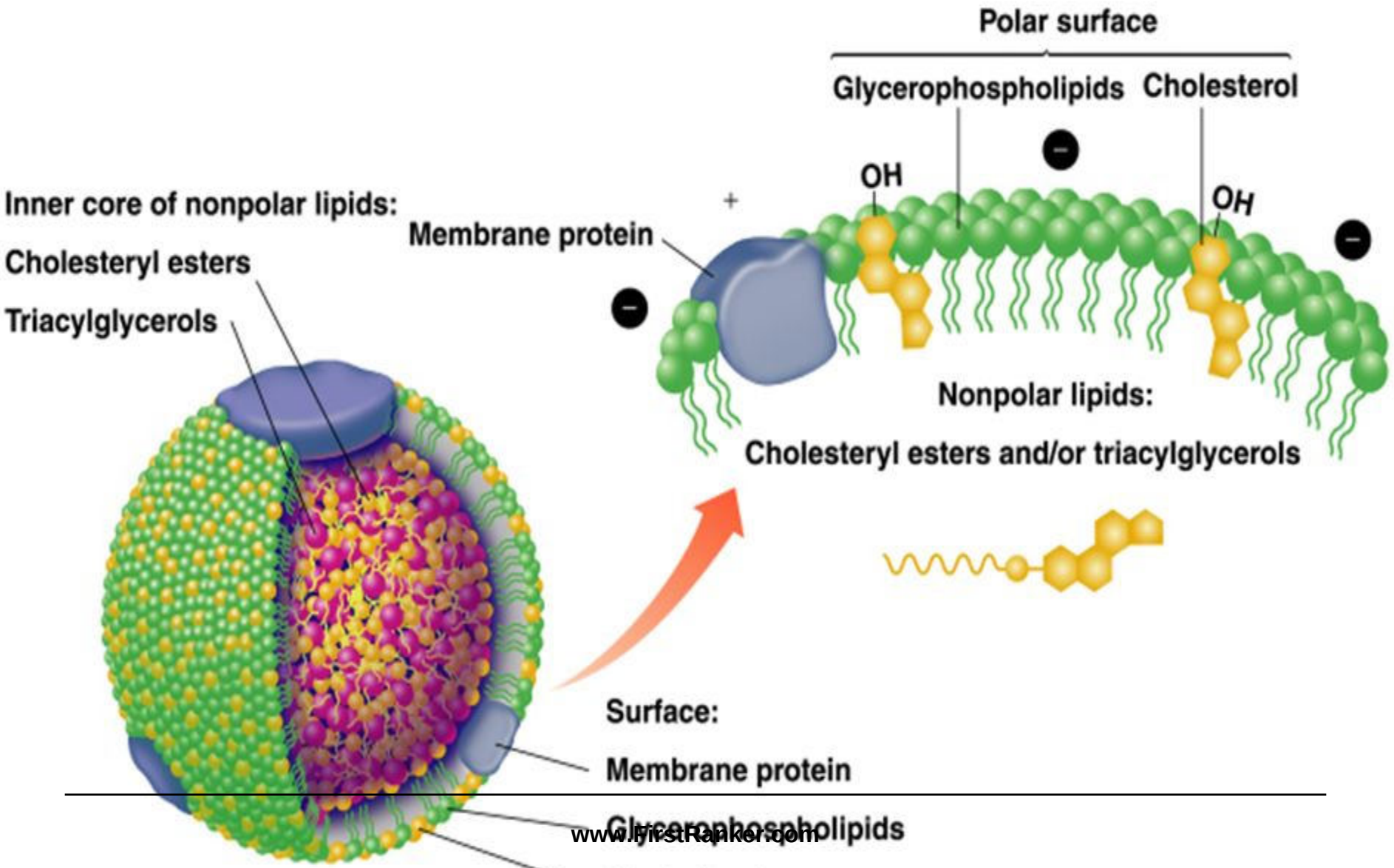
Amphiphilic lipids

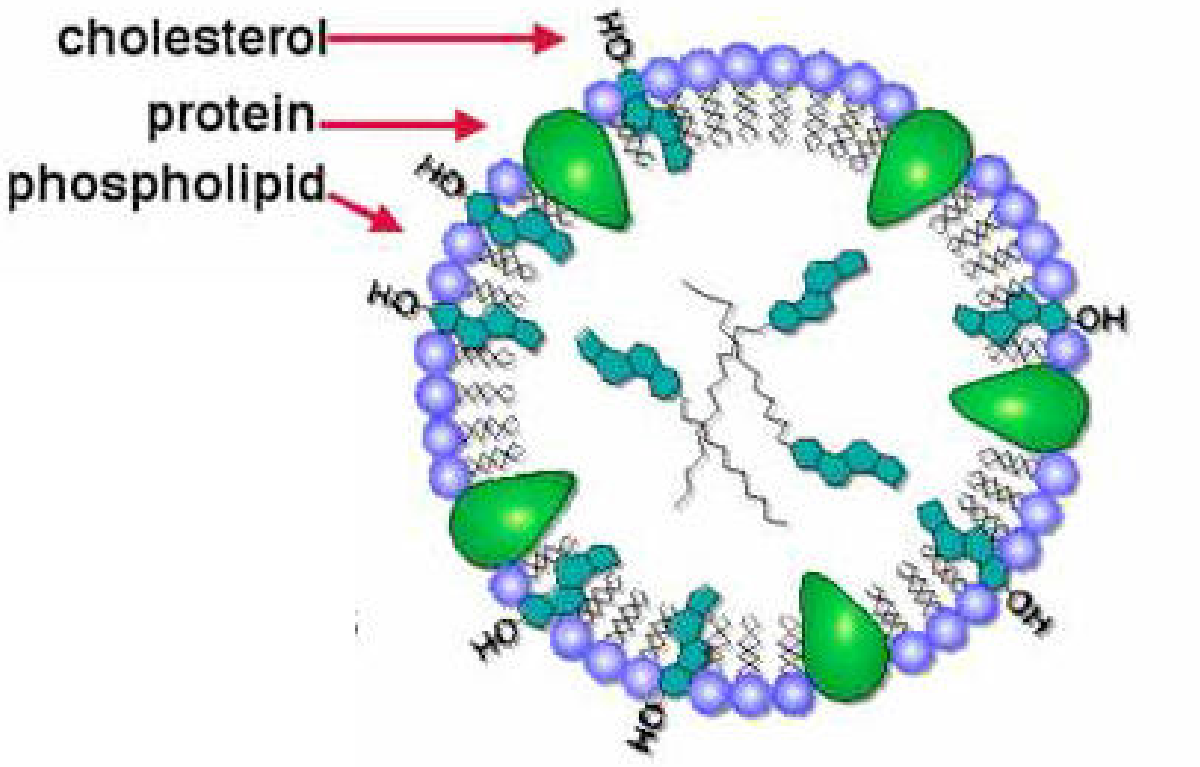


Phospholipid

- Lipoproteins
  - Lipids
    - Hydrophobic lipds
      - Triglyceride (TG)
      - Cholesteryl ester (CE)
    - Amphiphilic lipids
      - Phospholipid (PL)
      - Cholesterol (C)
  - Proteins
    - Apolipoprotein (Apo)
      - ApoAs
      - ApoBs
      - ApoCs
      - ApoE
      - ApoD
      - Apoa
    - Other proteins

Lipoprotein Complex Structure



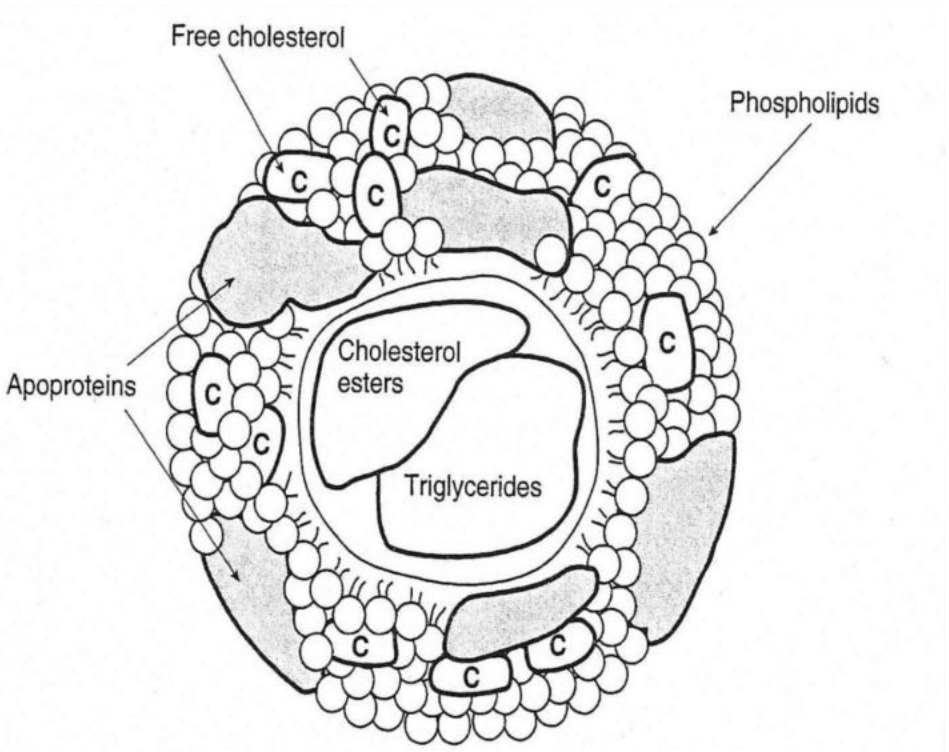


Structure of lipoprotein

Hydrophobic lipids (TAG, CE) in Core
Amphiphilic lipids (C, PL) and proteins on surface

Plasma Lipoproteins (Structure)

- Non-covalent assemblies of lipids and proteins
- LP core
  - Triglycerides
  - Cholesterol esters
- LP surface
  - Phospholipids
  - Proteins
  - Cholesterol



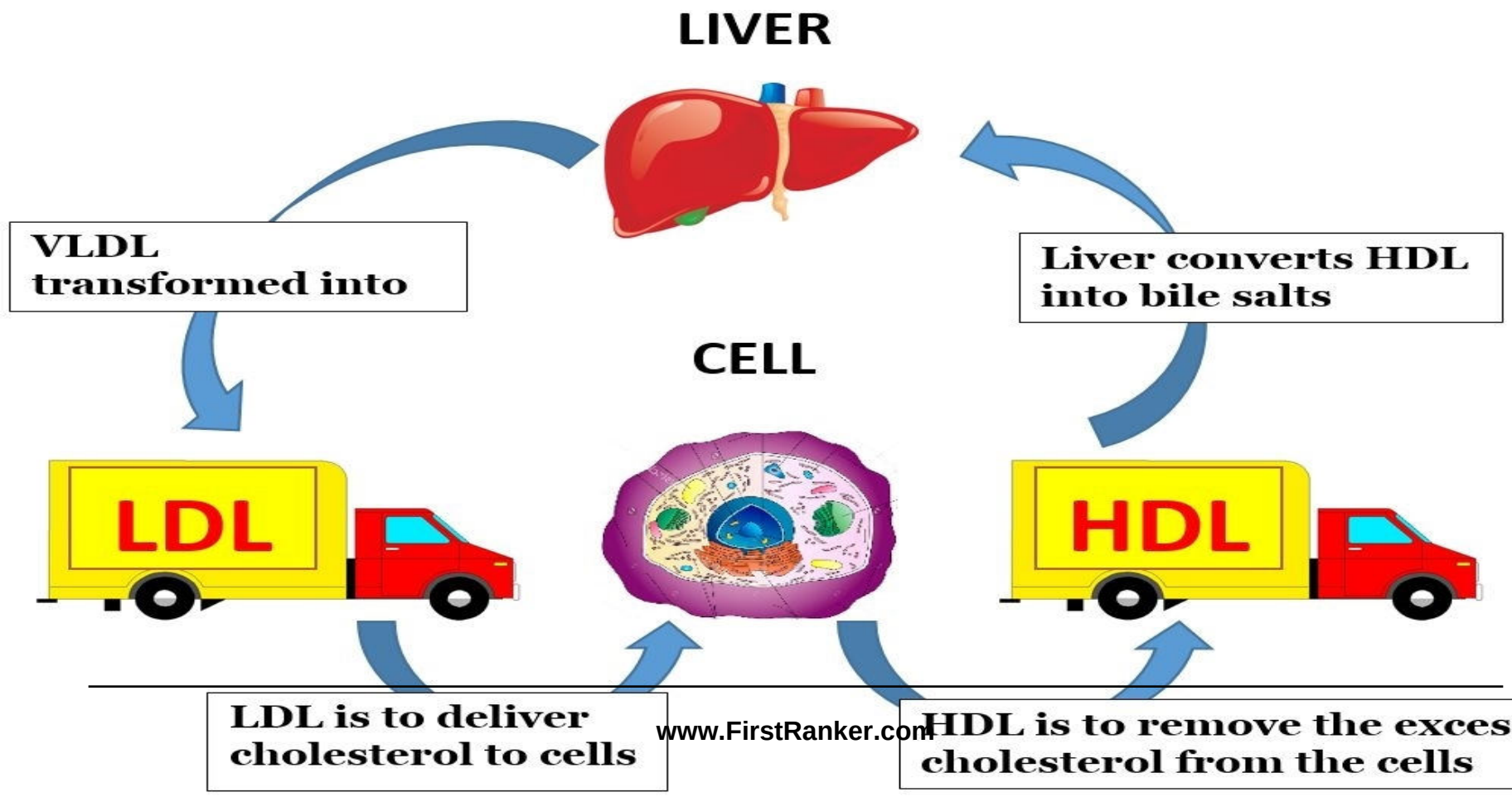
Function as transport vehicles for triacylglycerols and cholesterol in the blood

Contents Of Lipoproteins Structure

- **Non polar Lipids** are **at center**
- **Polar Lipids** and **Apoproteins** are **present at periphery.**

Function/Role Of Lipoproteins

Serves As Vehicles Of Lipid Transport Through Aqueous Phase



- **Lipoproteins function** as **transport vehicles**

- For **transportation of insoluble form of Lipids in blood plasma.**

- **Lipoproteins deliver lipid forms** (Cholesterol and TAG etc) **from one tissue to various other tissues for their utilization**.

- Various **Lipoproteins** formed within body cells
- **Serves in transportation of**
- **Exogenous** (Dietary Source)
- **Endogenous** (Lipids biosynthesized)
- **From one organ to another** through aqueous phase of **Lymph and blood.**

Role of Lipoproteins Components

- **Substrates for Energy Metabolism (TAG)**
- **Provide Essential components for cell structure (PL, Cholesterol)**
- **Precursors for Hormones (Cholesterol)**
- **Precursors for Bile acids and Bile salts (C)**
- **Carries Lipid soluble Vitamins**

Types Of Lipoproteins

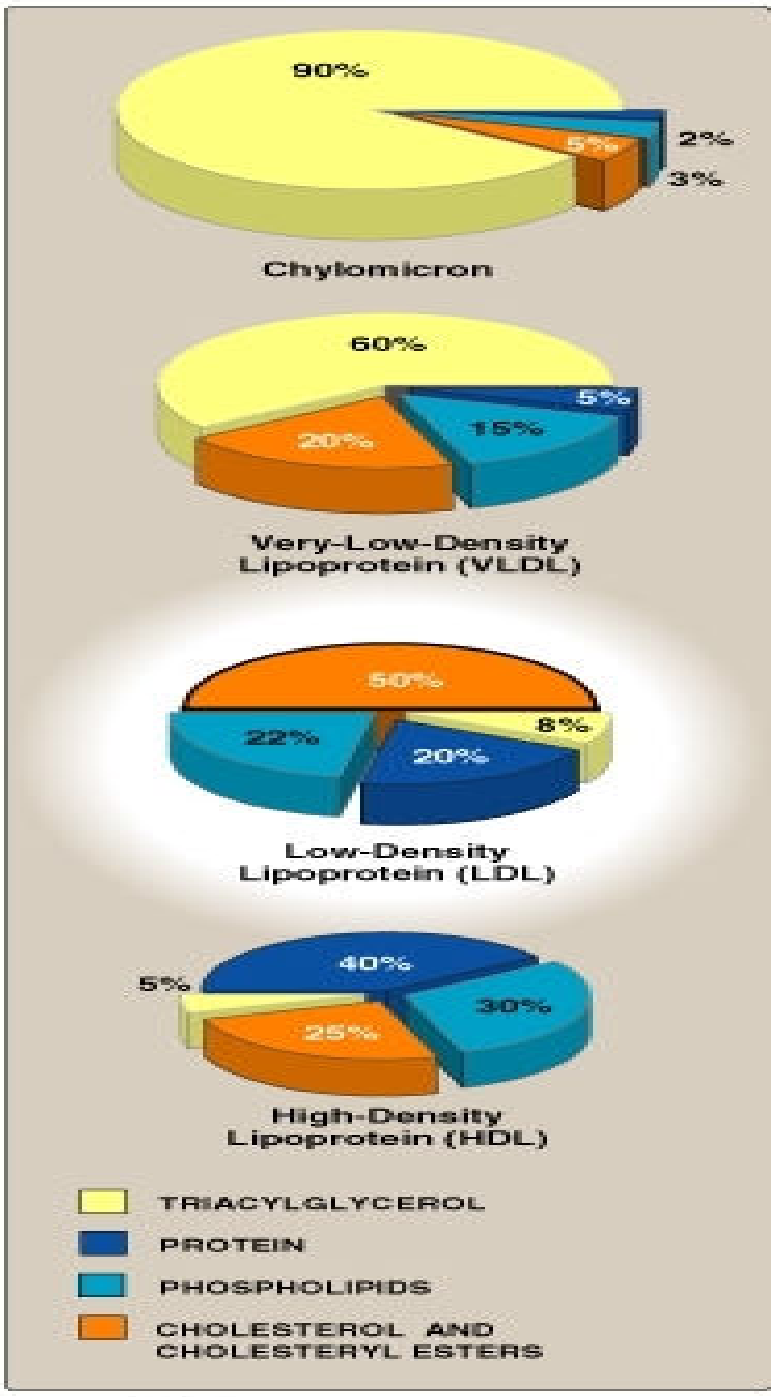
- **There are different types of Lipoproteins depending upon:**

I. Site of Lipoprotein Biosynthesis
II. Lipid Content of LPL
III. Apoprotein Type and Content
IV. Diameter /Size of LPL
V. Transport Destination
VI. Ultracentrifugation
VII. Electrophoretic Pattern

Lipoproteins	Site Of Synthesis	Destination	Major Lipids	Biochemical Functions
Chylomicrons	Intestine	Liver	Exogenous Triacylglycerol	Deliver lipids of dietary origin to Liver and Adiposecytes
VLDLs	Liver	Extra Hepatic Tissues	Endogenous Triacylglycerol	Deliver endogenously produced Lipids to Extrahepatocytes
LDLs	Intravascular by removal of Triacylglycerol from VLDL	Extra hepatic Tissues	Cholesterol	Deliver endogenously produced cholesterol to Extrahepatocytes
HDLs	Liver and intestine	Liver and steroid -hormone-producing glands	Phospholipid Cholesterol	Remove and degrade Cholesterol.

TABLE 25–1 Composition of the Lipoproteins in Plasma of Humans

Lipoprotein	Source	Diameter (nm)	Density (g/mL)	Composition: Protein (%)	Composition: Lipid (%)	Main Lipid Components	Apolipoproteins
Chylomicrons	Intestine	90-1000	<0.95	1-2	98-99	Triacylglycerol	A-I, A-II, A-IV,[a] B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45-150	<1.006	6-8	92-94	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	30-90	0.95-1.006	7-10	90-93	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	25-35	1.006-1.019	11	89	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	20-25	1.019-1.063	21	79	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylomicrons					Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D,[b] E
HDL_1		20-25	1.019-1.063	32	68		
HDL_2		10-20	1.063-1.125	33	67		
HDL_3		5-10	1.125-1.210	57	43		
Preβ-HDL[c]		<5	>1.210				A-I
Albumin/free fatty acids	Adipose tissue		>1.281	99	1	Free fatty acids	

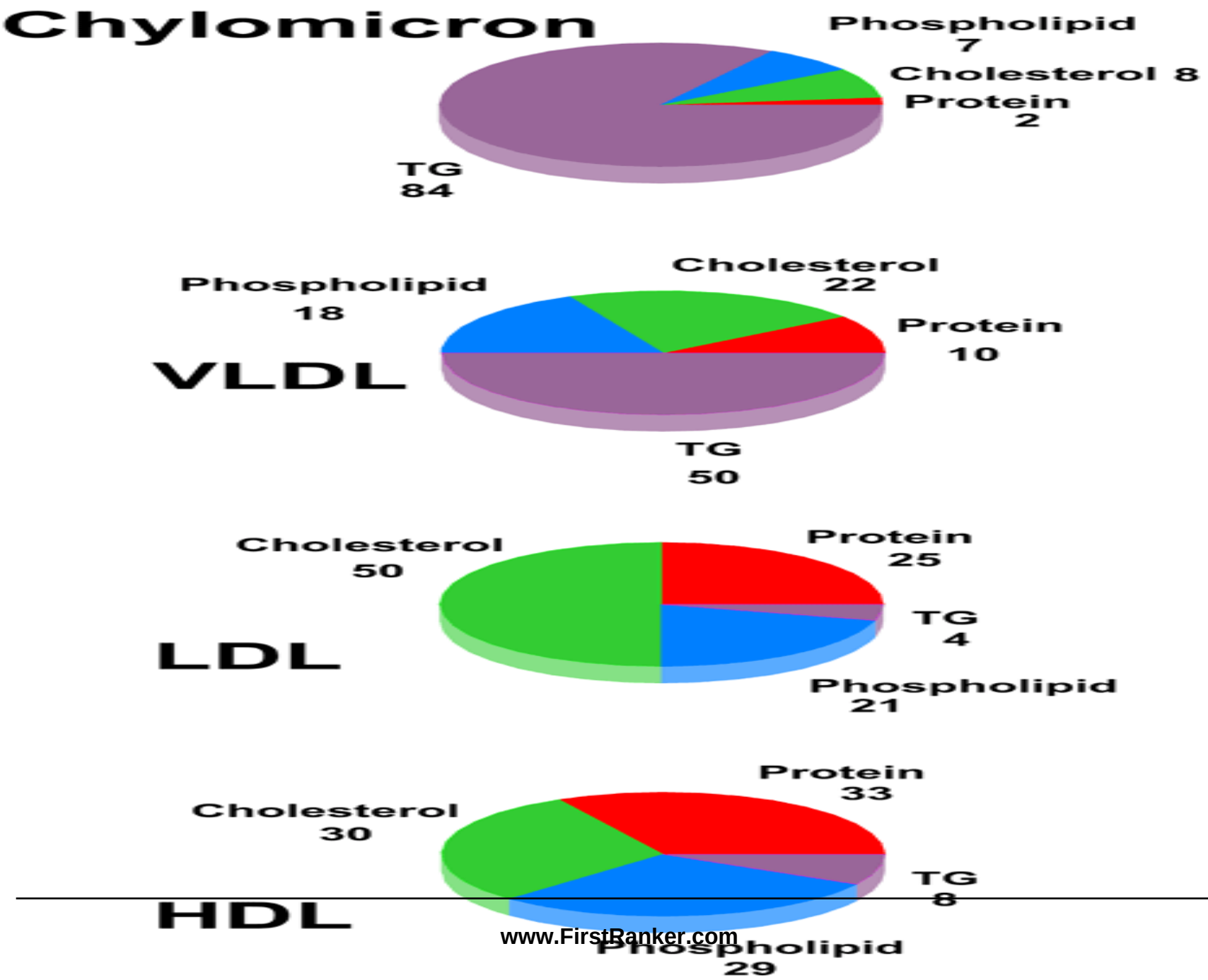


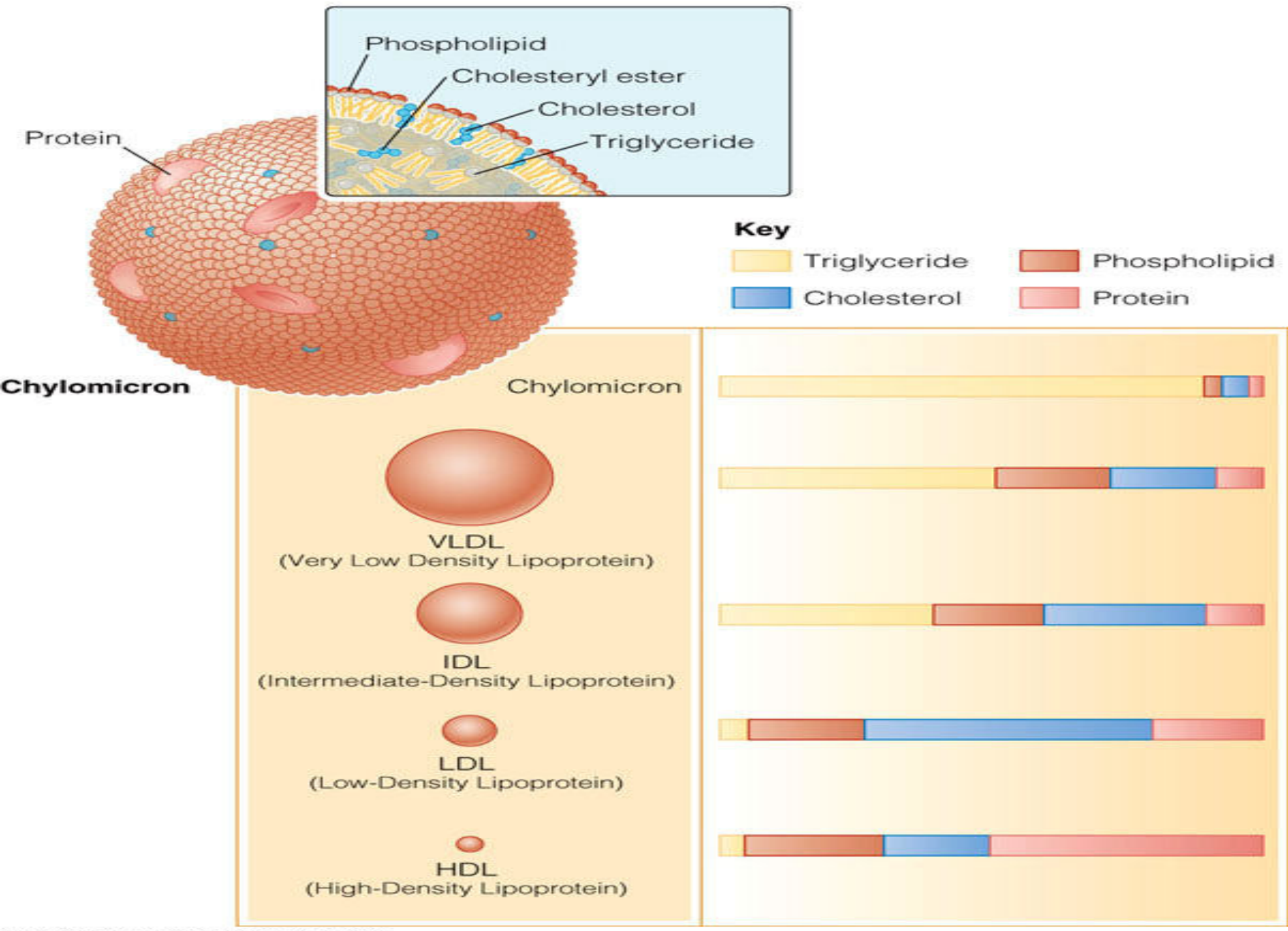
Chylomicrons

Very low density Lipoprotein (VLDL)

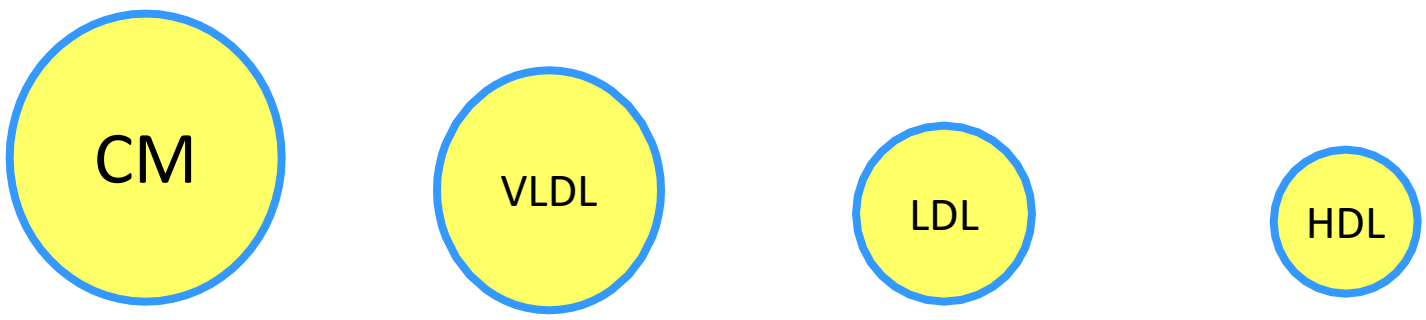
Low density Lipoprotein (LDL)

High density Lipoprotein (HDL)

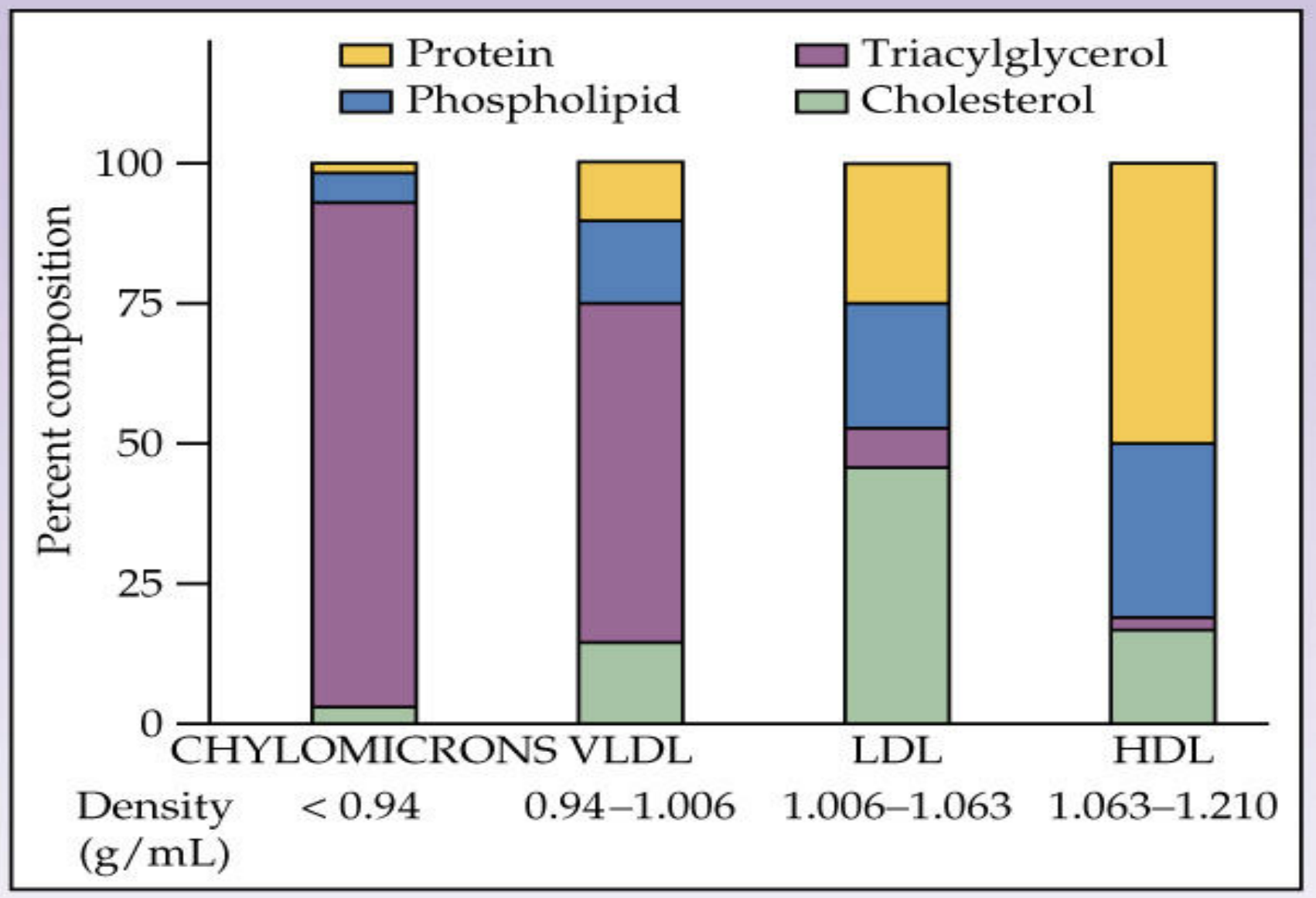




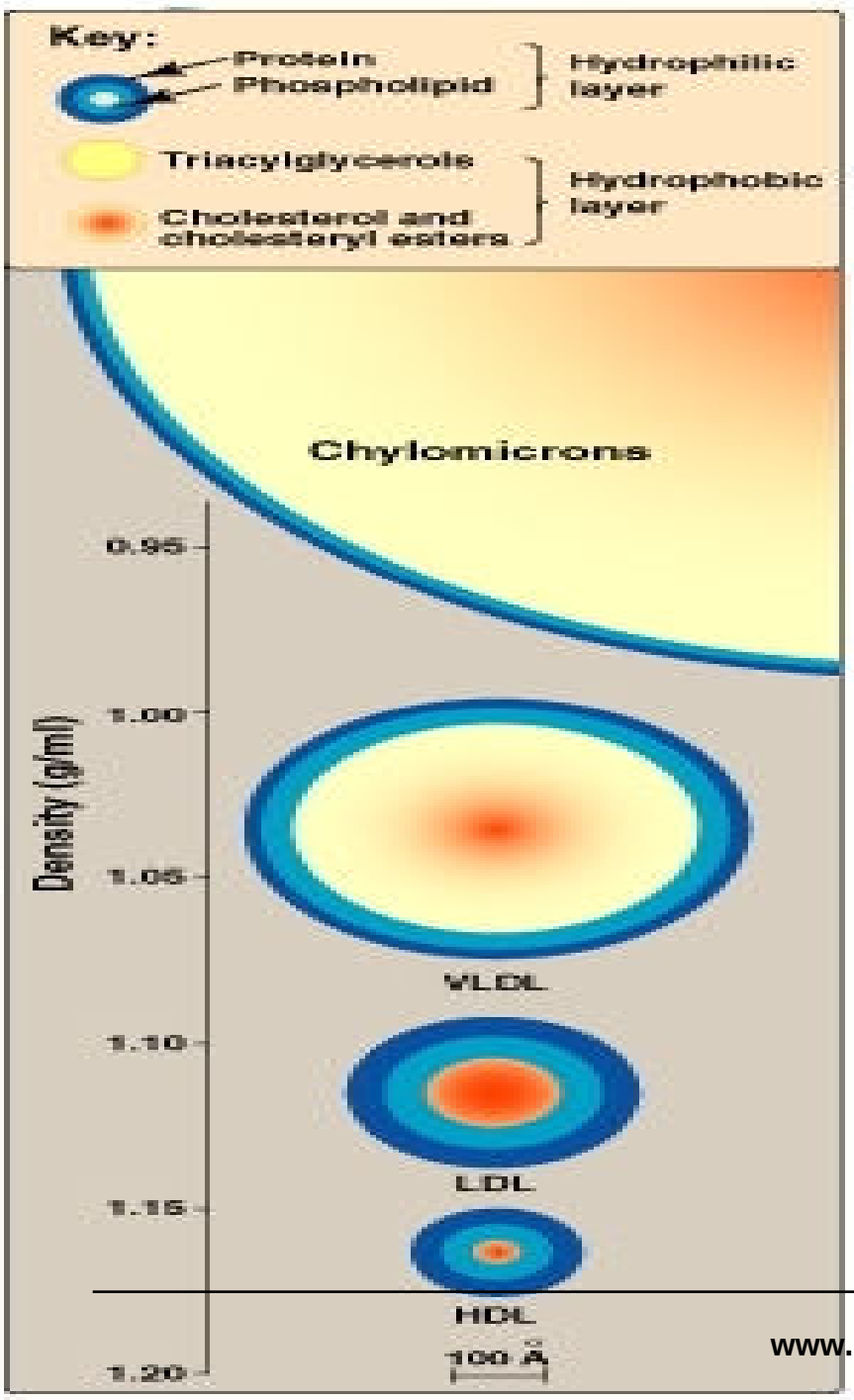
Lipoprotein Nomenclature, Composition and Separation



Major Protein	ApoB 48	ApoB 100	ApoB 100	ApoA-I
Major and CE Lipid	TAG	TAG	CE	PL

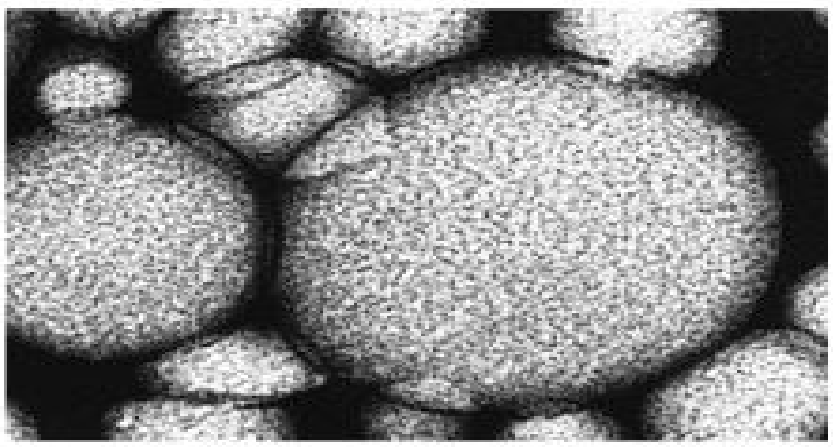


(b) Density and composition of lipoproteins

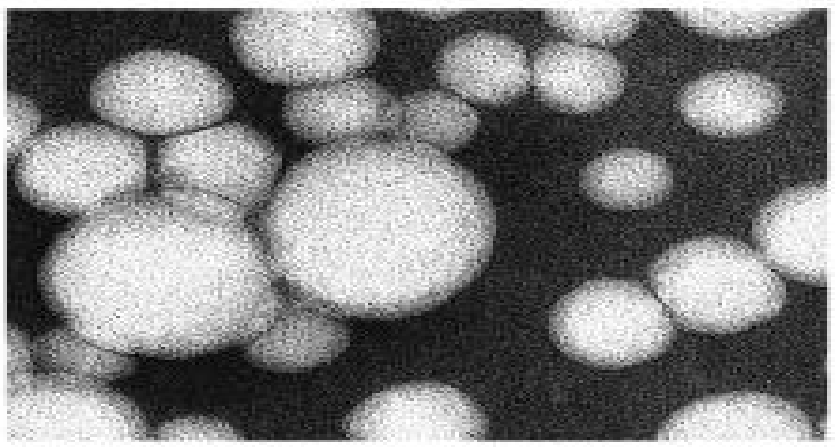


Ultracentrifugation of Lipoproteins

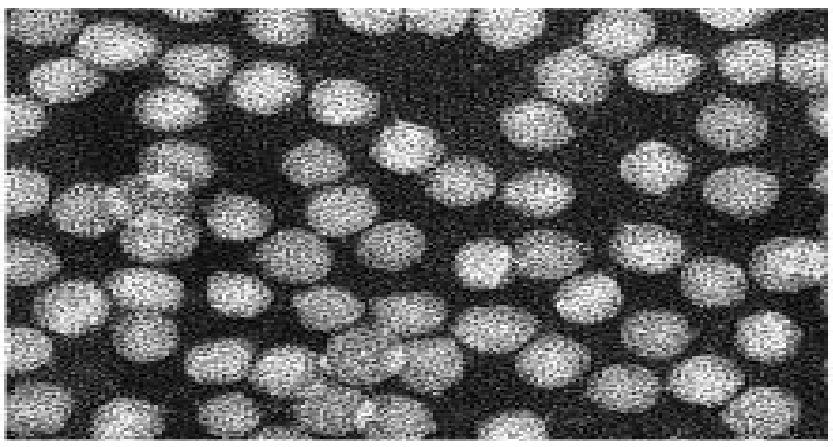
Lipoprotein
Particles with distinct densities



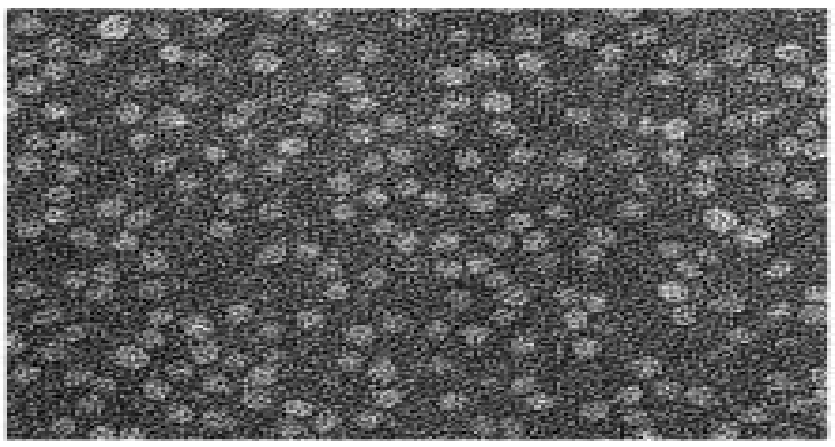
Chylomicrons (50–200 nm diameter)



VLDL (28-70 nm diameter)



LDL (20-25 nm diameter)



HDL (8-11 nm diameter)

(b)

1.Electrophoresis method:

CM (chylomicron)

Slow

β-Lipoprotein

pre β-Lipoprotein

Fast

α- Lipoprotein

2. Ultra centrifugation method:

CM (chylomicron)

Slow

very low density lipoprotein (VLDL)

low density lipoprotein (LDL)

high density lipoprotein (HDL)

High

Lipoprotein Electrophoresis

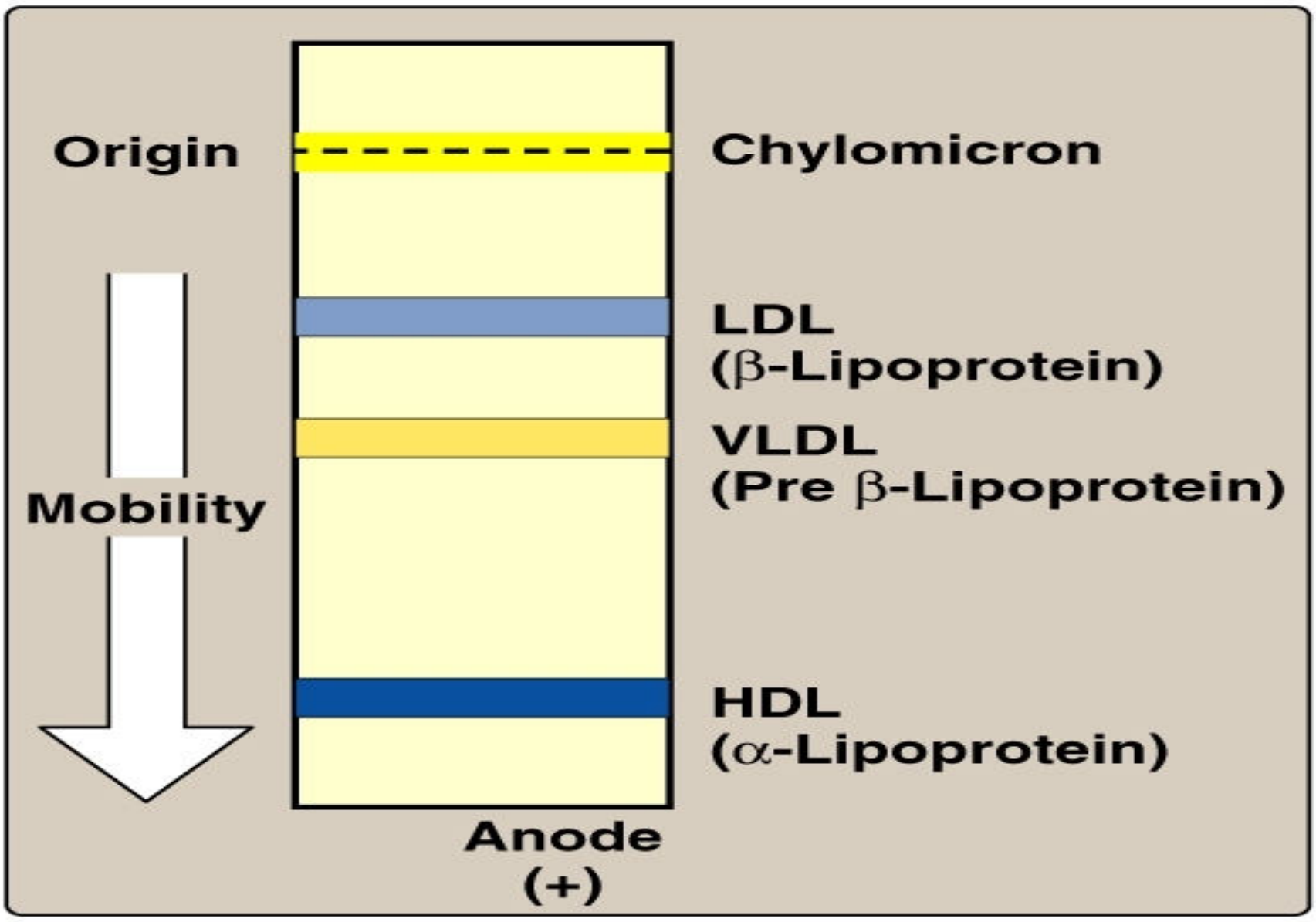


TABLE 26.1 Properties of plasma lipoproteins

Lipoproteins	Major core lipids	Apoproteins	Mechanism of lipid delivery
Chylomicron	Dietary triacylglycerols	B-48, C, E	Hydrolysis by lipoprotein lipase
Chylomicron remnant	Dietary cholesterol esters	B-48, E	Receptor-mediated endocytosis by liver
Very low density lipoprotein (VLDL)	Endogenous triacylglycerols	B-100, C, E	Hydrolysis by lipoprotein lipase
Intermediate-density lipoprotein (IDL)	Endogenous cholesterol esters	B-100, E	Receptor-mediated endocytosis by liver and conversion into LDL
Low-density lipoprotein (LDL)	Endogenous cholesterol esters	B-100	Receptor-mediated endocytosis by liver and other tissues
High-density lipoprotein (HDL)	Endogenous cholesterol esters	A	Transfer of cholesterol esters to IDL and LDL

Plasma Lipoproteins

For Triacylglycerol Transport (TAG-rich):

- **Chylomicrons: TAG of dietary origin**
- **VLDL:TAG of Endogenous (hepatic) synthesis**

For Cholesterol transport (cholesterol-rich):

LDL: Mainly Free Cholesterol

HDL: Mainly esterified Cholesterol

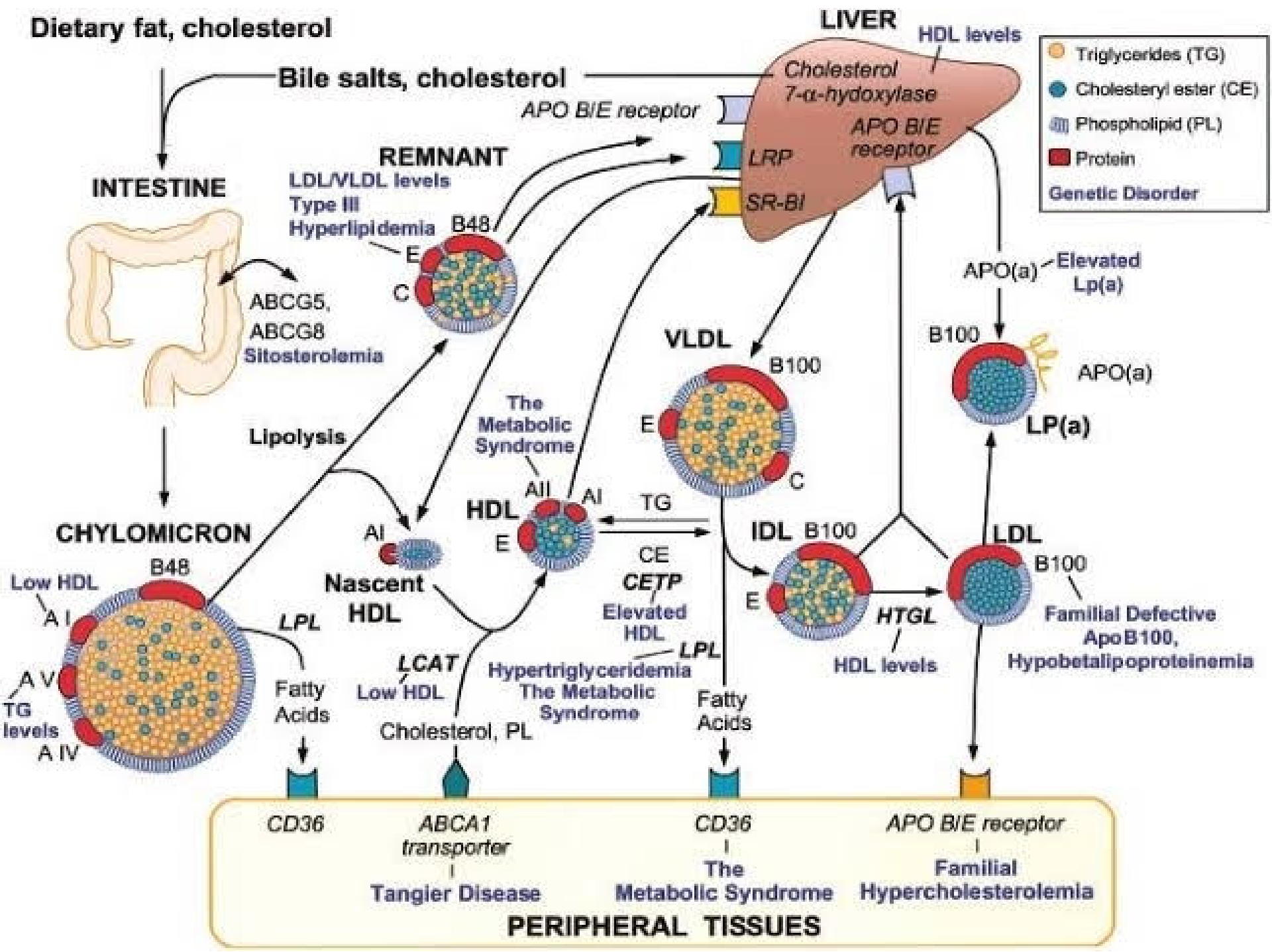
Features Of Lipoprotein Metabolism

Important Organs Involved In LPL Metabolism

- Intestine
- Liver
- Extra hepatocytes
- Adipose Cytes

Lipoprotein Metabolism

- Highly Complex
- Specific
- Highly Dynamic
- Regulated
- Well Communicated, Coordinated



Lipoproteins In Health Are In Dynamic State

- **Biosynthesized** at specific sites
- **Components** of Lipoproteins are responsible for its metabolism
- **Mobilized** out from cells /organs
- **Modified** in Blood circulation
- **Interrelated** with one another
- **Uptake Specific** dependent on specific receptor and transporters
- **Receptor mediated endocytosis**
- **Utilized** and Assimilated to very great extent
- **Highly Coordinated and Regulated**

Important Enzymes and Proteins

Involved in

Lipoprotein Metabolism

- Lipoprotein Lipase (LPL)
- Hepatic Lipase/HTGL
- LCAT
- CETP
- Apoproteins
- Transporters
- Receptors

Lipoprotein Lipase
OR
A Clearing Factor

Lipoprotein Lipase (LPL)

- **LPL is located in endothelial lining of blood vessels.**

Lipoprotein Lipase (LPL)

- LPL is an extracellular enzyme, anchored by Heparan sulfate to capillary walls of most tissues

- It is predominantly present in Adipose tissue, Cardiac & Skeletal muscle

- LPL requires Apo C-II for its activation

- LPL degrades TAG into Glycerol and free fatty acids by its activity.

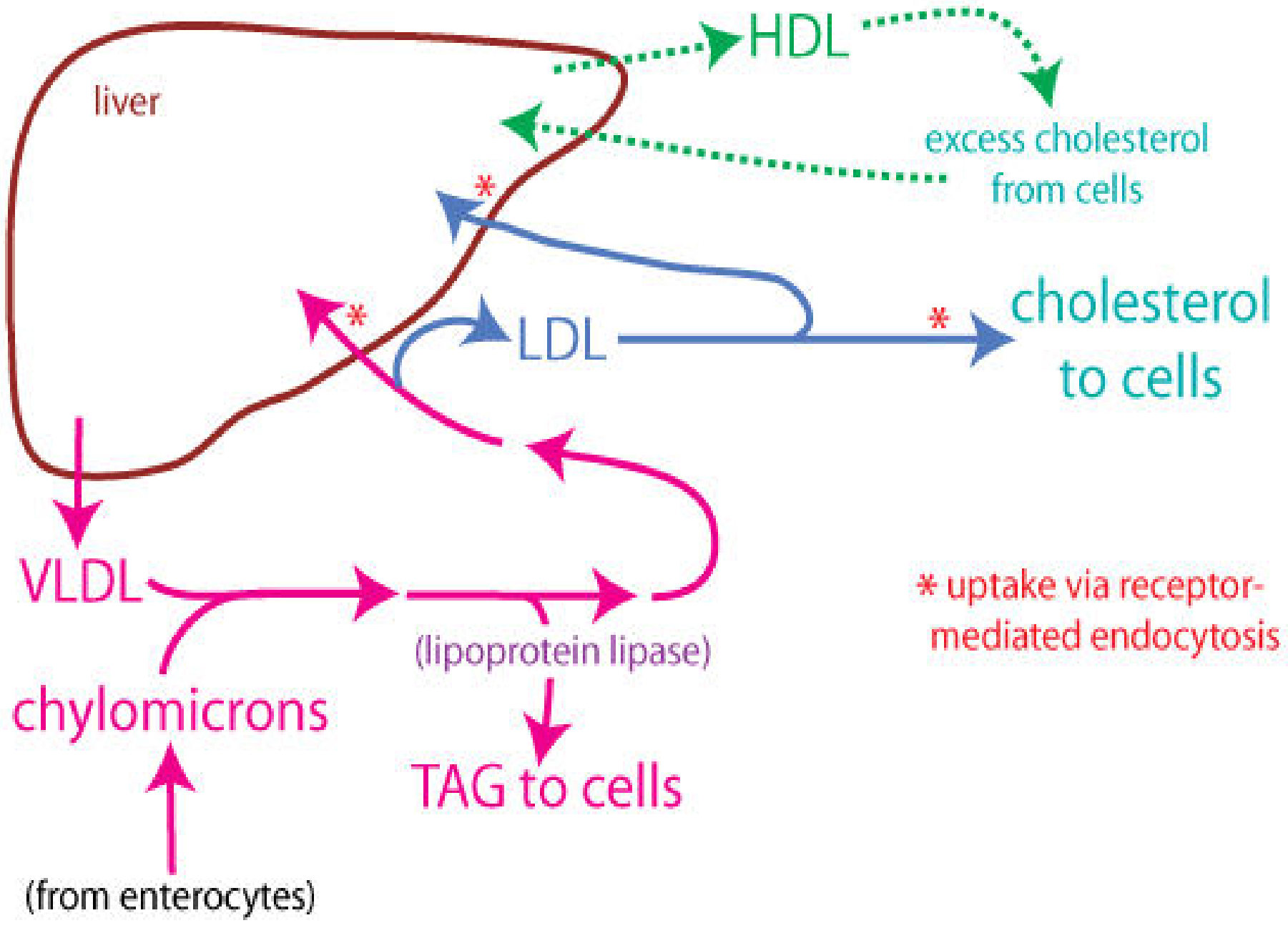
- Insulin stimulates its synthesis and transfer to luminal surface of capillary.

Lipoprotein Lipases

- **Lipoprotein Lipases in capillaries of adipose and muscle tissues hydrolyze TAG in VLDLs.**
- **VLDLs become IDLs**
- **IDLs looses more TAG and become LDLs.**
- **LDLs are less in TAG and rich in Cholesterol and Cholesterol-esters.**

- Lipoprotein Lipase **act upon TAG of Lipoproteins** and hydrolyze it

- **LPL Transforms –**
  - **–Chylomicron to Chylomicron remnant**
  - **–VLDL to LDL**

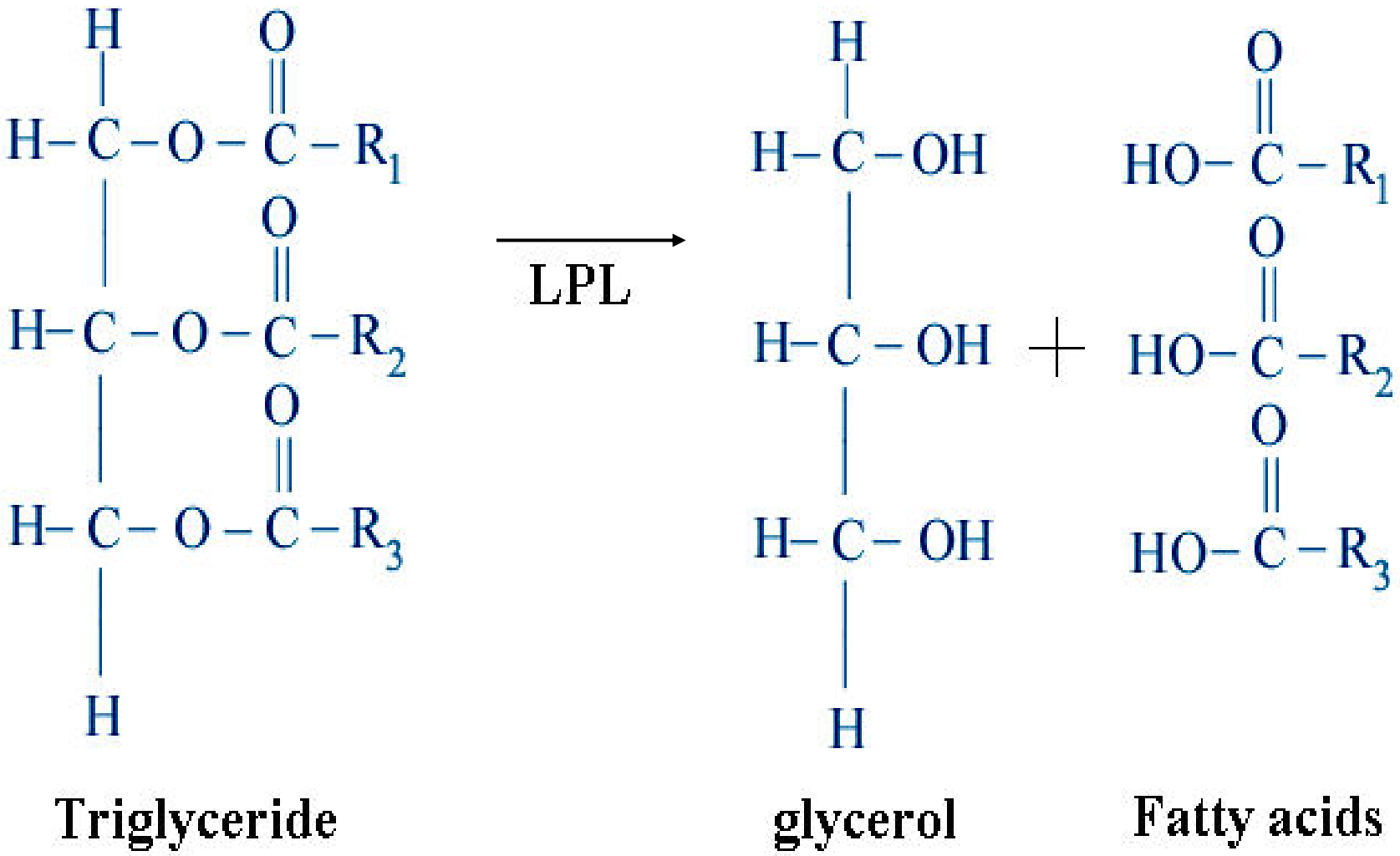


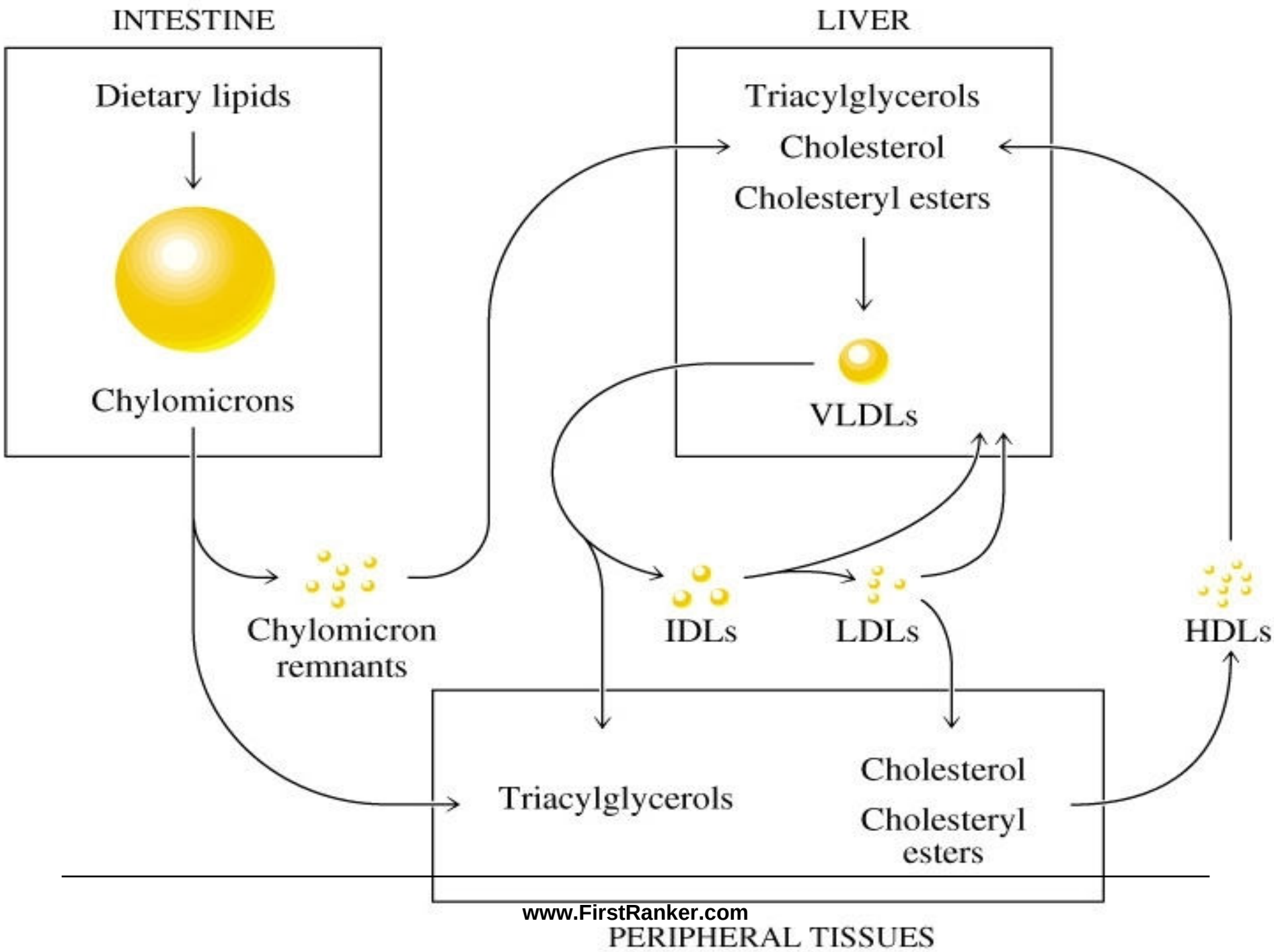
- **Thus LPL clear circulating Lipoproteins from blood** hence it is termed as **Clearing Factor.**

- **Type I Hypolipoproteinemia**
- **This is termed as Familial Lipoprotein Lipase deficiency**
- **Caused due to:**
  - **LPL defect**
  - **Apo C-II defect**

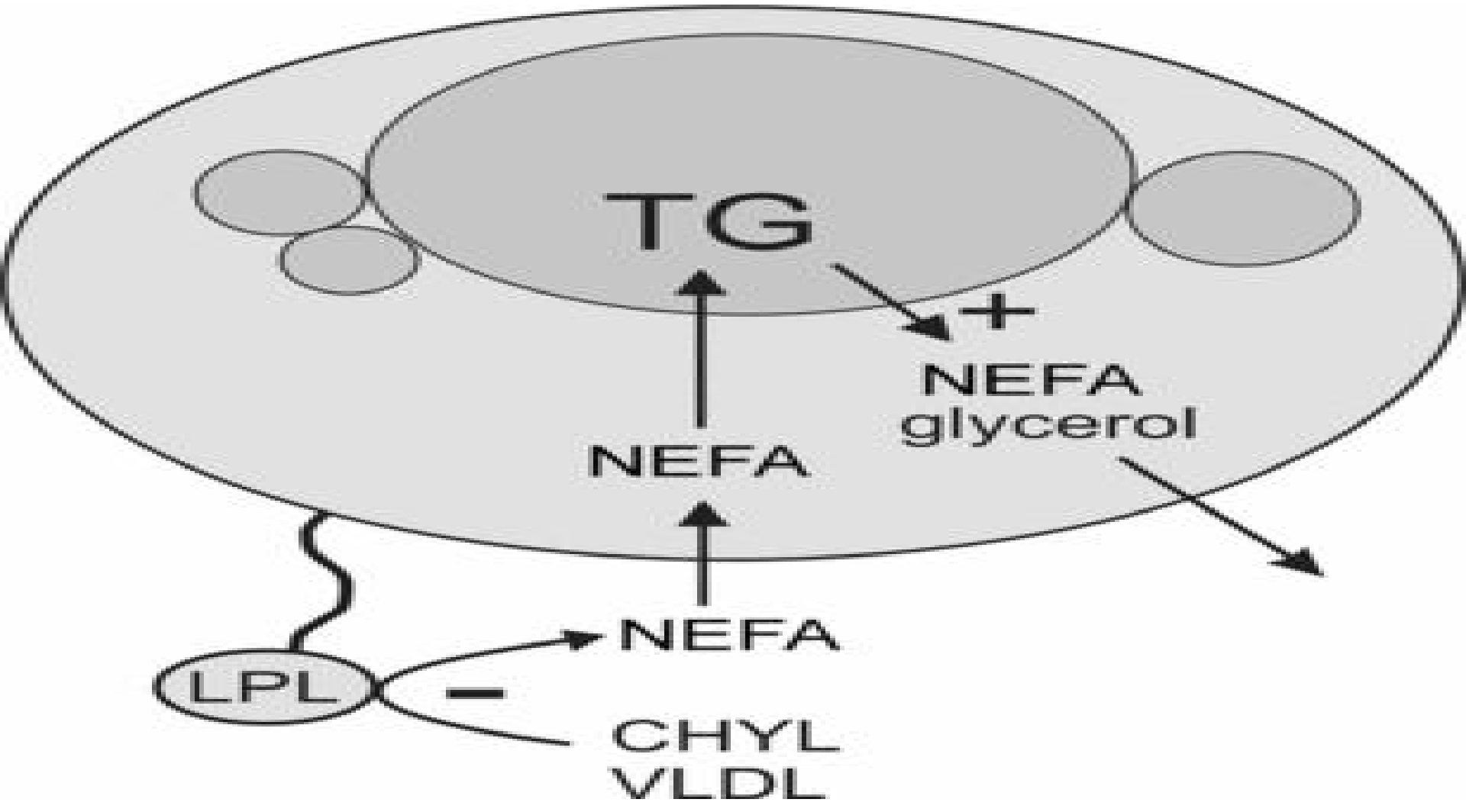
- **LPL Hydrolyzes Triacylglycerol (TAG) in core of CM and VLDL to free Fatty acids and Glycerol.**

- **Released free fatty acids and Glycerol**
- **Then enter into the tissue, mainly adipose, heart, and muscle (80%), while about 20% goes indirectly to the Liver.**





LPL Mediates Fatty Acid Uptake By Adiposecytes



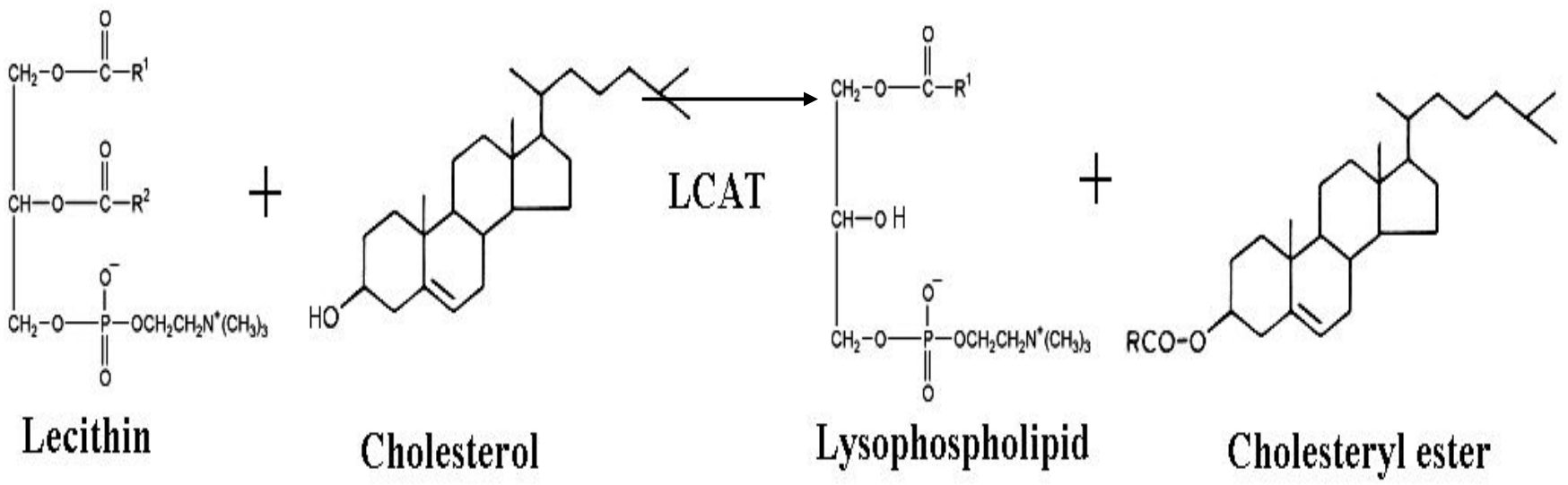
Hepatic Lipase (HL) Hepatic Triglyceride Lipase (HTGL)

- **HL is bound to the surface of Liver cells**
- **Hydrolyzes TAG to free fatty acids and Glycerol**
- **HL is concerned with TAG hydrolysis in Chylomicron remnants and HDL coming to Liver.**

LCAT

(Lecithin Cholesterol Acyltransferase)

Formation of Cholesterol Esters in Lipoproteins

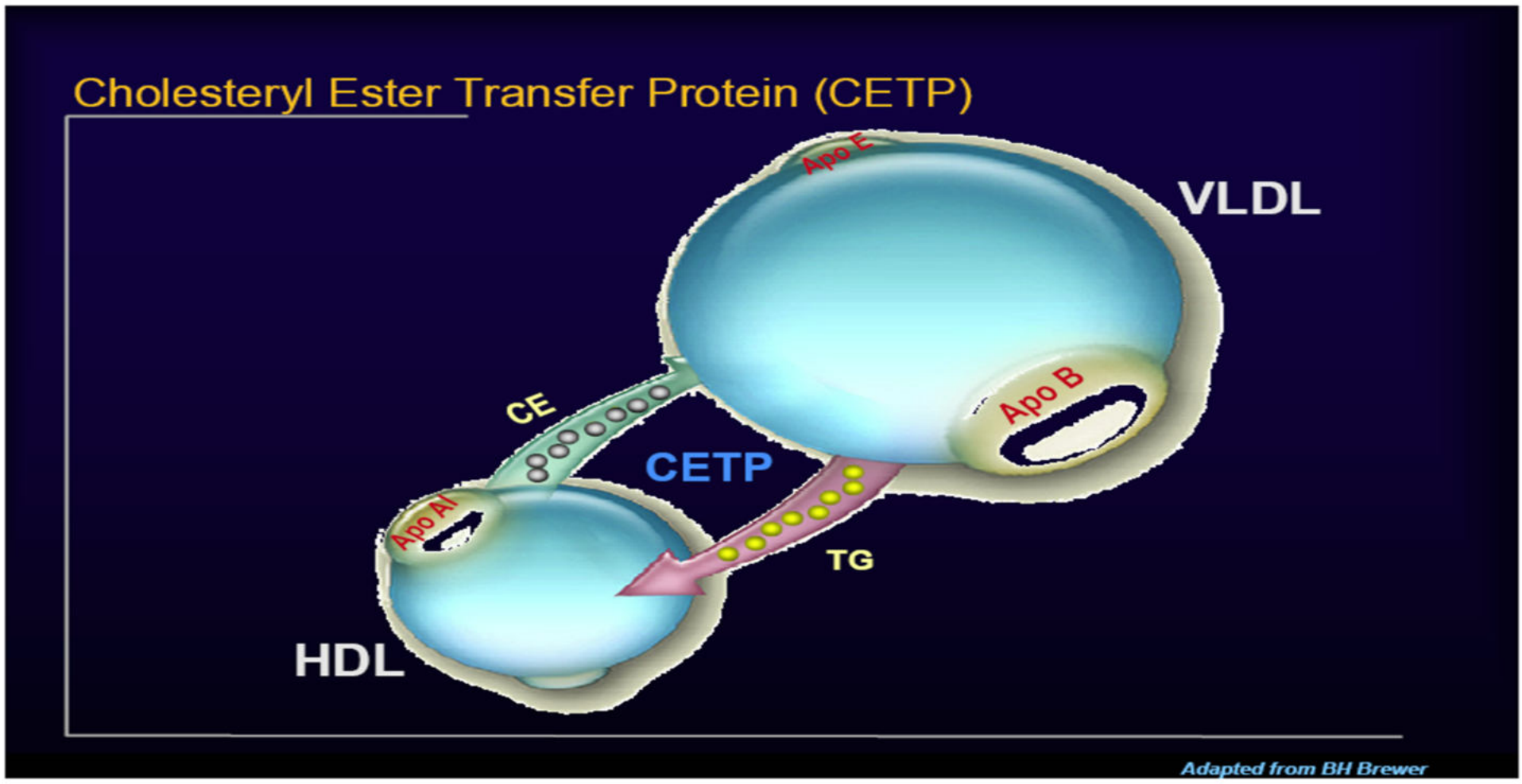


- **LCAT is associated** with **HDL Lipoprotein.**

- LCAT **esterifies Cholesterol and add to nascent HDL and form mature HDL.**

CETP

(Cholesteryl Ester Transfer Protein)



Cholesterol Ester Transfer Protein

CETP

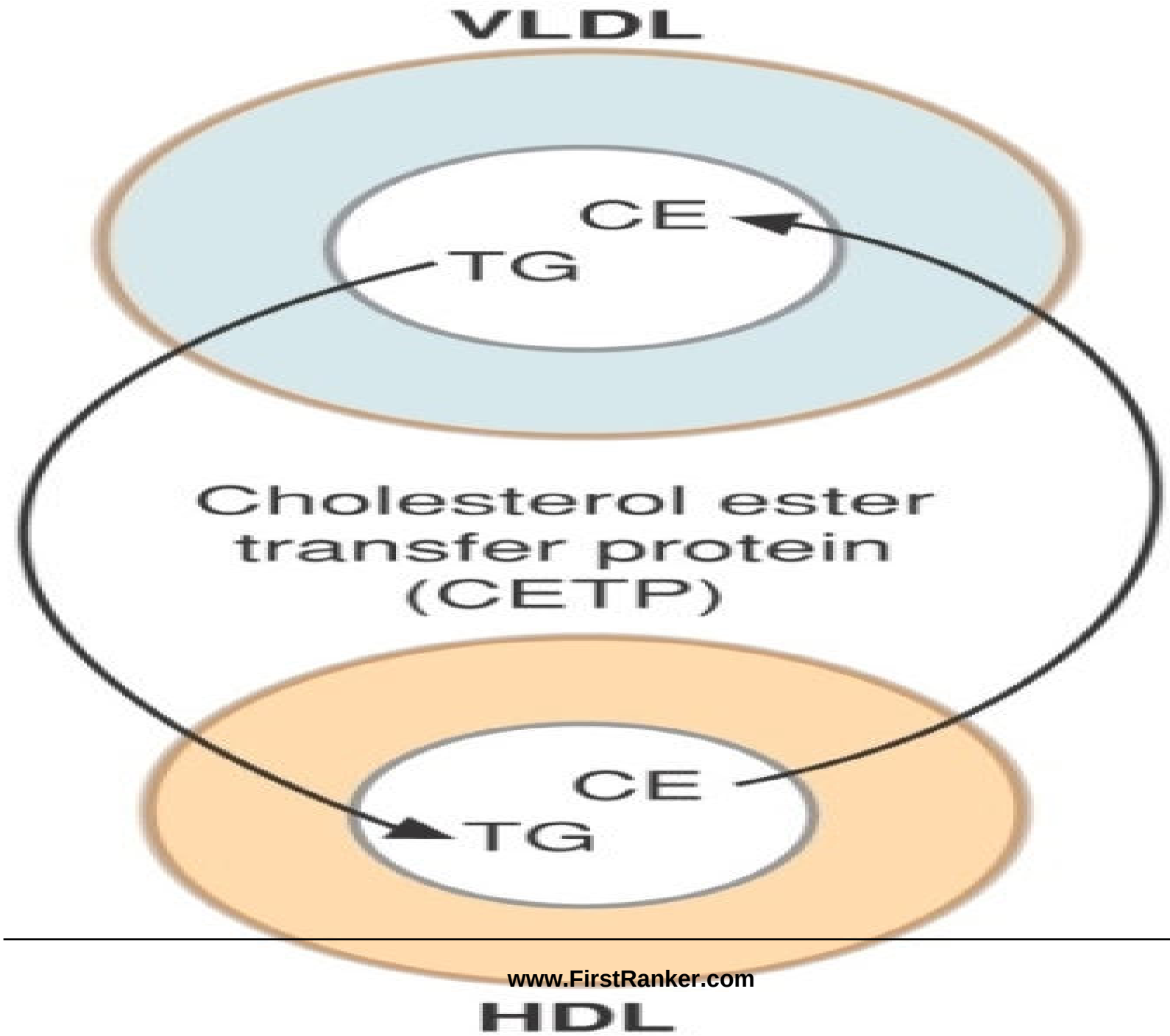
- **CETP is also termed as plasma lipid transfer protein.**

- **CETP exchanges Lipids from one Lipoprotein to another.**

CETP Activity

- **CETP** is a Plasma Protein that **facilitates transfer/exchange** of

- **Cholesteryl Esters** and **Triacylglycerol** between two Lipoproteins.



- By CETP activity **Cholesteryl Ester May be transferred from HDL to:**
  - **VLDL**
  - **IDL**
  - **LDL**

- **CETP transfers TAG** from **VLDL or LDL to HDL**

- In **exchange of Cholesteryl Esters from HDL to VLDL.**

- **HDL** either transfers **Cholesterol & Cholesterol esters.**

- **To Liver and extrahepatocytes by means of CETP activity.**

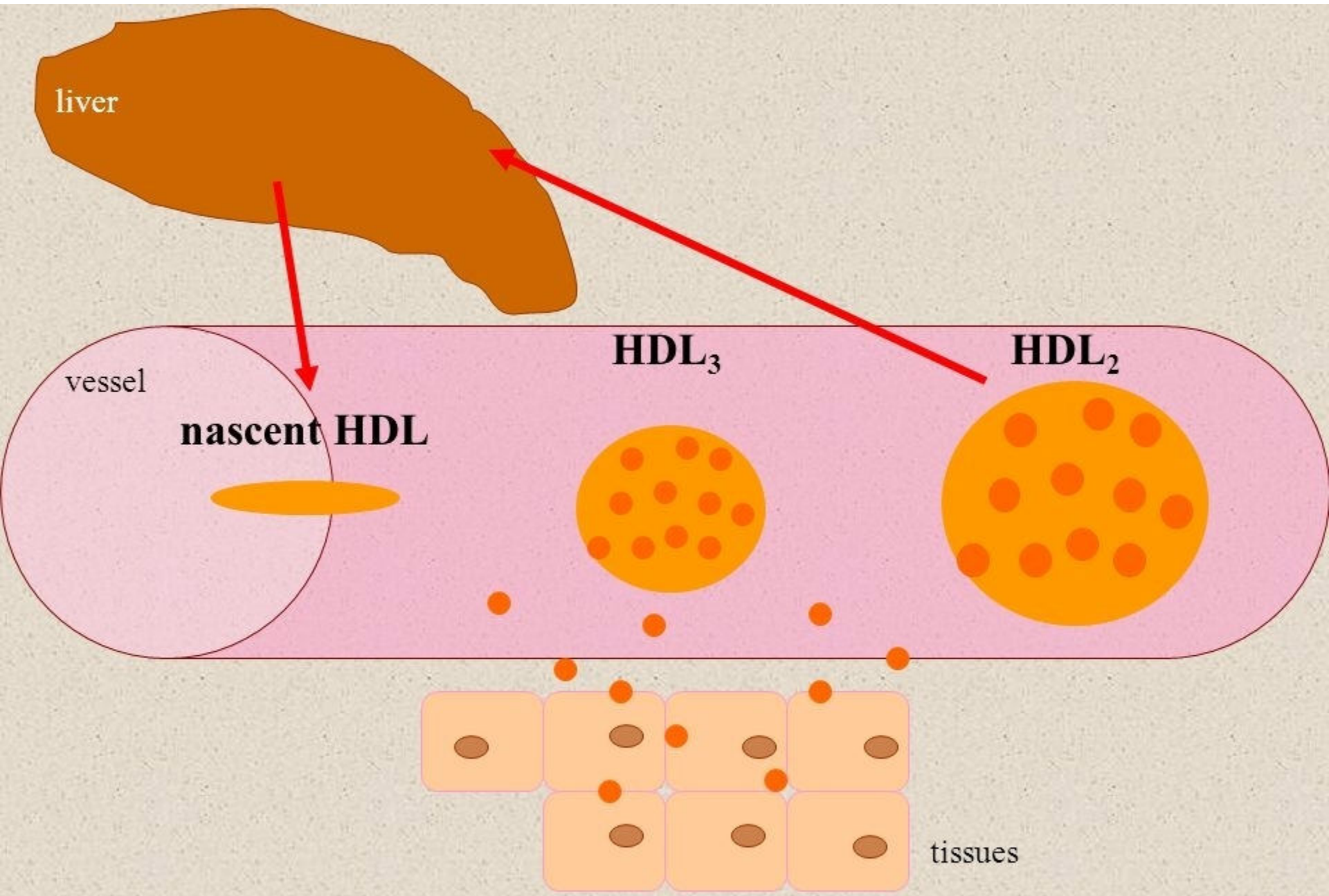
CETP activity Responsible For

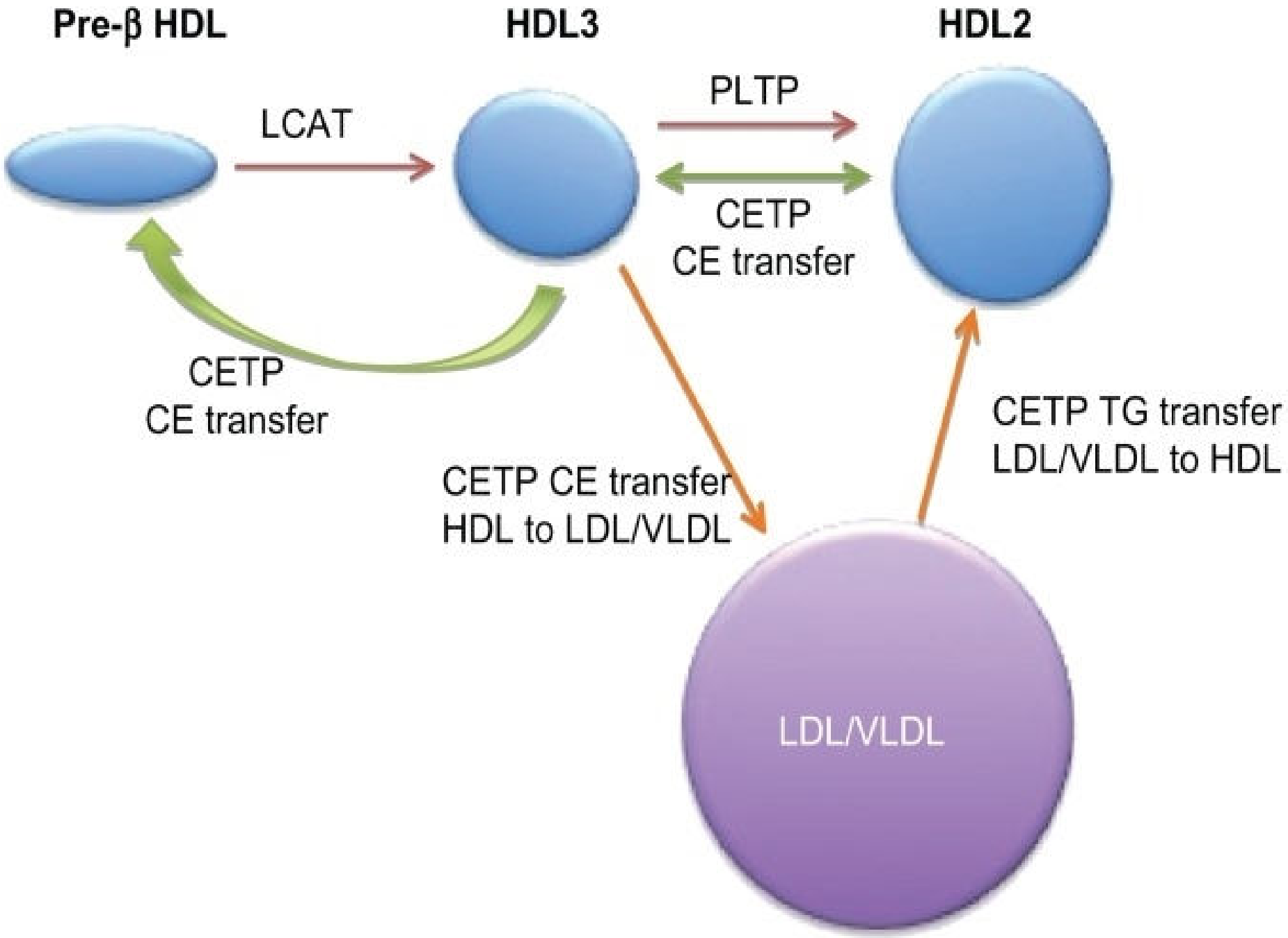
Sub fractions Of HDL

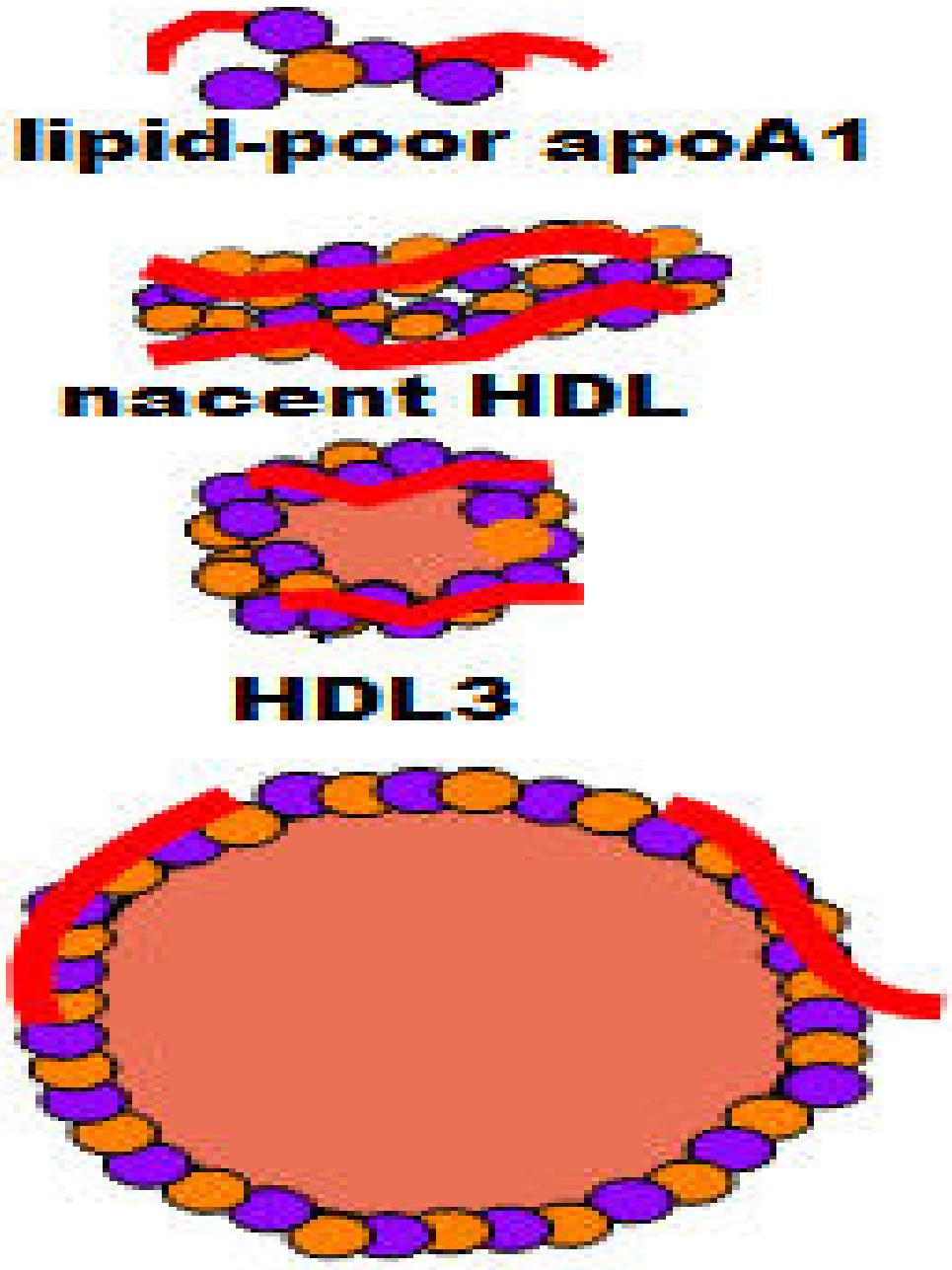
HDL_2 and HDL_3

CETP by its activity Transforms HDL

HDL 3 to HDL 2







- **Prior to CETP activity HDL is** smaller particle termed as **HDL_3**

- **Post CETP activity HDL3** become larger TAG rich and termed as **HDL_2**

- **HDL 3** is **Cholesteryl Ester rich** biomolecule.

- **HDL 2** is **TAG and CE containing.**

- **Receptors Scavenger Receptor Class B1 (SR-B1/SCARB1) present on Hepatocytes and other organs** are for **HDL 2.**

- **HDL 2 is internalized in hepatocytes** and components of it get metabolized.

Significance Of CETP Activity

CETP Activity

- **Modifies** HDL to its subtractions
- **Exchange and Utilizes** Lipoprotein components to its best without waste.
- **Regulates** and Internalizes HDL

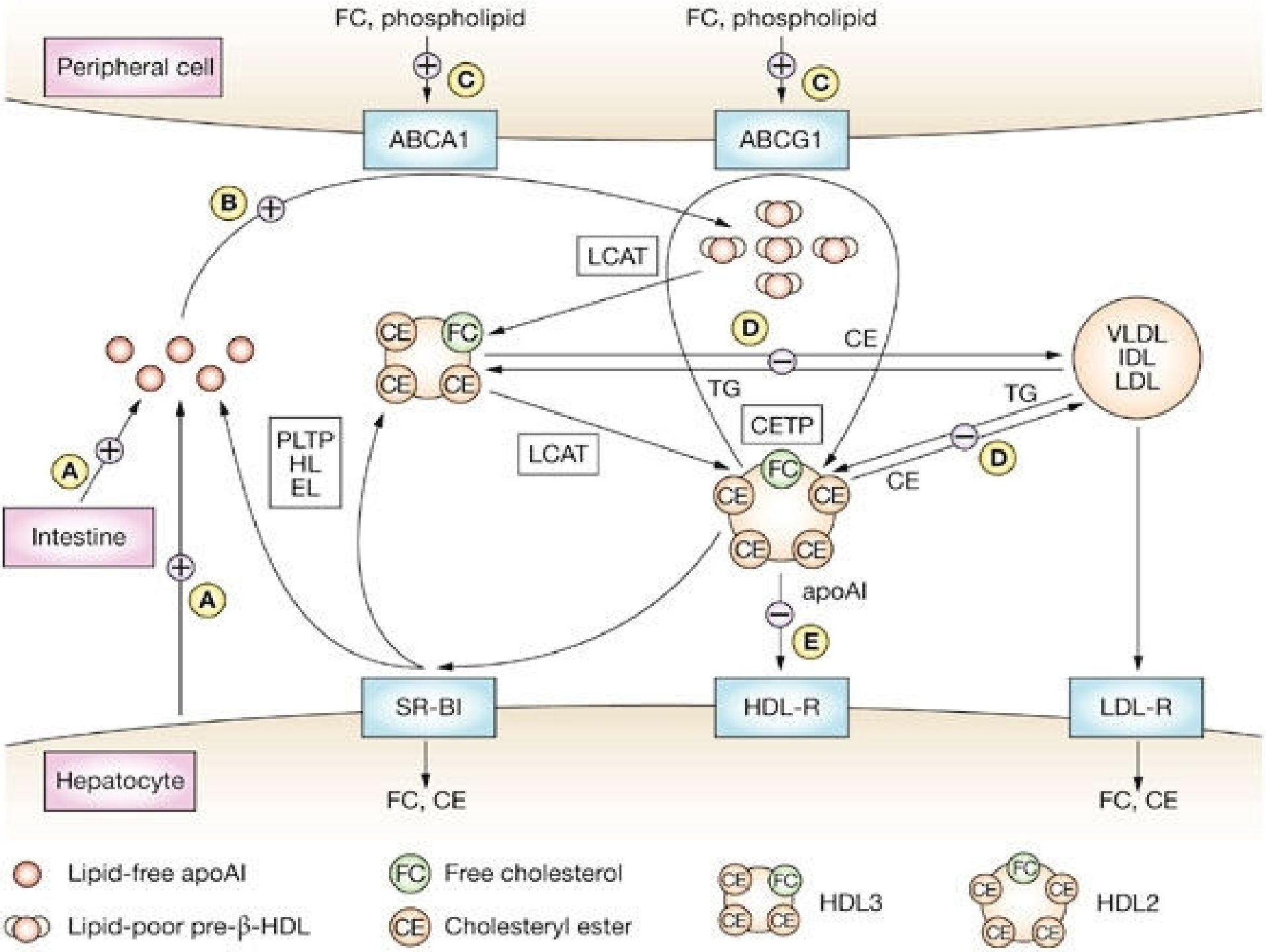
- **Significance of CETP activity is to transfer**
- **Valuable functional compound Cholesterol from HDL to VLDL** and get transported to extrahepatocytes **when** it is required for its use.
- Hence **CETP activity is induced when there is need of Cholesterol to Extra hepatocytes.**

- **CETP activity reduces content of Cholesteryl Ester of HDL.**

CETP and LCAT are Interrelated

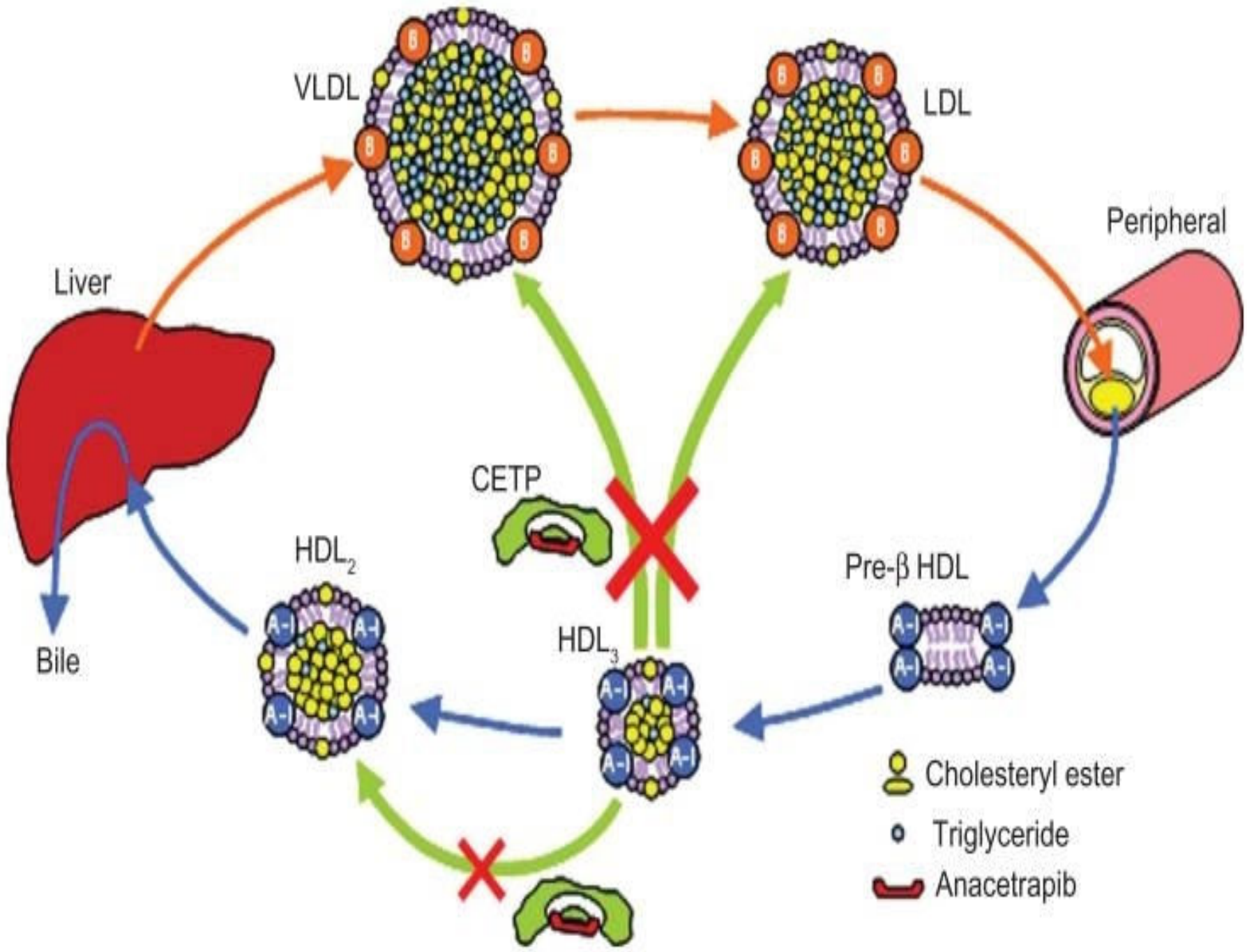
- **Low Cholesterol Ester content of HDL** after CETP activity

- **Increases HDL associated LCAT activity**.



Inhibition Of CETP Activity

Causes High HDL levels In Blood Circulation



- **Effects of Inhibition of CETP**

- CETP will not transfer the HDL Cholesteryl Ester to VLDL, for use by extra hepatocytes.
- **Not modify HDL3 to HDL2**
- **No internalization of HDL3 by Hepatocytes**.
- This may **elevate levels of HDL3 in blood.**
- **Defective Scavenging role of HDL**
- Leading to its **bad consequences of Atherosclerosis.**

- **Inhibition of CETP increases HDL3 levels.**
- But highly reduced CETP activity **accelerates very high HDL3 levels.**
- This **abnormal high levels of HDL3** evidenced showing **development of Atherosclerosis and Coronary Heart Diseases.**

- Recent Studies have evidenced
- **CETP inhibiting drugs**
- **Elevates levels of HDL3**
- **Increases mortality rate.**

Failure of CETP Inhibitor Drugs

- Torcetrapib, failed in 2006 due to excess deaths in Phase III clinical trials.
- Dalcetrapib, development halted in May 2012 when Phase III trials failed to show clinically meaningful efficacy.
- Evacetrapib, development discontinued in 2015 due to insufficient efficacy.
- Obicetrapib (TA-8995, AMG-899), Phase II results reported in 2015, discontinued in 2017

Apolipoproteins

Functions of Apolipoproteins

- Apoproteins are protein parts of Lipoprotein structure
- Apoproteins act as structural components of Lipoproteins
- Apoproteins are polar moieties which impart solubility to Lipoprotein structure.

- **Functions Of Apoproteins**

- **Recognizes Lipoprotein receptors on cell membrane surface as ligand.**
- **Which further facilitates uptake of LP by specific tissues.**

Apoproteins Activate /Inhibit Enzymes Involved in Lipoprotein Metabolism.

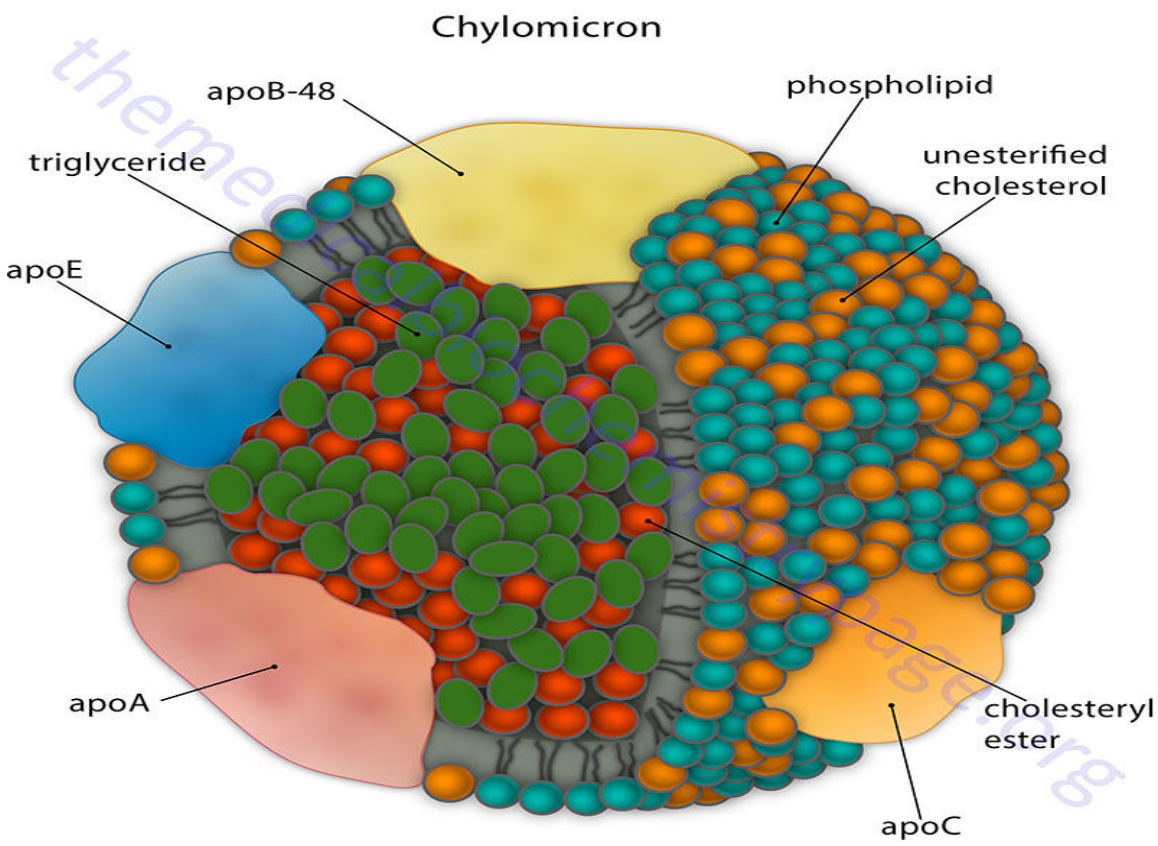
- **Apo A I, C I, A-IV : Activators of LCAT**
- **Apo C-II: Activator of LPL**
- **Apo C-III: Inhibitor of LPL**
- **Apo AII: Inhibitor of Hepatic Lipase (HL)**

- **Chylomicrons contain ApoB-48.**
- **VLDLs, IDLs and LDLs has ApoB-100.**

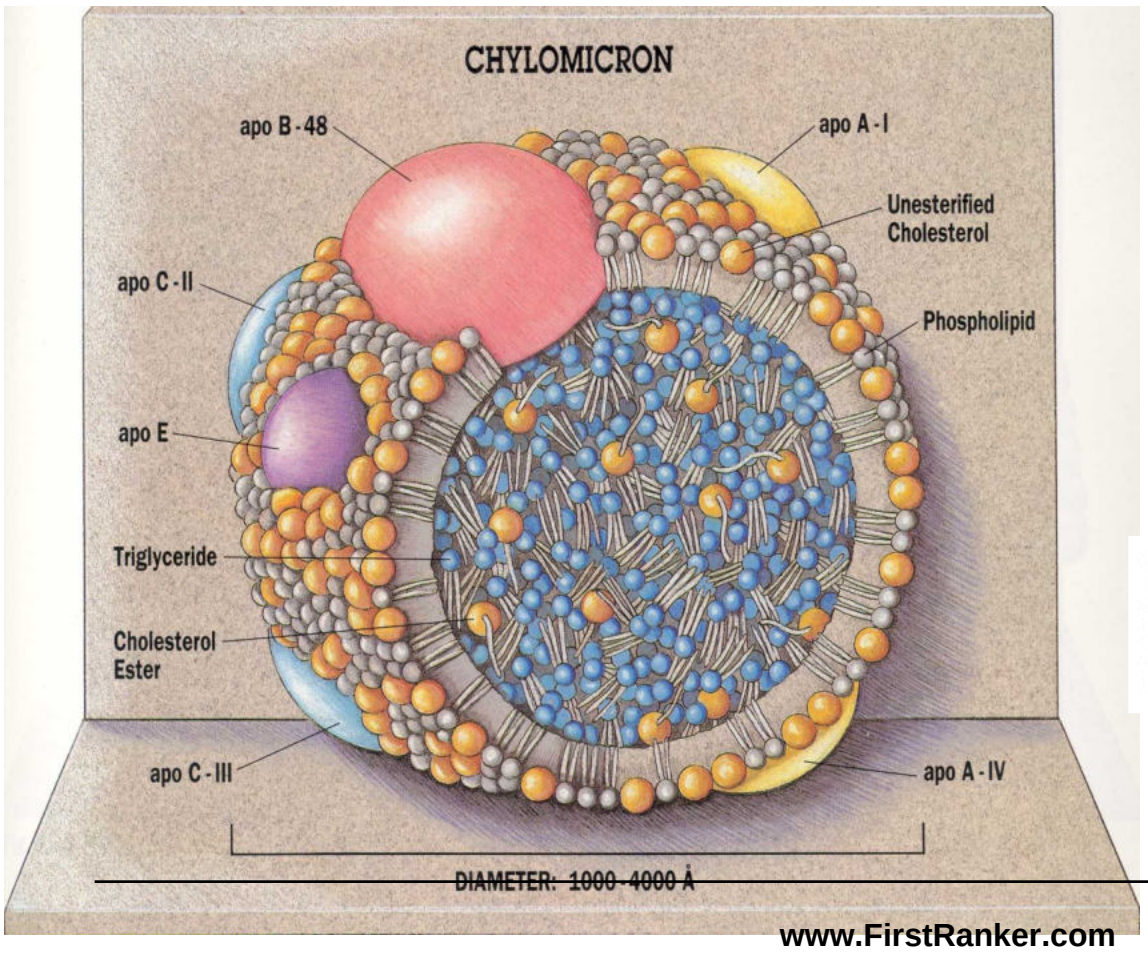
HDL transfers Apo E & Apo CII to Chylomicrons & VLDL

Different Lipoprotein Metabolism

Chylomicron Metabolism



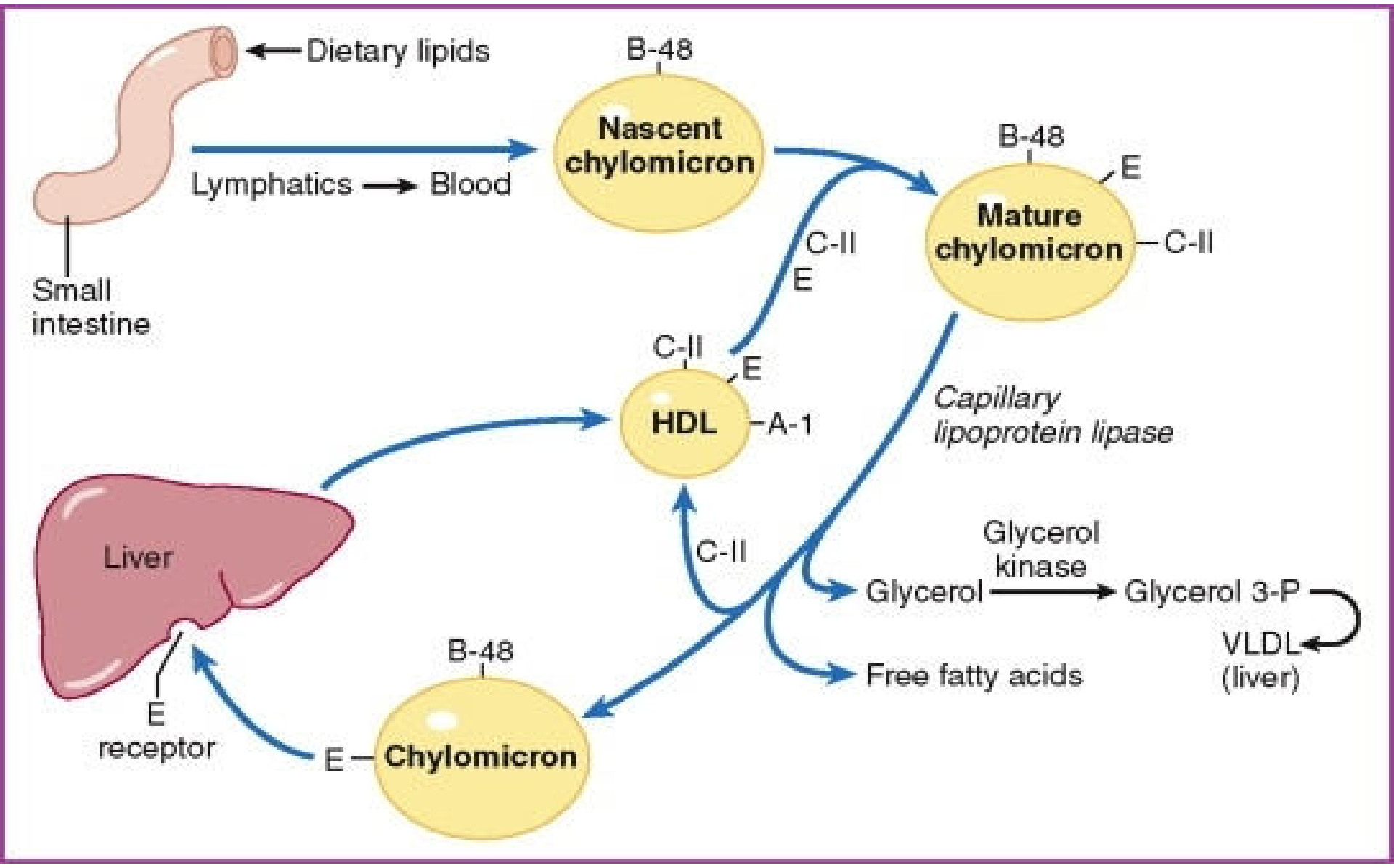
Metabolism of Chylomicrons



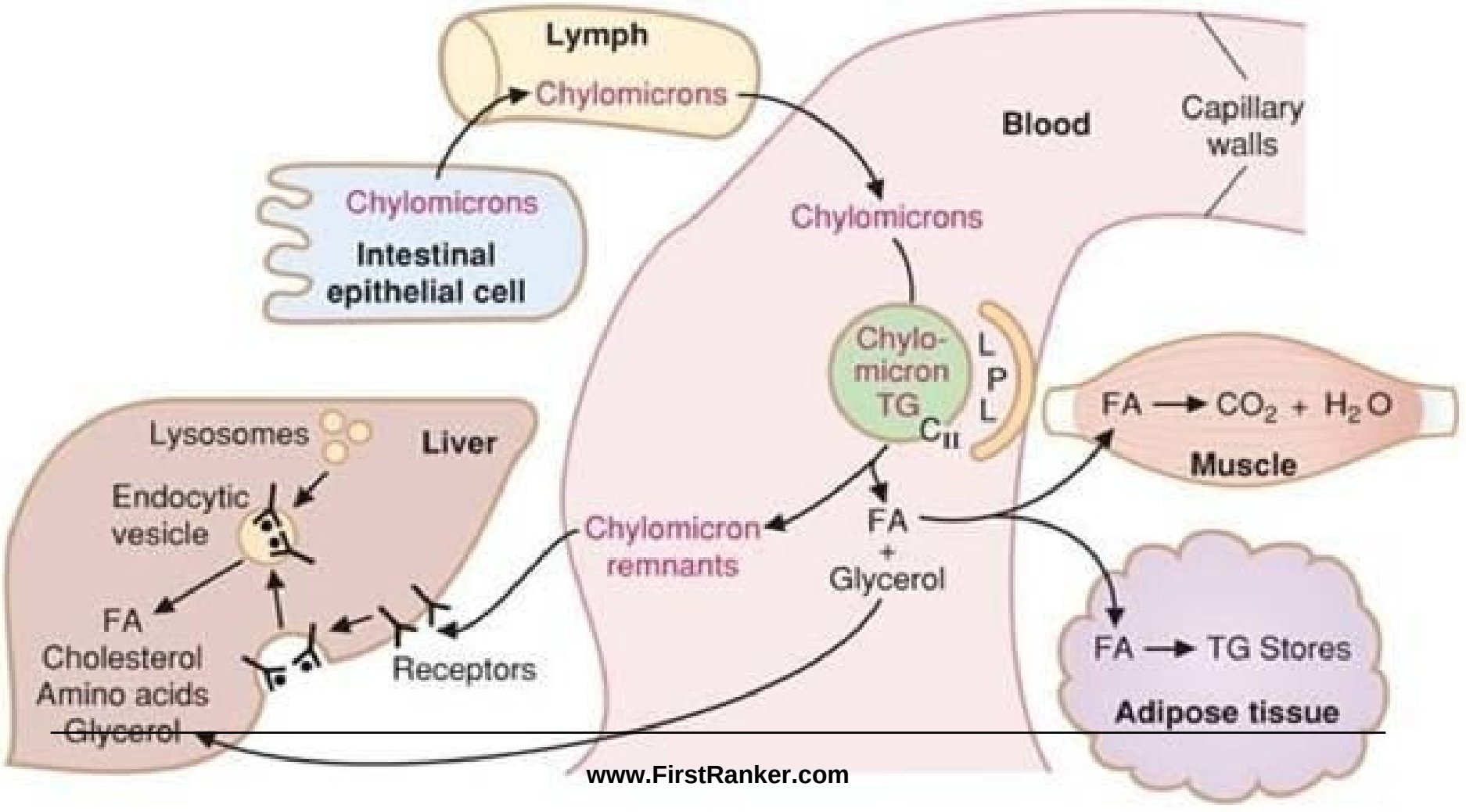
Surface Monolayer
Phospholipids
Free Cholesterol
Protein

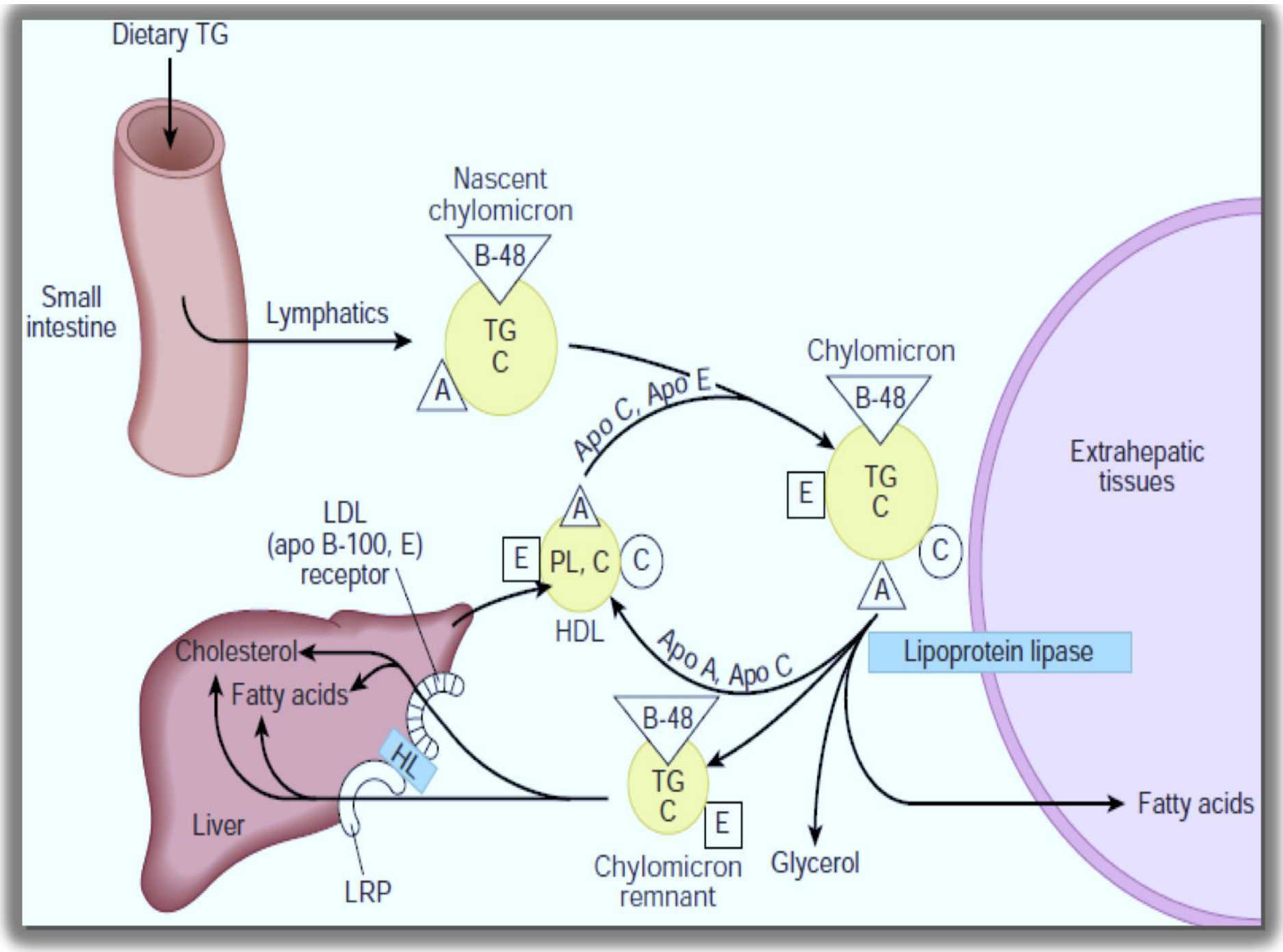
Hydrophobic Core
Triglyceride
Cholesteryl Esters

Chylomicron Metabolism



Chylomicron Transport and Uptake





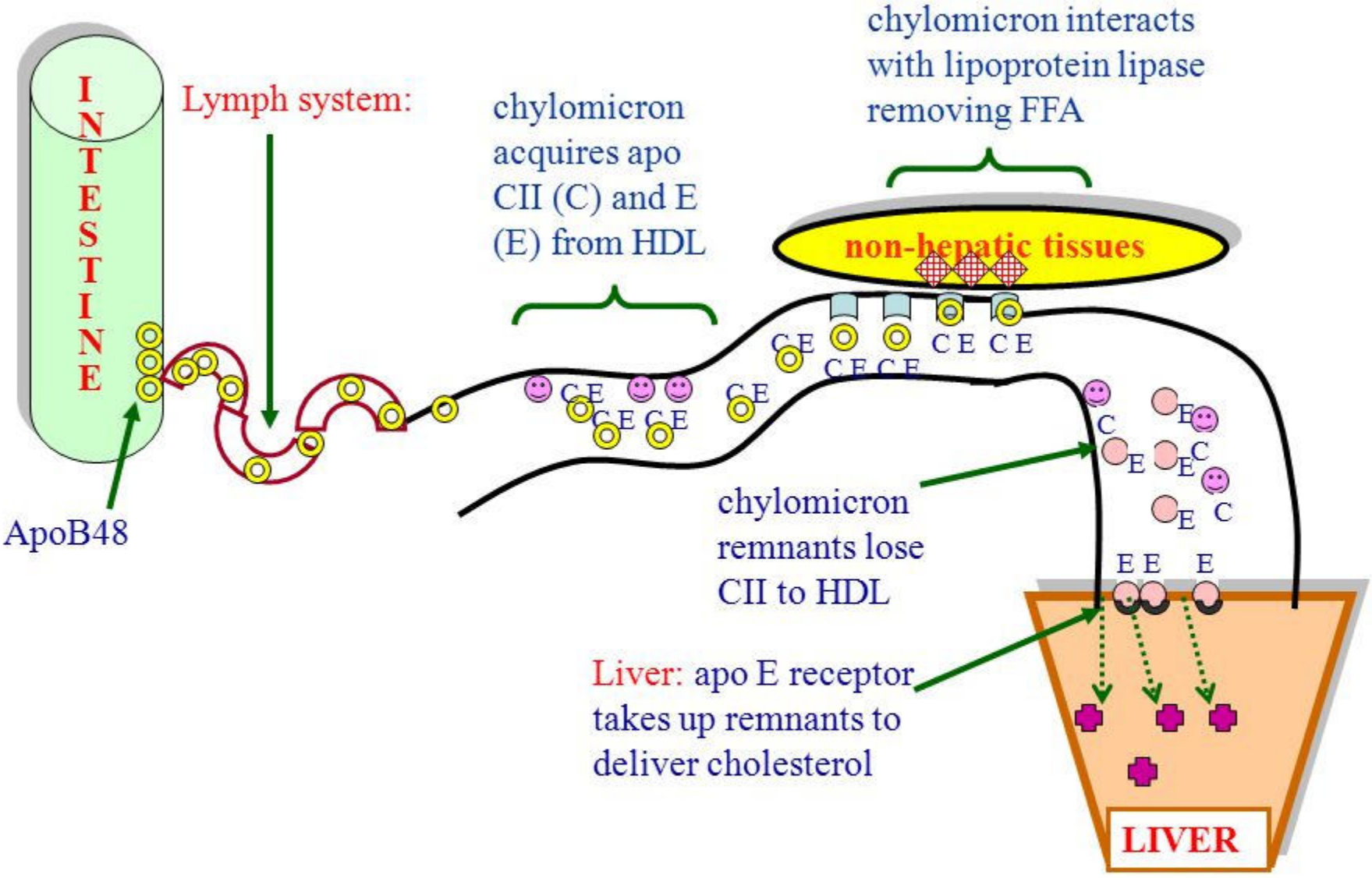


Figure 3. Exogenous pathway of lipid transport. Chylomicrons carry dietary fatty acids to tissues and the remnants take cholesterol to the liver

Chylomicrons

- Assembled in intestinal mucosal cells
- Has lowest density
- It has largest size
- Highest % of lipids and lowest % proteins

- Highest concentration of Triacylglycerol **(dietary origin)**
- Chylomicrons carry **dietary lipids** from intestine to Liver
- Responsible for physiological milky appearance of plasma **(up to 2 hours after meal)**

- **Chylomicron** is a type of Lipoprotein
- **Formed in the intestinal mucosal cells**
- Due to aggregation of dietary digested and absorbed Lipids.

- The Chylomicrons has 99% Lipids and 1% Proteins
- The predominant Lipid present in Chylomicrons is Triacylglycerol (TAG) of dietary origin.

- The Apoprotein of Chylomicron is B48
- Significant role of Chylomicron is to transport dietary Lipids from intestinal mucosal cell to Liver via Lymph and Blood.

- Chylomicrons formed in intestinal mucosal cells are
- First released in lymphatic system
- Which then enters systemic blood circulation via thoracic duct.

- Chylomicrons in blood circulation are not moved inertly

- But **receives Apo C II and Apo E from the circulating HDL** and gets mature.

- ***Apo C II then stimulates the enzyme Lipoprotein Lipase*** present in endothelial lining of blood vessels of Adipose tissue and Cardiac tissue.

- Activated Lipoprotein Lipase acts upon TAG of Chylomicrons ,

- Hydrolyze it into free fatty acids and Glycerol ,which then enters to adjacent adiposecytes.

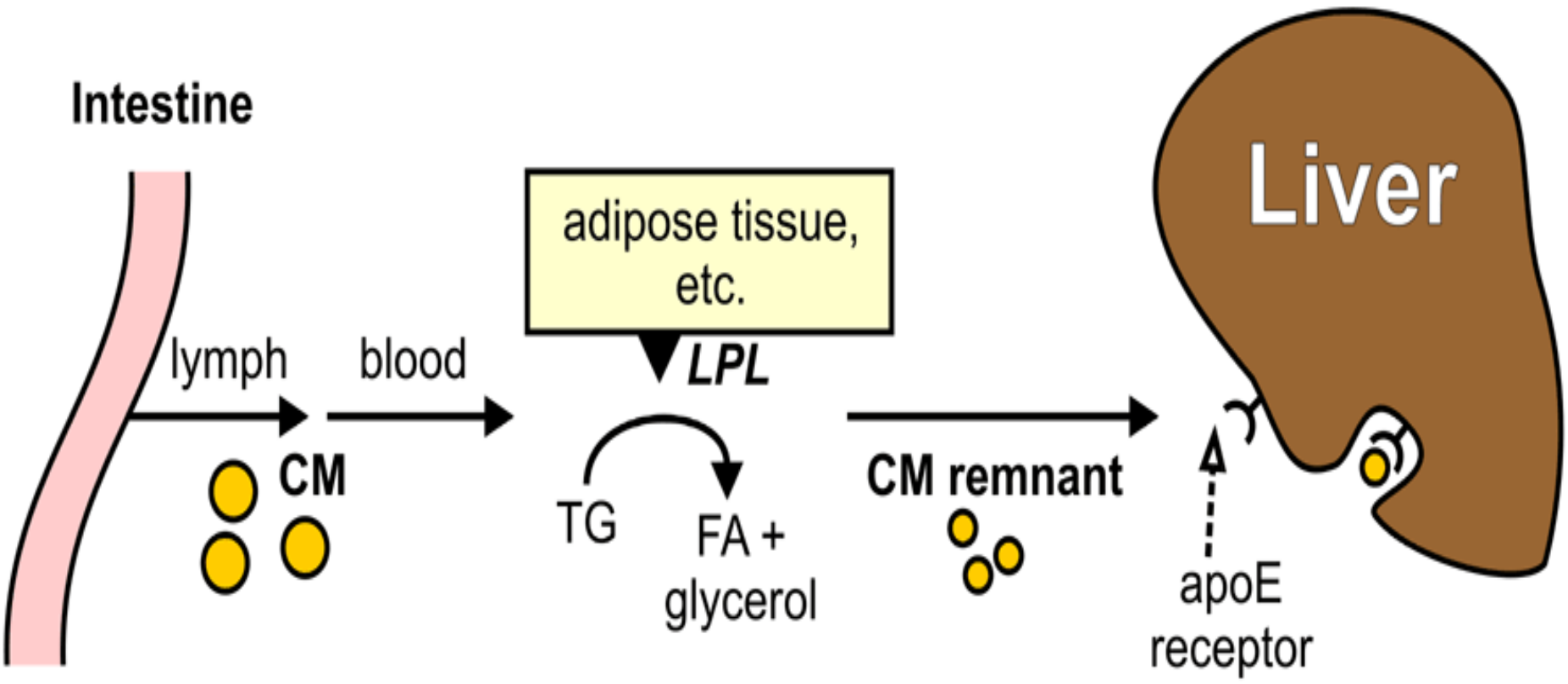
- Entered Free fatty acids TAG and stored as reserve food material.

- The circulating Chylomicrons are continuously acted upon by Lipoprotein Lipase
- Most of the TAG is removed from it and transformed to Chylomicron remnant till they reach Liver.

- The **Liver has receptors for Chylomicron remnant.**

- Chylomicron remnant linked to receptors of hepatocytes are **internalized and metabolized in Liver.**

- **Chylomicrons transport dietary TAG and Cholesterol from the intestine to the peripheral tissues**

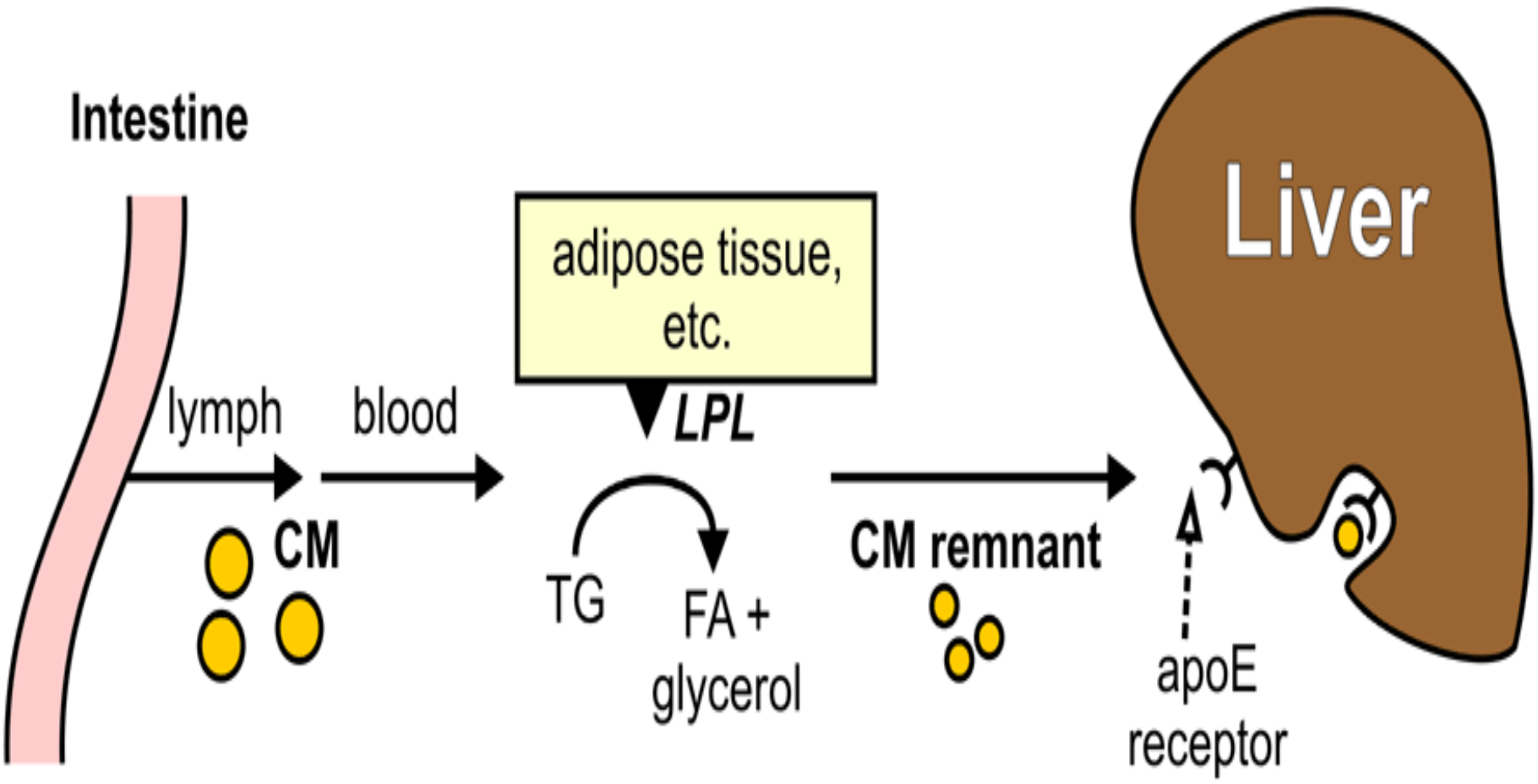


- **Lipoprotein lipase (LPL) is activated by Apo C-II**
- **After most of the TG is removed, Chylomicrons become Chylomicron remnants. During the process, CM give ApoC and ApoA back to HDL**

•CM remnants bind to specific receptors on the surface of liver cells through apo E and then the complex is Endocytosed.

•Remnant receptor or ApoE receptor or LRP (LDL receptor-related protein)

- Chylomicron remnants deliver dietary cholesterol and some cellular cholesterol (via HDL) to the liver.
- Half life of CM is short, less than 1 hour.



Chylomicrons

Nascent Chylomicron are formed in the intestinal and consists of rich in dietary TG + minimal amount of dietary cholesterol + Apo (B-48)

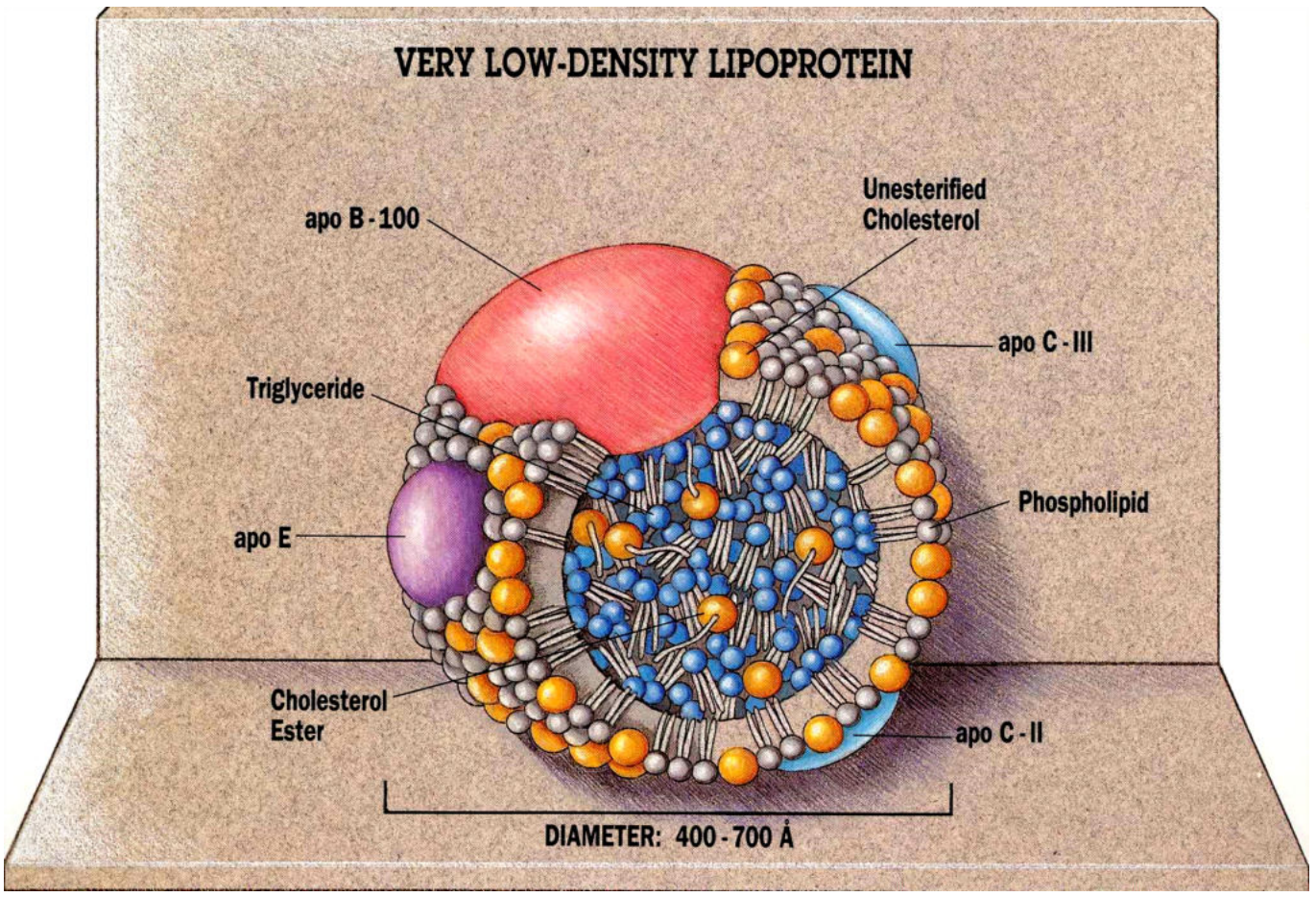
Mature Chylomicron after Nascent chylomicron passage to blood, addition of Apo C II and Apo E from HDL

Lipoprotein lipase hydrolyzes TAG present in Chylomicrons

Chylomicron remnant taken up by the liver through endocytosis.

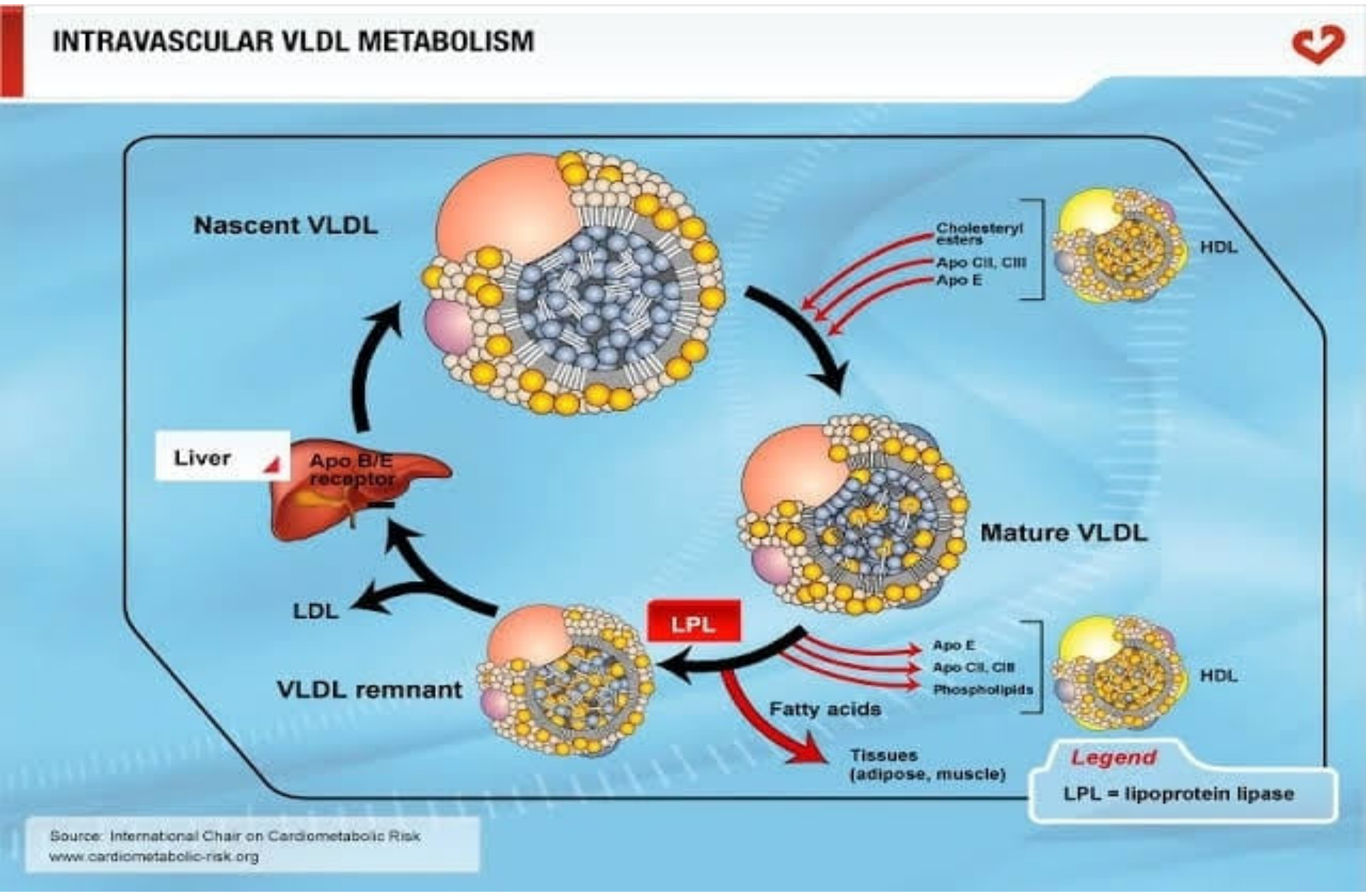
Apo C removed and returns back to HDL

Metabolism of VLDL and LDL



Formation and Fate Of VLDL

VLDL Metabolism



- **The Lipoprotein Very Low Density Lipoprotein (VLDL)**
- Biosynthesized in **Hepatocytes and Intestinal Mucosal Cells**.

- The **endogenously biosynthesized Lipids** are aggregated
- Along with **Apoprotein B-100** to **form VLDL.**

- **VLDL predominantly contains Triacylglycerol of endogenous origin.**

Role Of VLDL

- VLDL facilitates in **mobilizing out the endogenously synthesized Lipids** in Hepatocytes and Intestinal mucosal cells.

- **VLDL transports endogenous Lipids from Liver to Extra Hepatocytes via blood**.

- **Nascent VLDL accepts Apo CII and Apo E from HDL**
- This modify it to **mature VLDLs** in blood.

- **Nascent VLDL: contains Apo B-100**
- **Mature VLDL: Apo B-100 plus Apo C-II and Apo E (from HDL)**

- **Apo C-II is required for activation of Lipoprotein lipase**

- **Lipoprotein lipase is required to degrade VLDL TAG into Glycerol and fatty acids**

- **Circulating VLDL on action by Lipoprotein Lipase hydrolyzes most of its TAG.**
- **VLDL gets modified to IDL and LDL.**

- Thus **intermediate product of IDL and end product LDL** are **formed from VLDL**

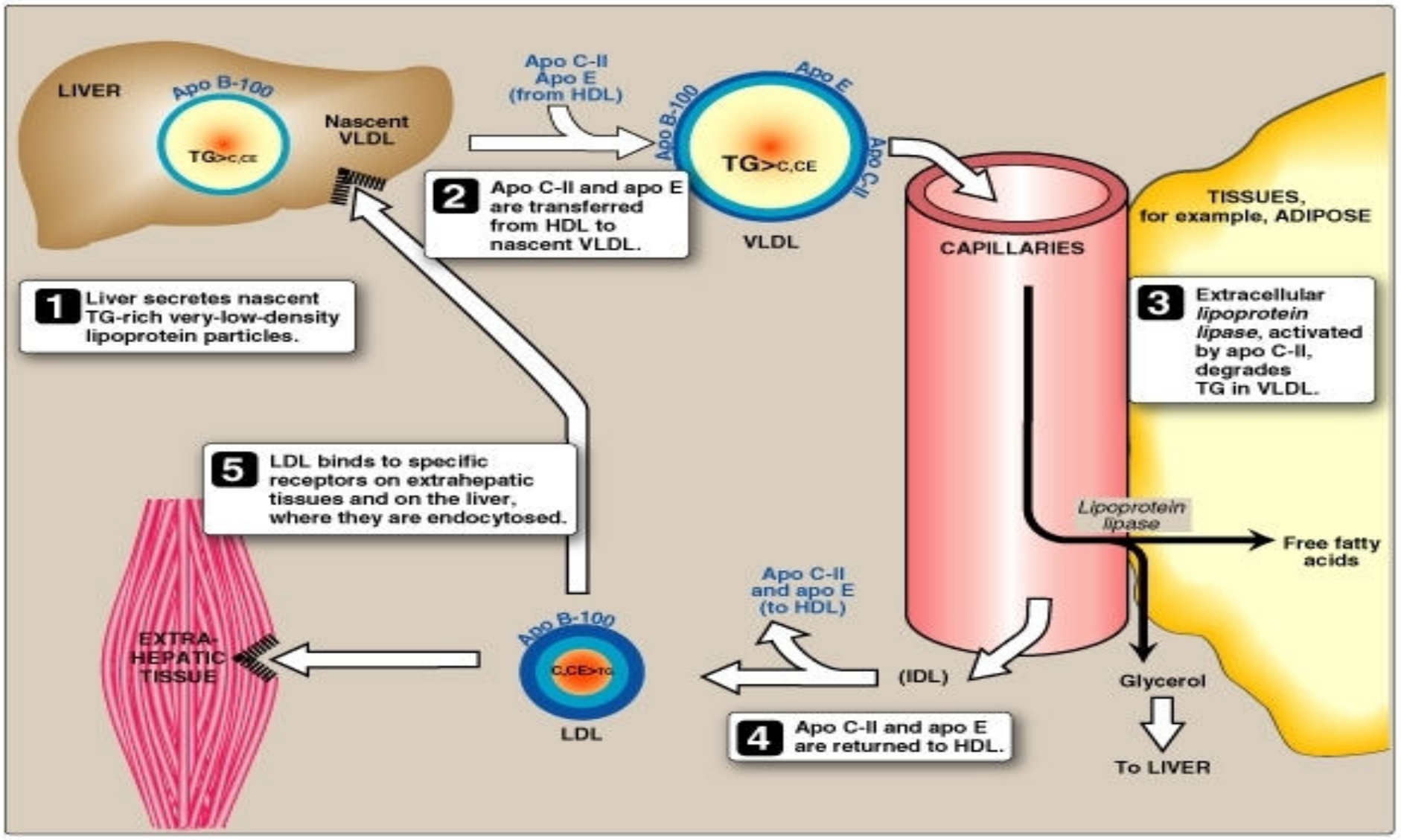
- **In blood circulation by action of LPL on VLDL and removal of TAG from it.**

Normal VLDL Metabolism Prevents the person to Suffer from Fatty Liver

- VLDL help in mobilizing out the endogenously biosynthesized Lipids of Hepatocytes.
- Normal Formation and mobilization of VLDL prevents from accumulation of excess Fat in the Liver and develop Fatty Liver.

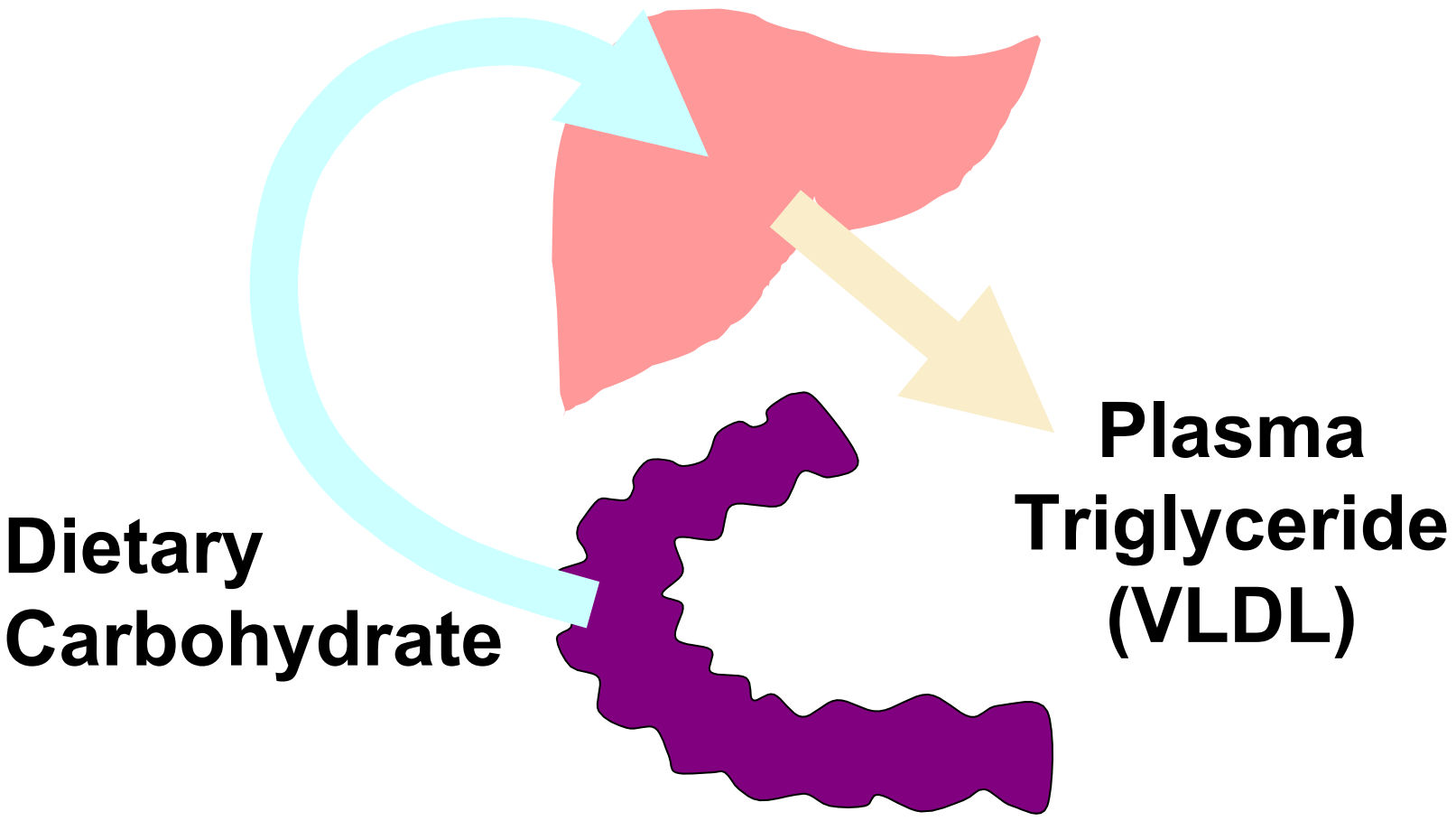
Modifications of Circulating VLDLs

VLDL ⟶ IDL (returns Apo E to HDL) ⟶ LDL



VLDL Metabolism

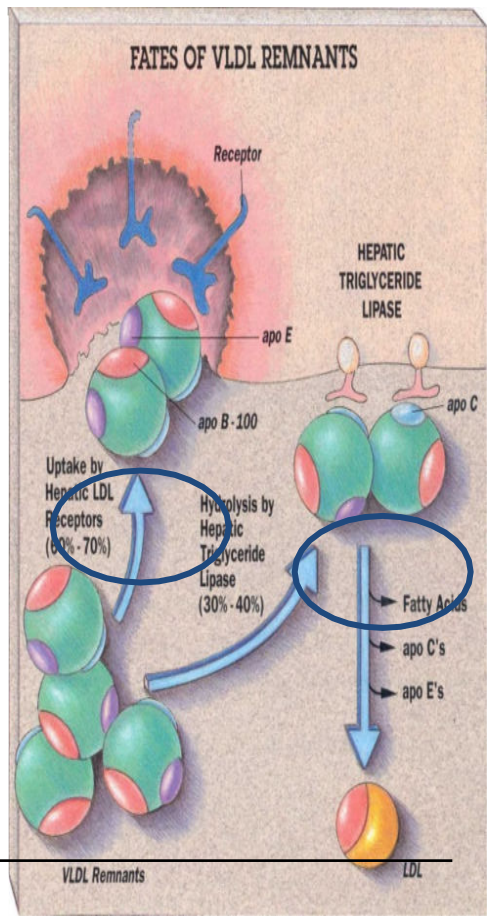
Dietary Carbohydrate Increases VLDL Production

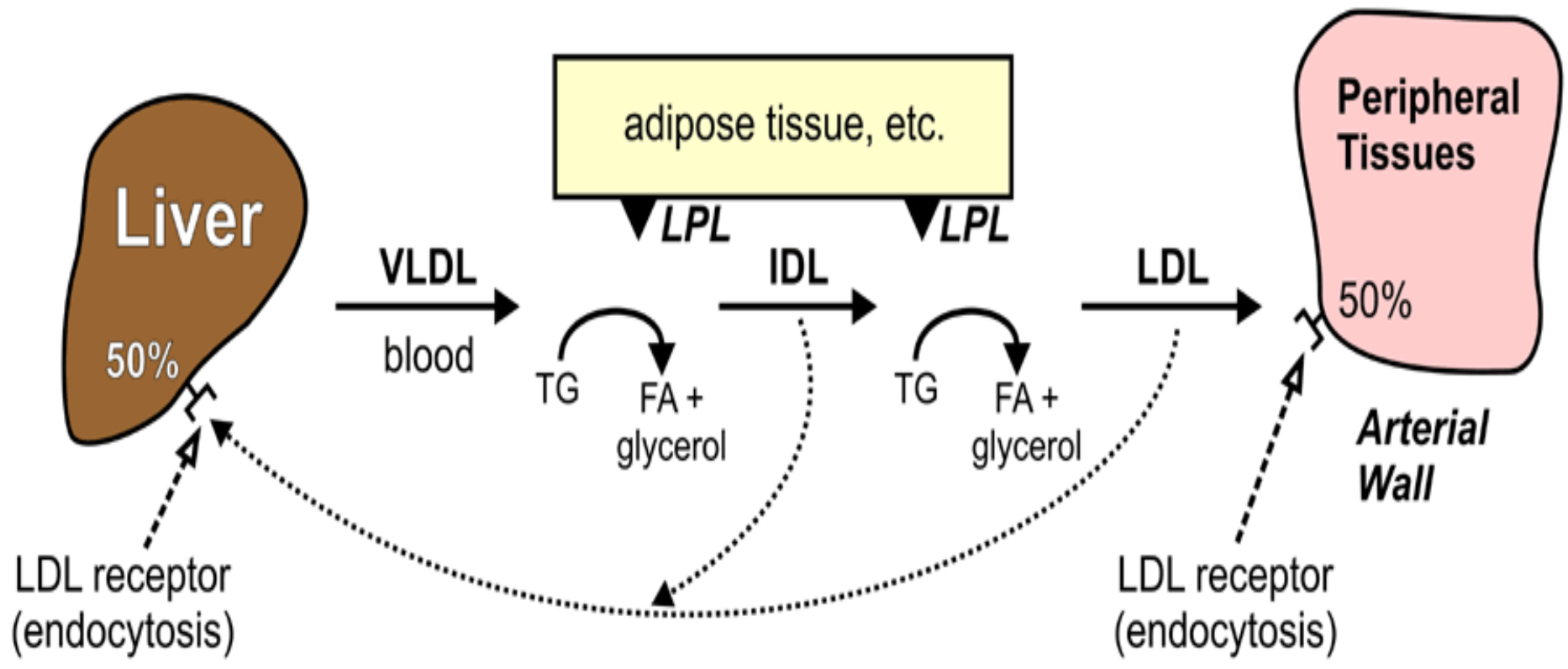


VLDL Remnants

IDL and LDL

- LDL results from loss of TAG in VLDL
- LDL contains relatively more Cholesterol esters
- LDL looses all Apo lipoproteins ~~except ApoB100~~.





Very Low Density Lipoprotein (VLDL)

Nascent VLDL are formed in the liver and consists of endogenous TG + 17 % cholesterol + Apo (B-100)

Mature VLDL after Nascent VLDL passage to blood, addition of ApoC II, ApoE and cholesterol esters from HDL

Lipoprotein lipase (LPL) hydrolyzes TAG present in VLDL

VLDL remnant containing less of TG and more of cholesterol and taken up by the liver through endocytosis.

Apo C removed and returns to HDL

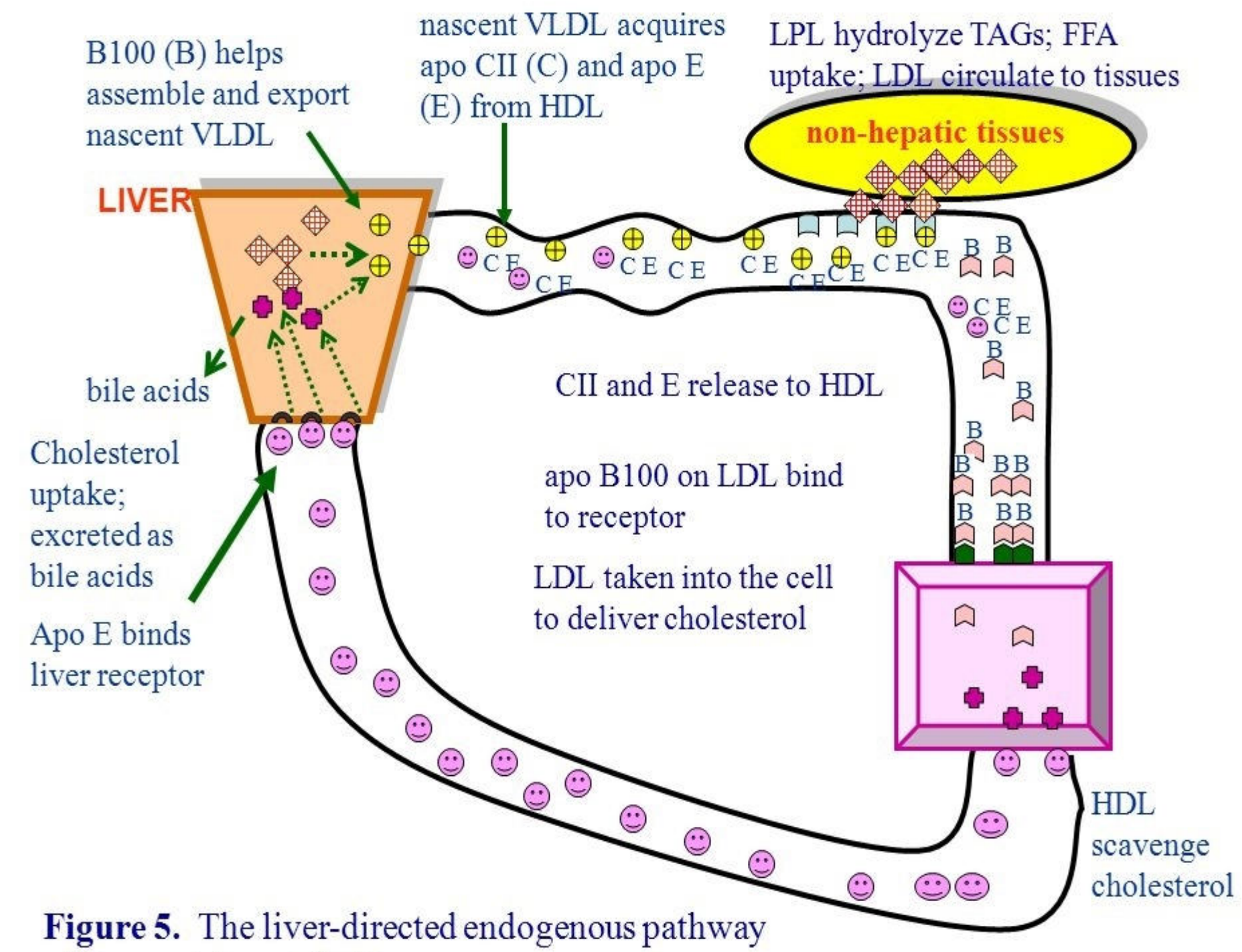
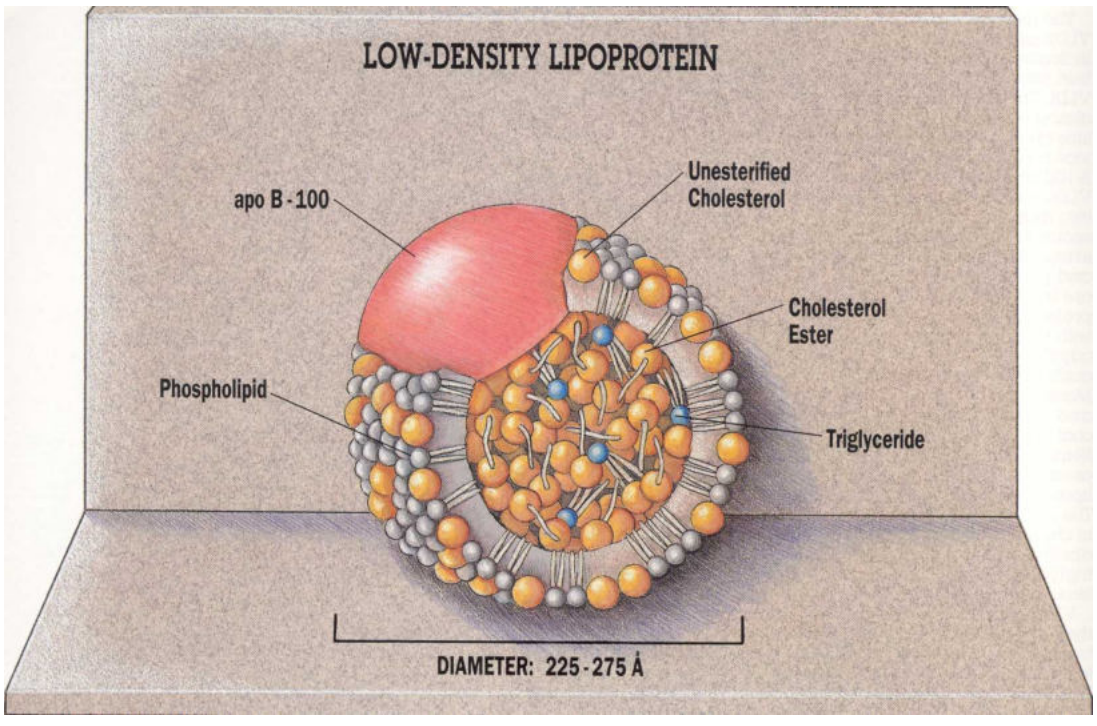


Figure 5. The liver-directed endogenous pathway

LDL Metabolism

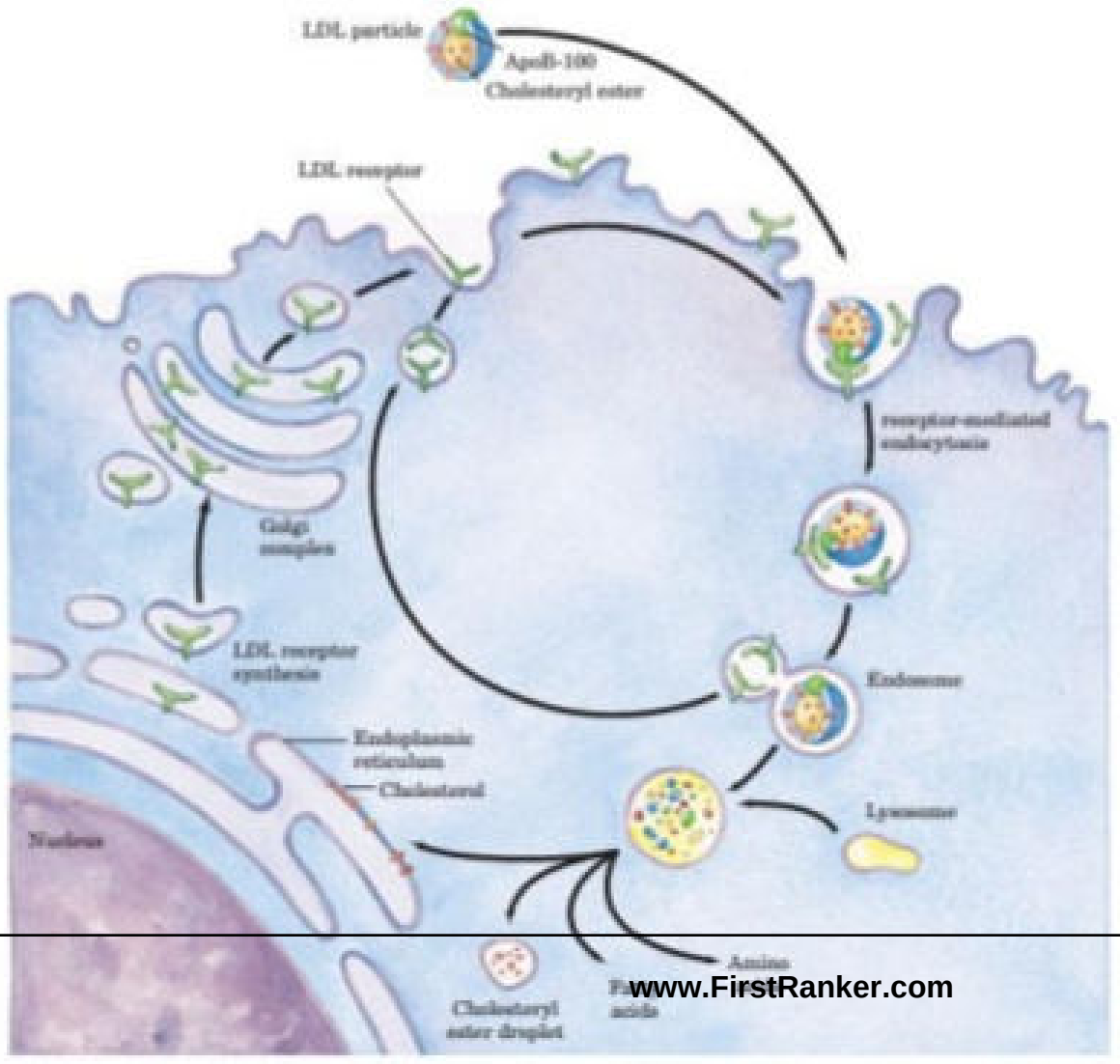


Most core lipid in LDL is Cholesterol ester.

ApoB100 is only Apolipoprotein in the surface.

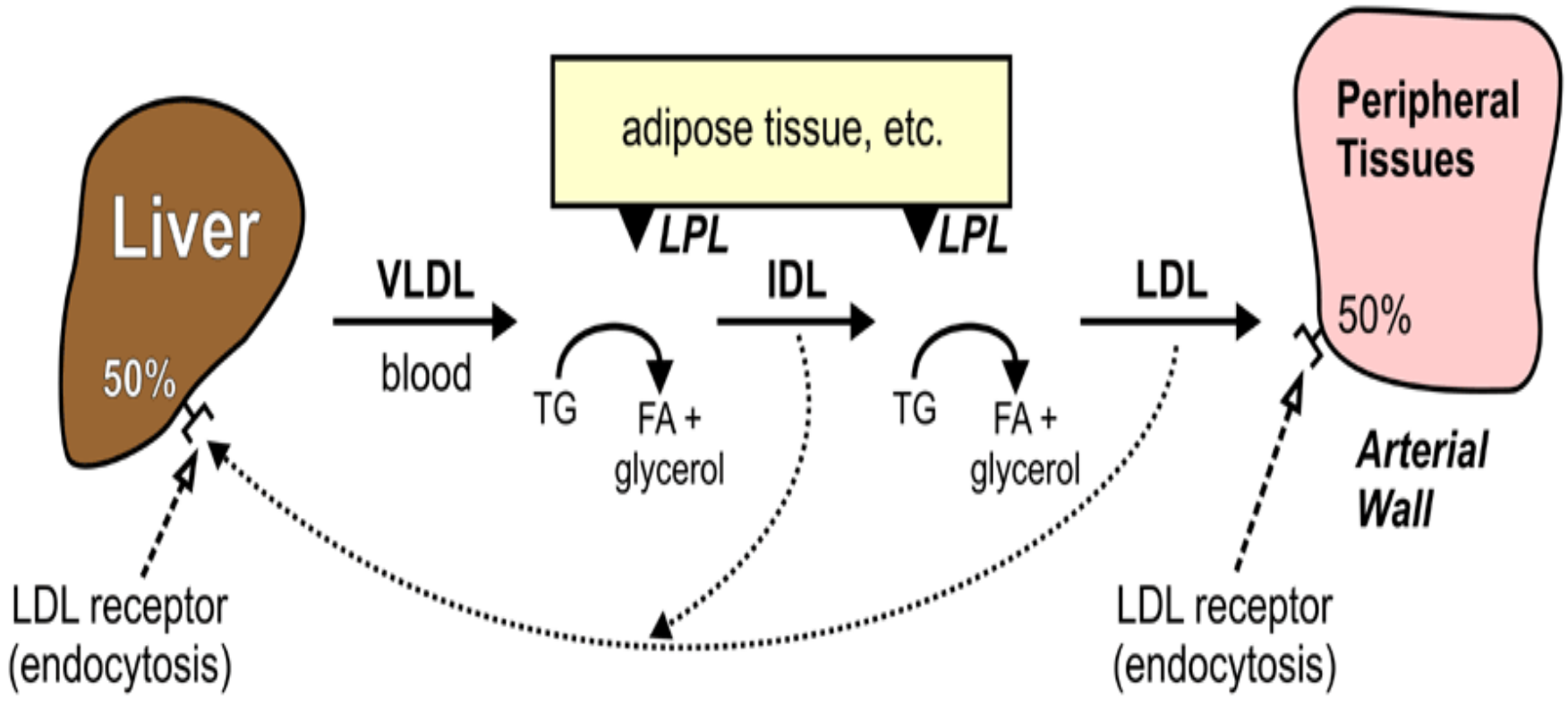
Formation and Fate Of LDL

Uptake of cholesterol by receptor-mediated endocytosis



- Low Density Lipoprotein (LDL) is a Lipoprotein **formed from VLDL in blood circulation.**
- VLDL in blood circulation receives Apo CII and Apo E from the circulating HDL.

- **Apo CII then stimulates the Lipoprotein Lipase enzyme** present in the endothelial lining of blood vessels.
- Lipoprotein Lipase then acts upon TAG present in VLDL ,hydrolyze it to Glycerol and free fatty acids



- **LDL is the modified form of VLDL** formed in blood circulation.
- **LDL is remnant of VLDL**

- LDL is mostly associated with **Cholesterol and Phospholipids with minimal TAG**
- Of endogenous origin mobilized out from Liver.

- The **major Apoproteins** of **LDL is Apo B100**
- Same as VLDL **since LDL is derived from VLDL**

- **Function of LDL is to transport endogenously biosynthesized Cholesterol from Liver to the peripheral /extrahepatic tissues.**

LDL Receptor

- Cell surface protein
- Recognizes Apolipoprotein B-100, present in VLDL, IDL, LDL, and probably Apo-E
- LDL receptor is an integral membrane protein of 115 kDa,
- LDL receptor is highly regulated
- Intracellular cholesterol concentration increases, the LDL receptor production is inhibited

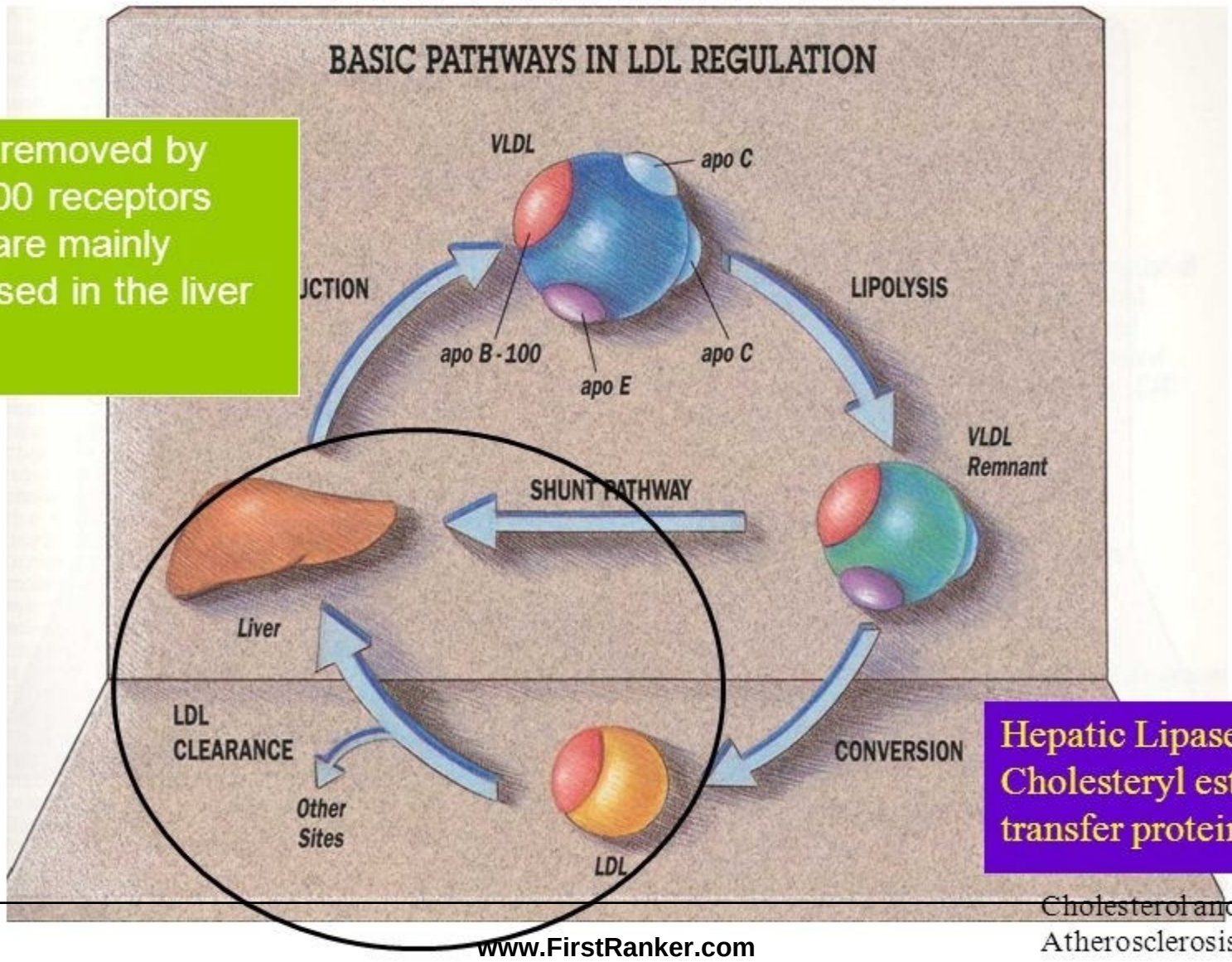
LDL Receptor

- LDL receptor is also named as ApoB100/ApoE receptors
- **Since ApoB-100 of LDL binds to LDL receptor.**
- The complexes of LDL and receptor are taken into the cells by endocytosis,
- Where LDL is degraded but the receptors are recycled

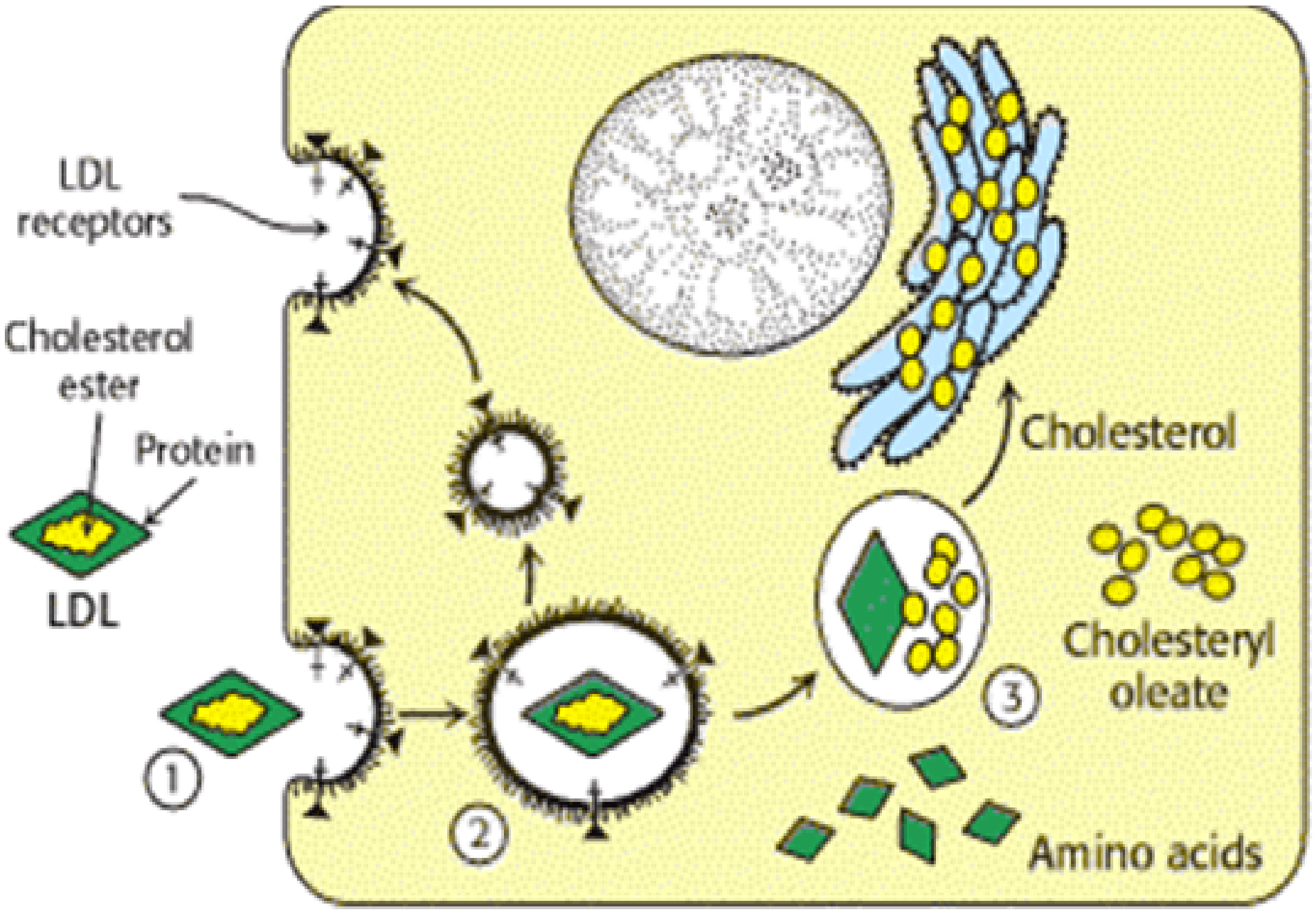
- **LDL receptors are found on cell surface of many cell types of extrahepatocytes.**

- **LDL is internalized by the tissues when LDL get fixed to the LDL receptors.**

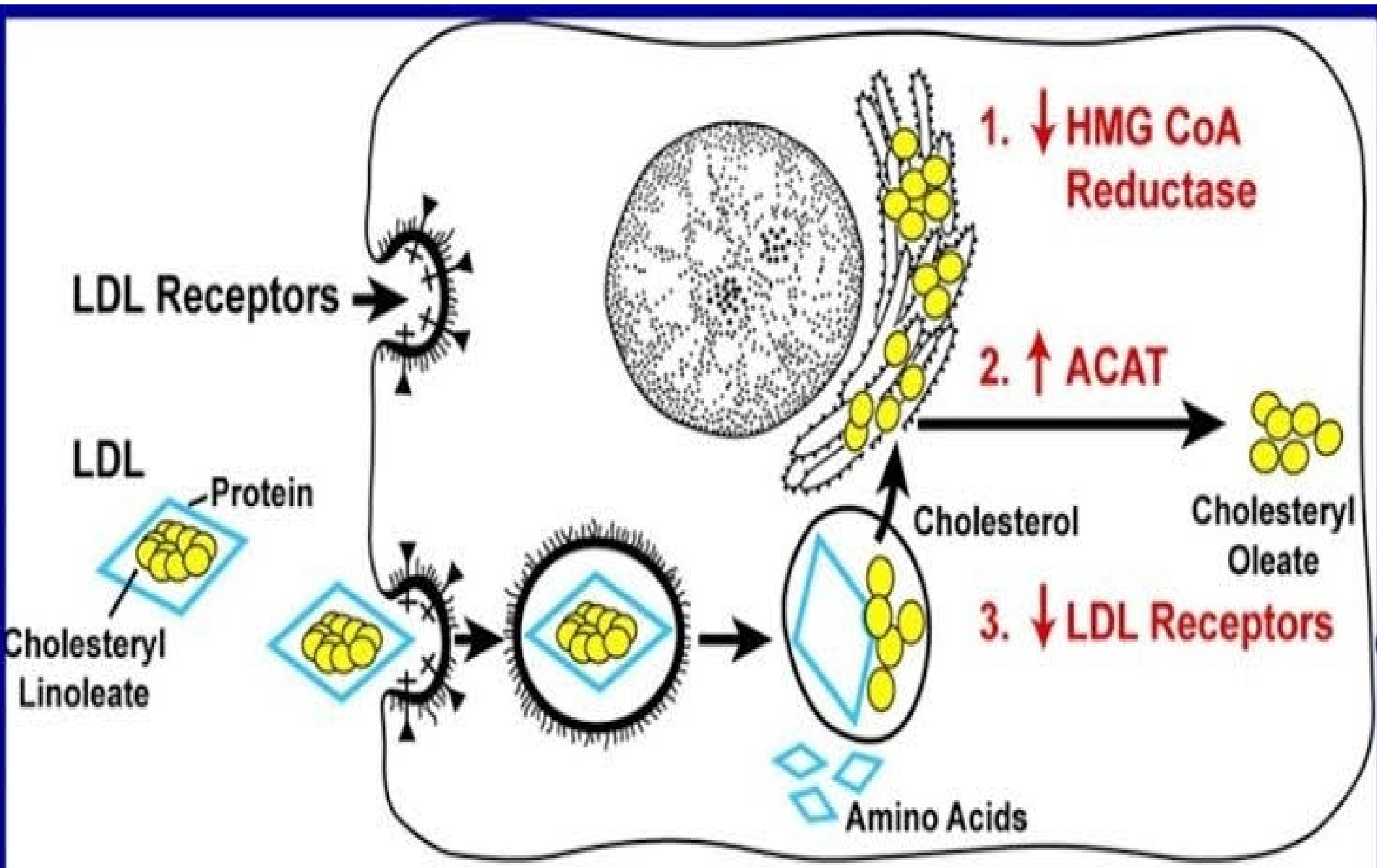
LDL Metabolism



Cholesterol and Atherosclerosis, Grundy)



LDL binding → Internalization → Lysosomal hydrolysis



LDL Binding → Internal-ization → Lysosomal Hydrolysis → Regulatory Actions

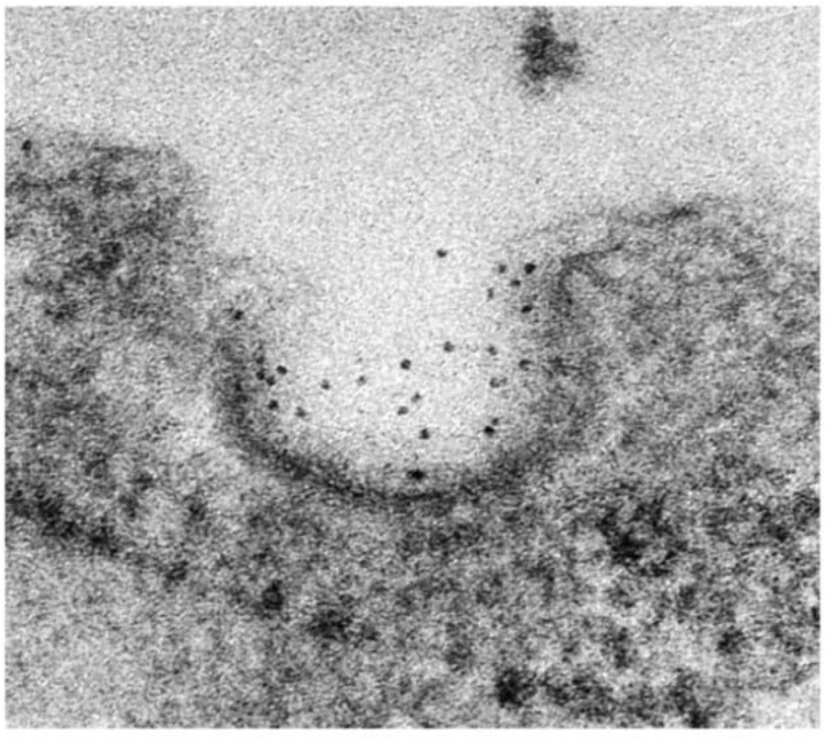
- **LDL receptor mediates delivery of Cholesterol**

- **By inducing endocytosis and fusion with Lysosomes.**

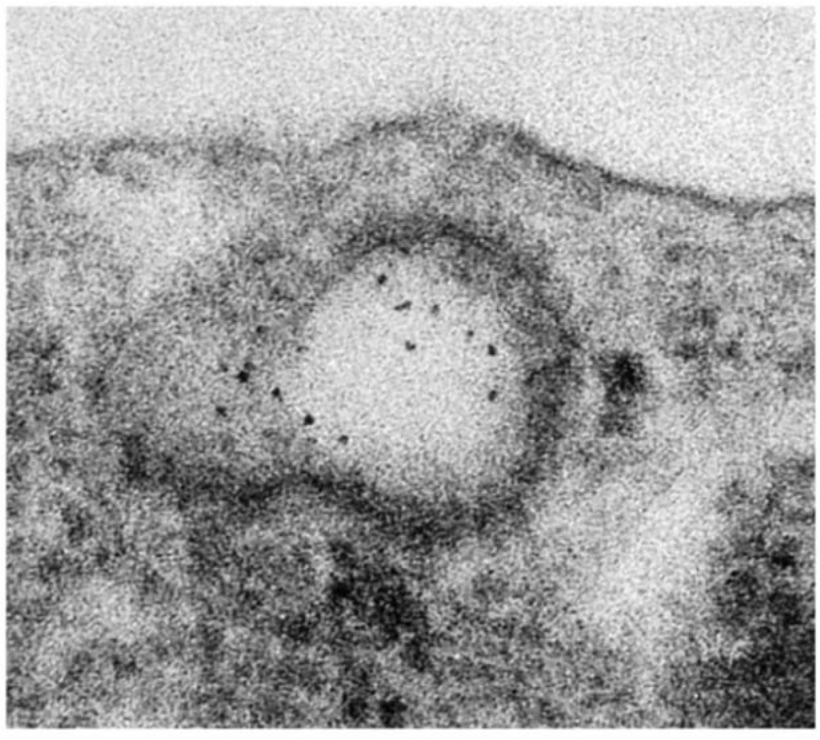
- **Lysosomal lipases and proteases degrade the LDL.**

- **Cholesterol then incorporates into cell membranes or is stored as cholesterol-esters of extrahepatocytes.**

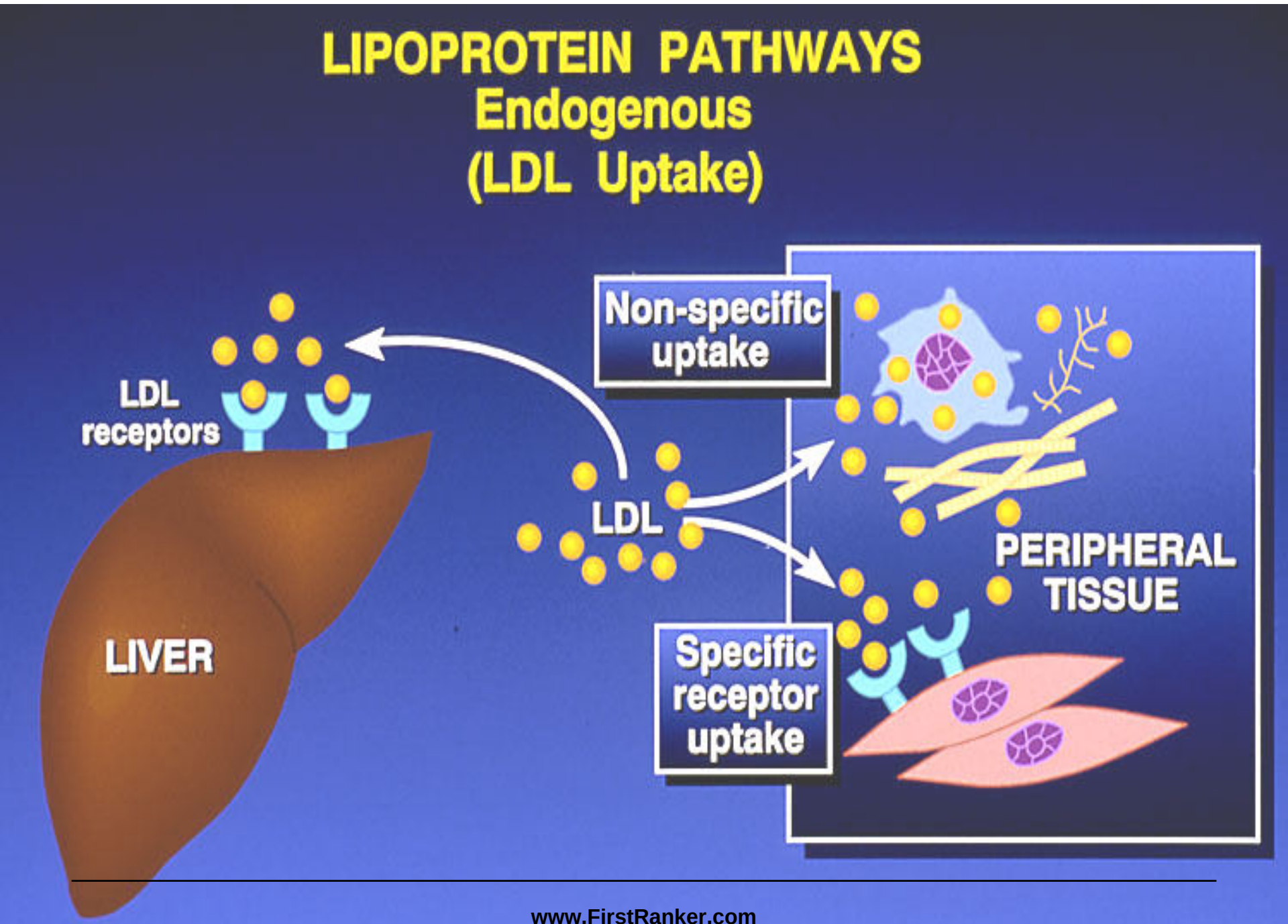
LDL Receptor



(A)



(B)



LDL-Receptor-Related Protein-Associated Protein (**LRPAP1)**

- **Chaperone Protein** which in humans is encoded by LRPAP1 gene.
- Involved with **trafficking** of certain members of LDL receptor family including LRP1 and LRP 2
- Acts to inhibit binding of all known ligands for these receptors
- **Prevent receptor aggregation** and degradation in endoplasmic reticulum, thereby acting as a molecular chaperone.

Mutations and diseases related to LRPAP1

- Abnormal ECM remodeling in neurons, eye
  - **Dementia**
  - **Myopia**
  - **Marfans Syndrome**

LDL Cholesterol levels are positively related to risk of Cardiovascular Disease.

- LDL values within normal range is an indication of healthy status.
- But the high LDL levels are abnormal .

- **Cholesterol associated to this high levels of LDL molecules increases risk of Atherosclerosis and CVD.**

- **Hence this LDL associated Cholesterol is termed as "bad Cholesterol"**

Defect/Absence of LDL Receptors

Leads to Accumulation of LDL in Blood Circulation

Causing Hypercholesteremia and Atherosclerosis

- **Defect in LDL receptors** on tissues **impairs LDL metabolism**.

- **Decreases LDL internalization within the tissues.**

- Increases abnormal levels of LDL in blood (< 130 mg%).

- **Increased LDL levels** in blood circulation **due to defect in LDL receptors** is termed as **Type II a Hyperlipoproteinemia**.

- The major form of **Lipid associated** with **LDL is Cholesterol .**
- Hence increased LDL levels is characterized by Hypercholesterolemia.
- The Cholesterol associated with **elevated levels of LDL (more than its normal range) is termed as bad Cholesterol**,
- Since it **increases the risk of Atherosclerosis and its complications .**

- **Persons lacking the LDL receptor suffer from Familial Hypercholesteremia**
- **Due to result of a mutation in a single autosomal gene**
- **Total plasma cholesterol and LDL levels are elevated.**

– Cholesterol Levels of:

– Healthy person = < 200 mg/dl

– Heterozygous individuals = 300 mg/dl

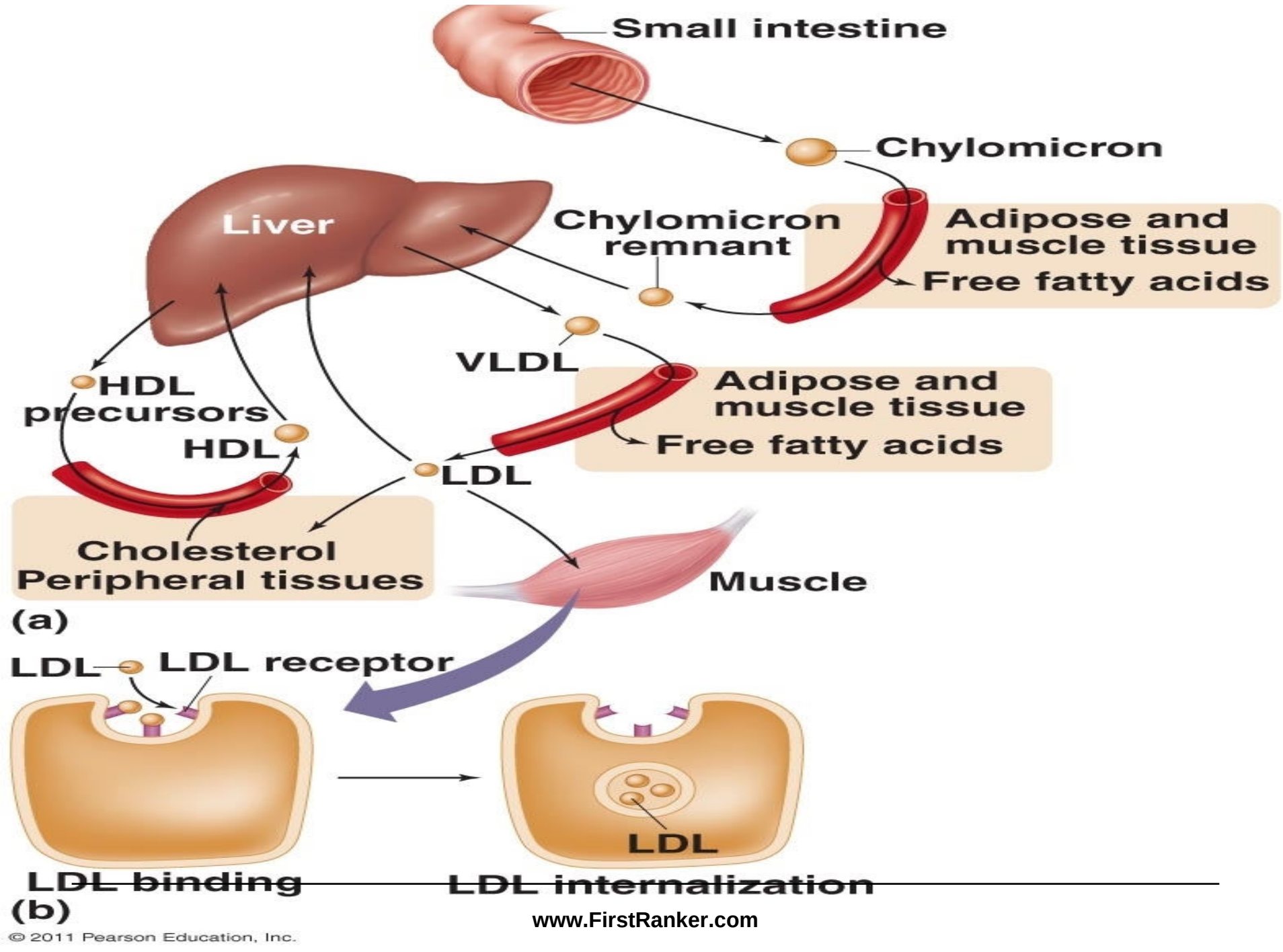
– Homozygous individuals = 680 mg/dl

High LDL levels can lead to Cardiovascular Disease

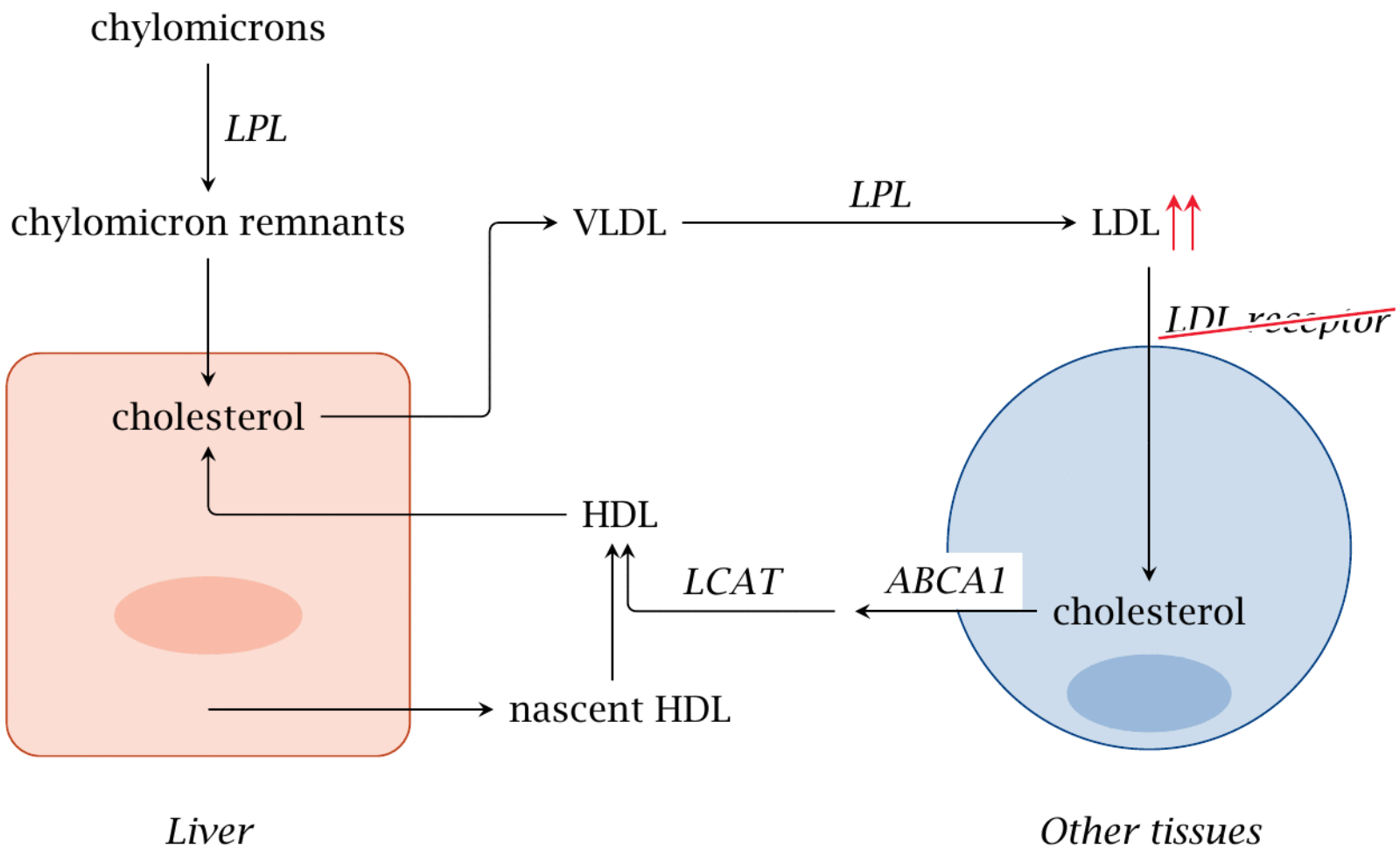
Most Homozygous individuals die of cardiovascular disease in childhood

- LDL can be oxidized to form oxidized LDL
- Oxidized LDL is taken up by immune cells called macrophages.
- Macrophages become engorged to form foam cells.

- **Foam cells** become trapped in the walls of blood vessels and contribute to the formation of **atherosclerotic plaques.**
- Causes narrowing of the arteries which can **lead to MI/heart attacks.**



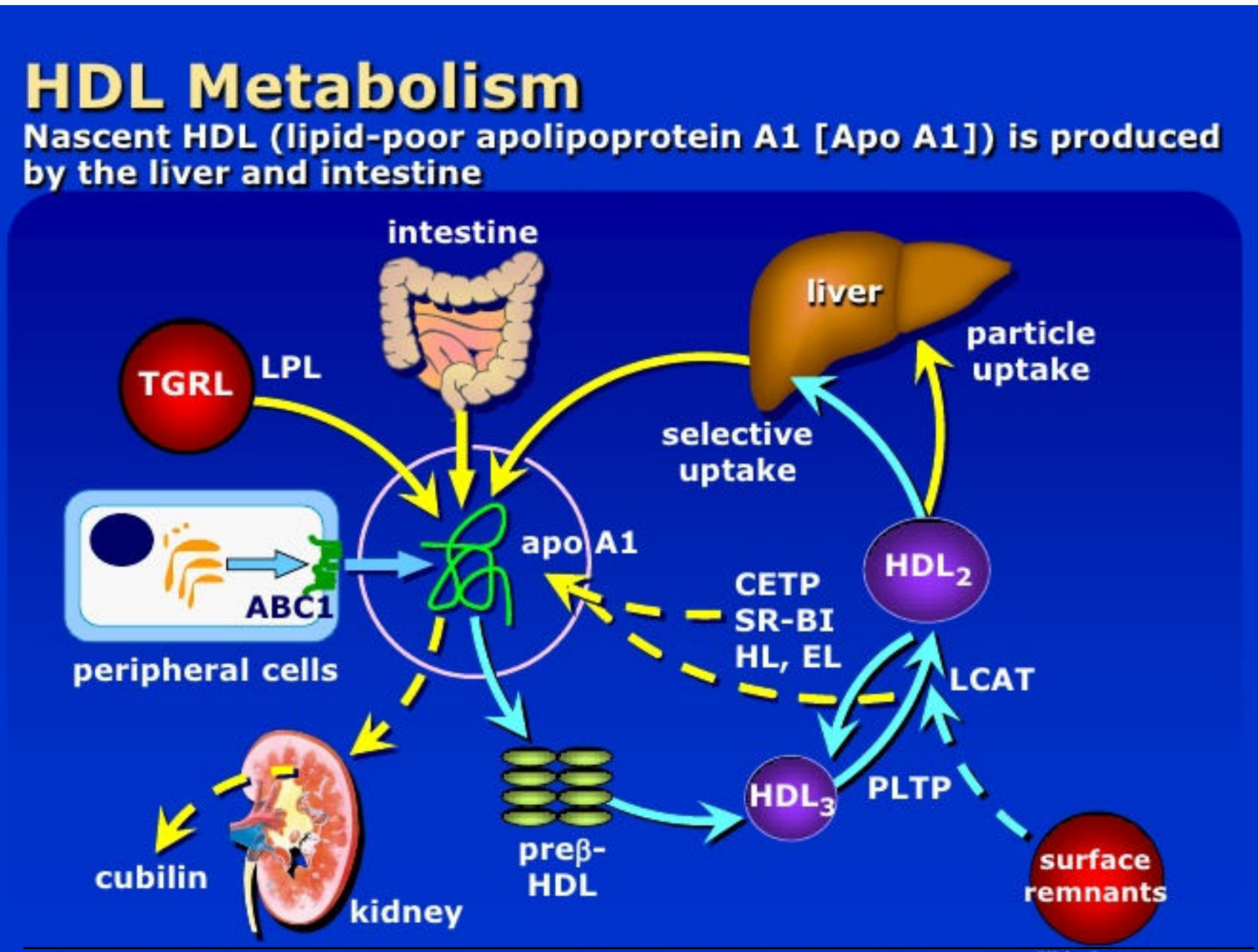
Familial hypercholesterolemia is due to a gene defect in the LDL receptor

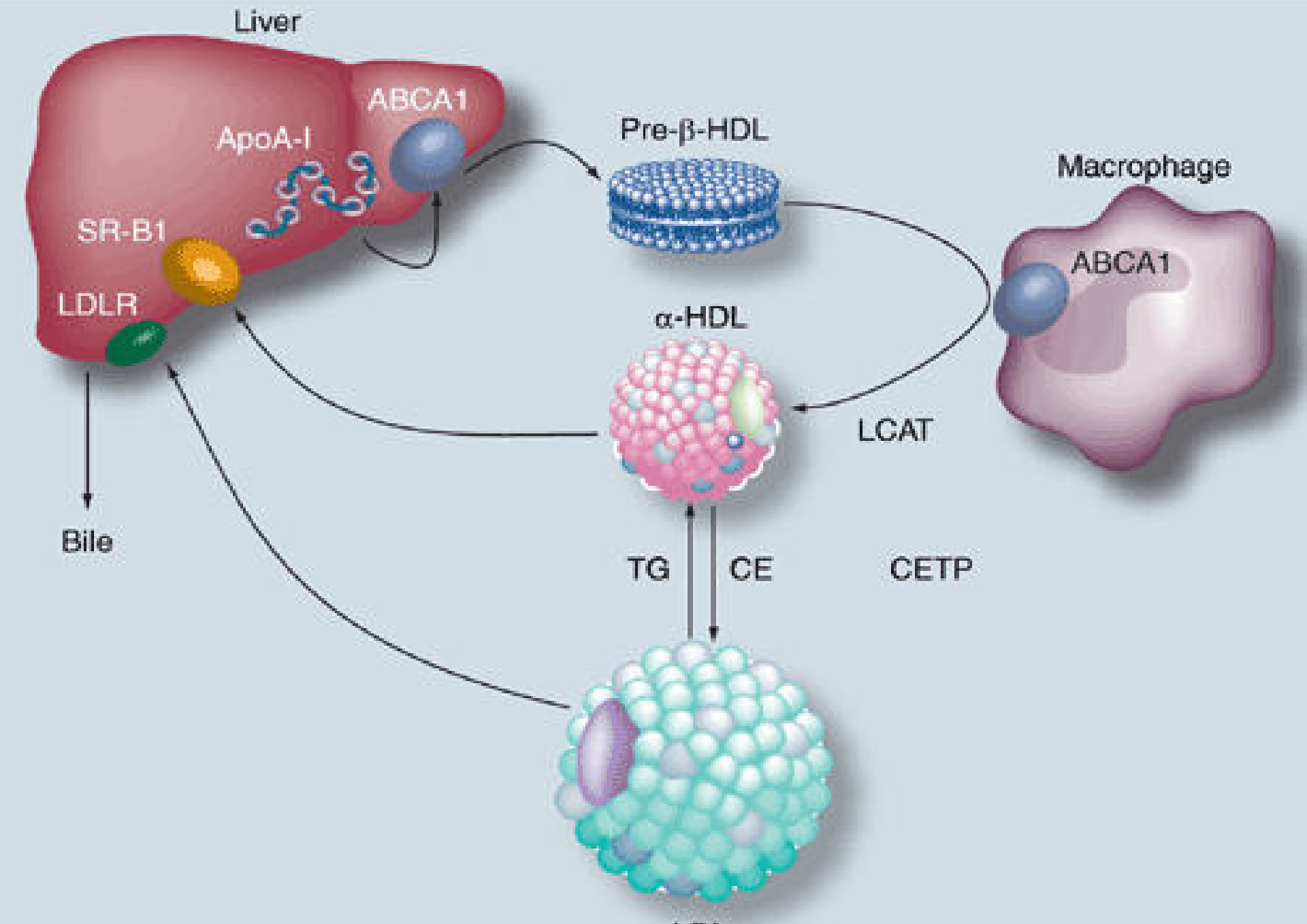


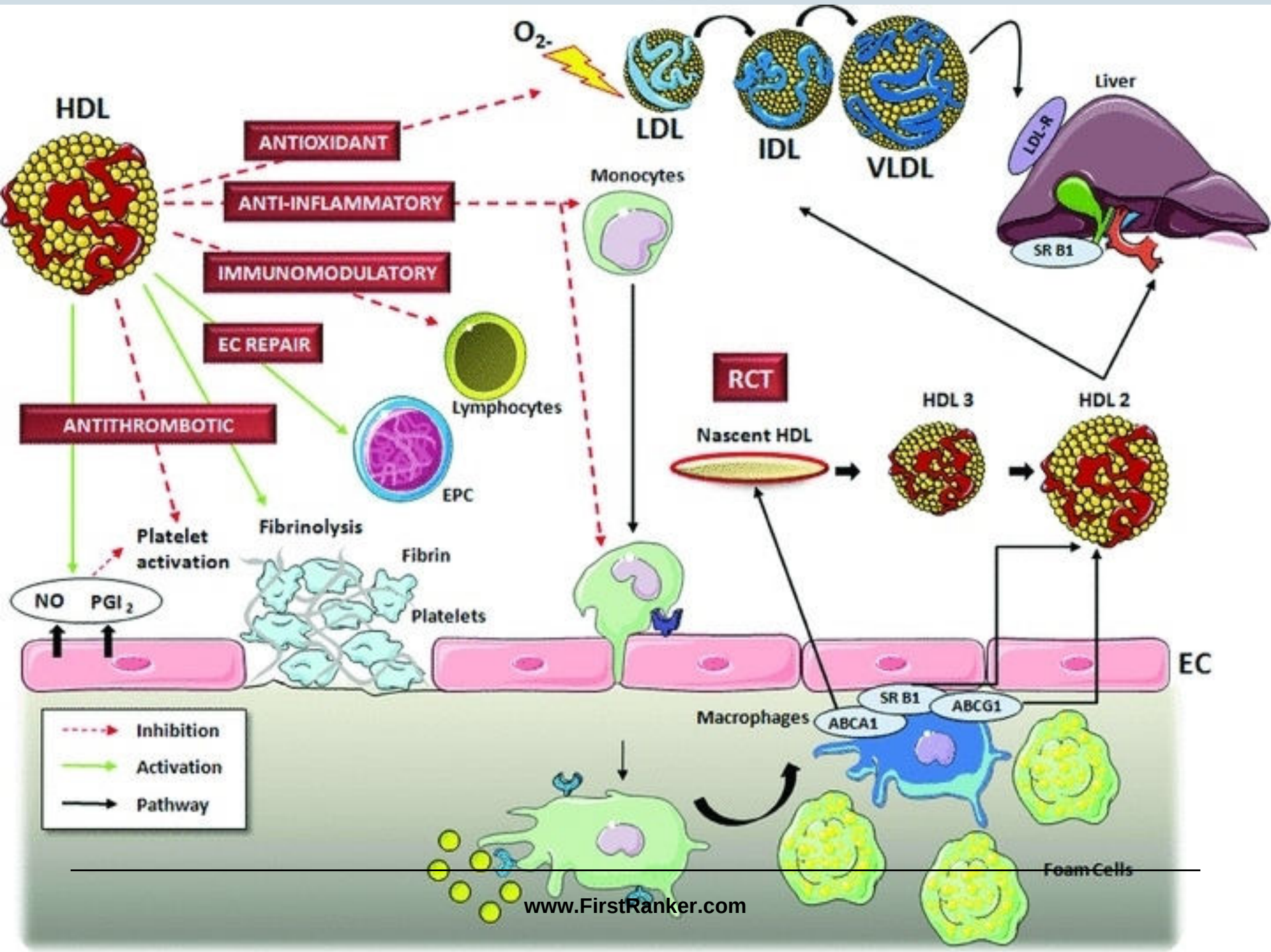
Role Of HDL Reverse Transport Of Cholesterol

- HDL is a **high density Lipoprotein.**

- **Nascent HDL** is biosynthesized in Liver.
- It is **reservoir of Apoproteins**







- **HDL is the Lipoprotein, with highest density.**
- Since it is associated with 40-50% of Apoproteins.
- The Apoproteins of HDL are Apo A I, Apo A II, Apo C I,C II, Apo D and Apo E.

- **HDL serves as a reservoir of Apoprotein during its circulation.**
- HDL gives it Apo CII and Apo E to circulating nascent Chylomicrons and VLDL .

- **Nascent HDL** of **discoid shaped** (Empty Bag) **biosynthesized in Liver**
- It is **released in the blood circulation for scavenging action.**

The HDL has Scavenging Action

It serves as a Scavenger For Unwanted Body Lipids

- The Enzyme **Lecithin Cholesterol Acyl Transferase** (LCAT) is **associated with HDL metabolism.**

- **Apo A I,A IV and CI stimulates the LCAT activity of HDL.**

- LCAT by its activity help in **esterification of free Cholesterol to Esterified Cholesterol/Cholesterol Ester.**

- HDL by its scavenging action collects the extra non functional Cholesterol lying in blood vessels and peripheral tissues.

- **HDL esterifies Choleserol by its LCAT activity and to HDL bag.**

- **The nascent HDL bags changes to spherical shape .**

- HDL is more associated with Phospholipids and Cholesterol.

- The receptors for HDL are present on Liver cells.

- **HDL transports the excess, unused Lipids** from extra hepatic tissues back to Liver for its metabolism and excretion.

- **The role of HDL is opposite to LDL.**

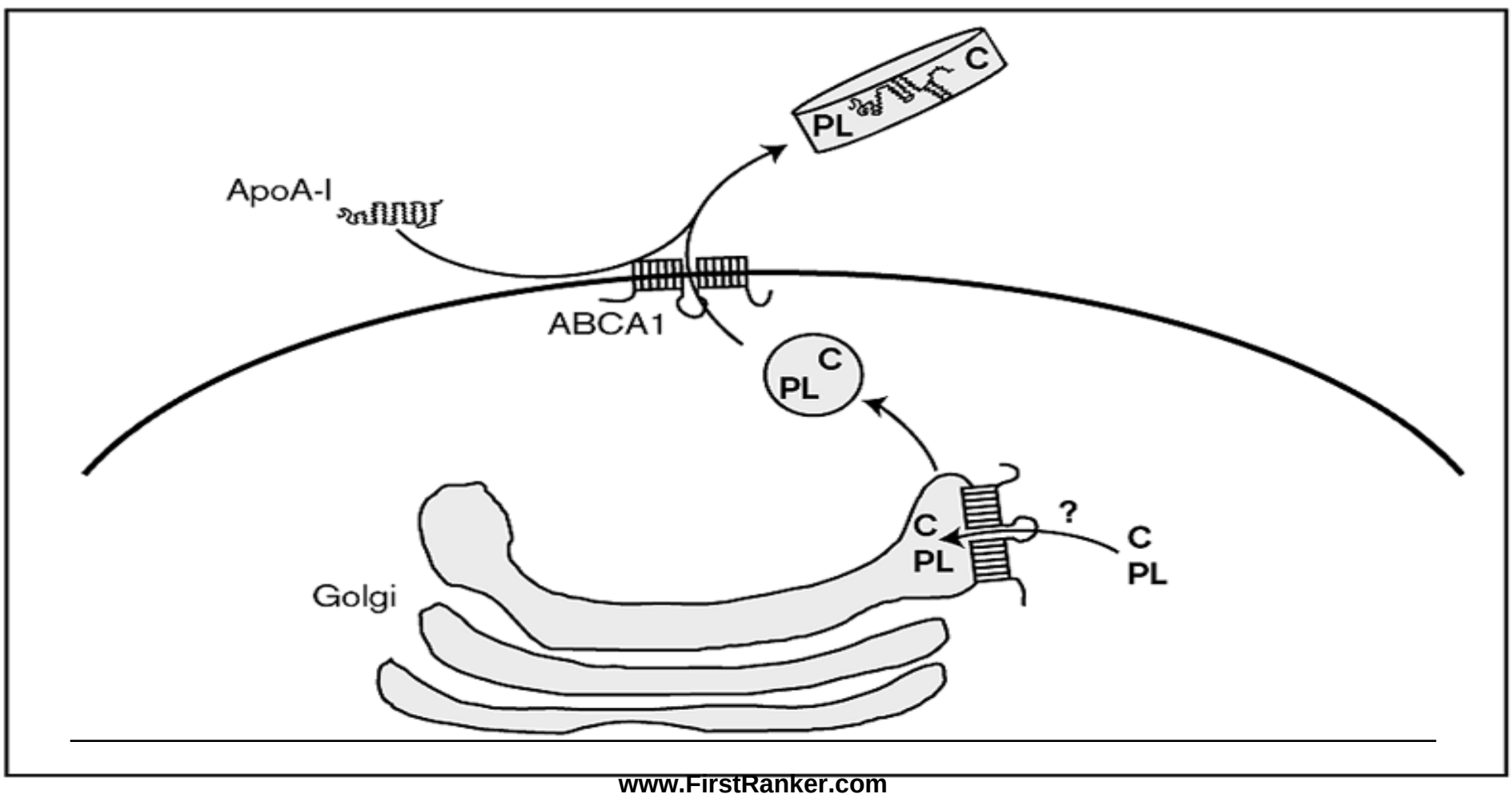
- **HDL transports Cholesterol From extra hepatic tissues back to Liver.**

- Thus the role of HDL is termed as **reverse transport of Cholesterol.**

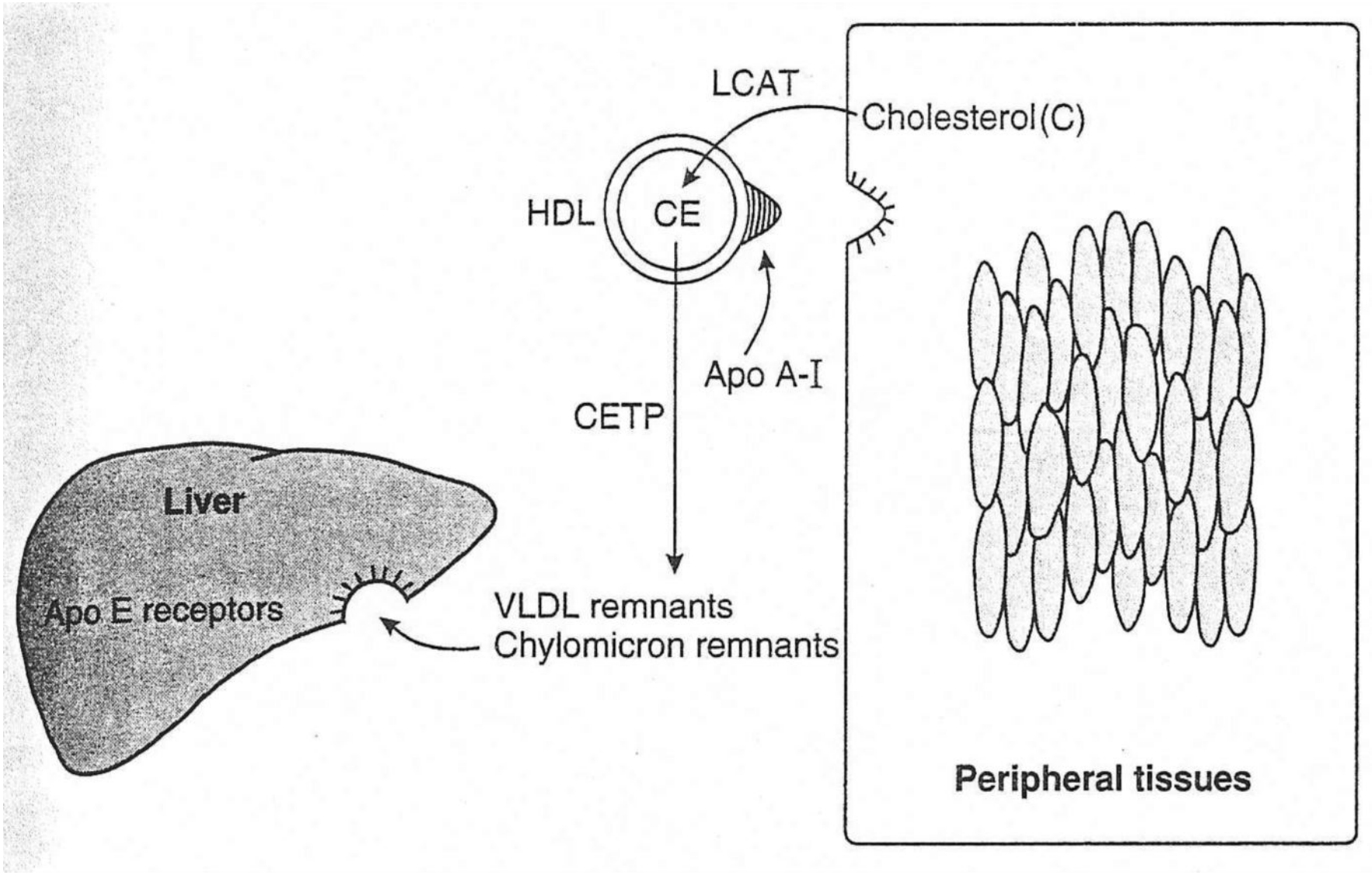
- **Normal serum HDL levels** are **30-60 mg%.**

- The efficient activity of HDL is good to the body
- As it prevents risk of Atherosclerosis and their complications.

Reverse Cholesterol Transport (RCT)



High Density Lipoproteins (HDL – Good)



- **CETP by its activity modifies HDL 3 to HDL 2.**
- **HDL2 is then get internalized in Hepatocytes for its final use**.
- Cholesterol Ester carried by HDL to hepatocytes **is degraded to Bile acids and Bile salts and get excreted out.**

Fate of HDL

HDL 2 binds SR-B1 receptor on Hepatocytes And Other Cells

↓

Transfers Cholesterol & Cholesterol ester to cell

↓

Depleted HDL dissociates & re-enters circulation

- HDL can bind to specific **hepatic receptors SR-B1**

- But primary HDL clearance occurs through uptake by **scavenger receptor SR-B1.**

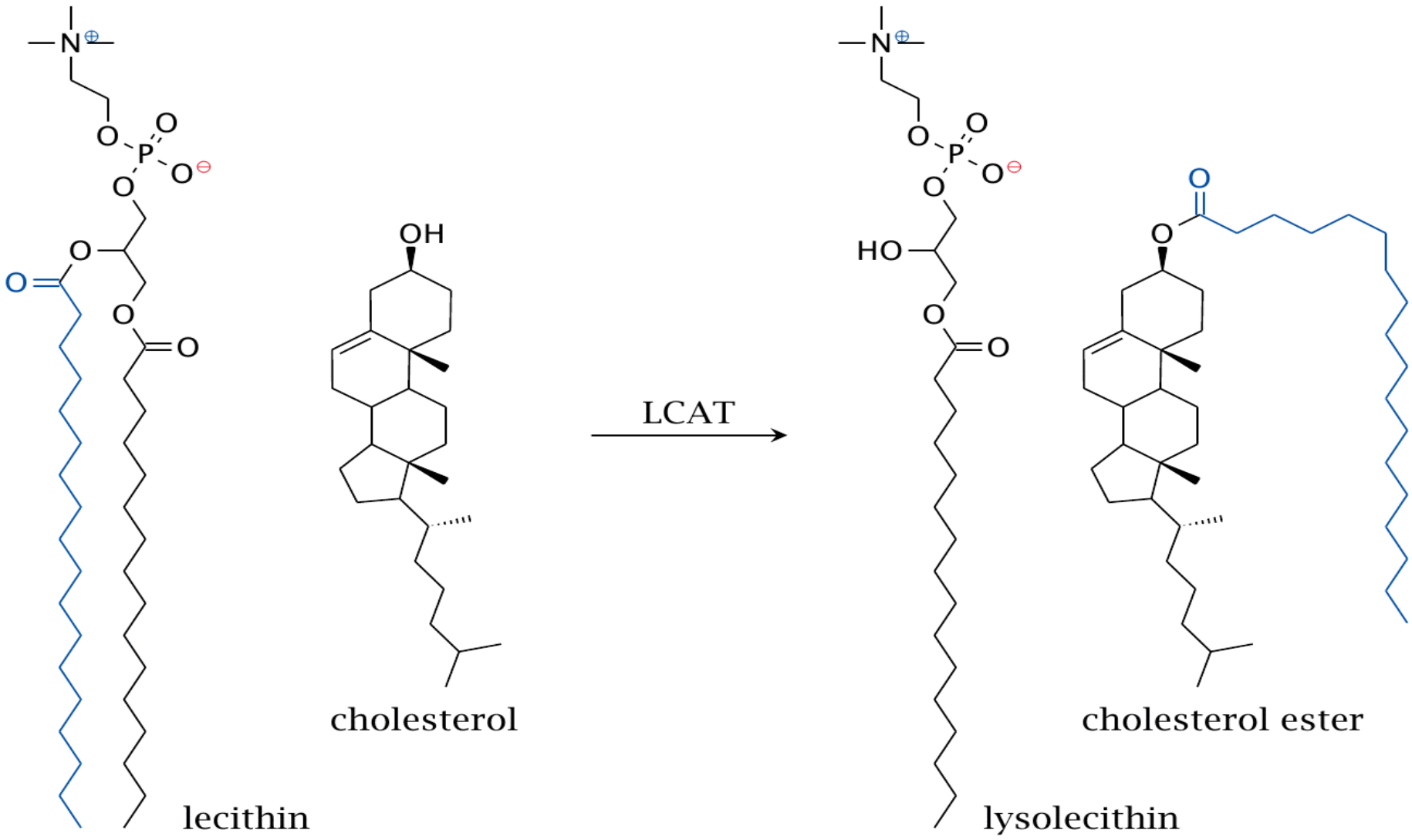
- **SR-B1** can be upregulated in cells when Cholesterol levels are low in hepatic cells.

- **SR-B1** is down regulated when cholesterol levels are high in cells.

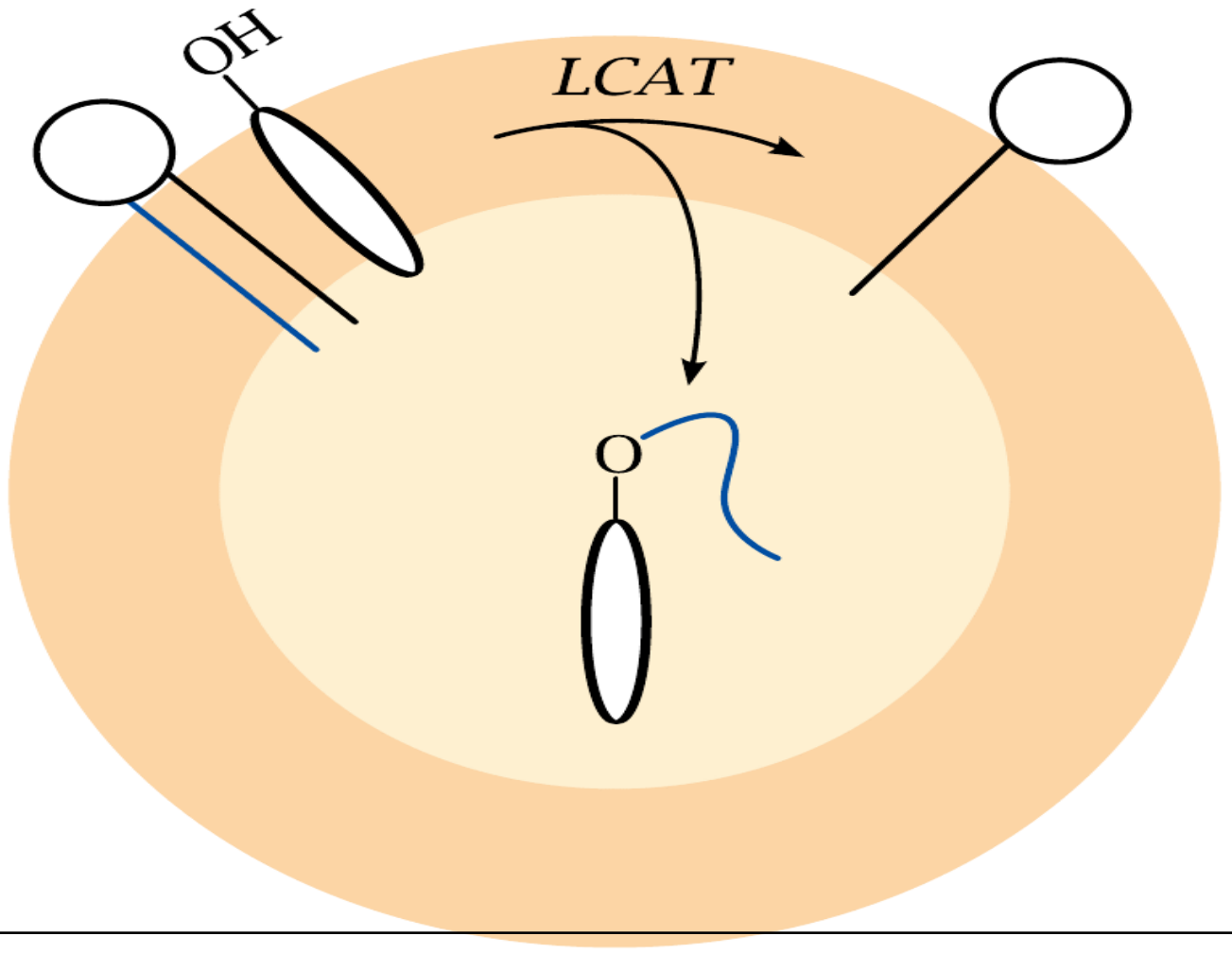
- **Defect in low HDL synthesis in Liver** lowers the HDL activity and **increases the risk of Atherosclerosis.**

- **Defect in HDL receptors** on Liver may abnormally increase the HDL levels in blood circulation and also increases the risk of Atherosclerosis.

The Lecithin-Cholesterol Acyltransferase (LCAT) reaction

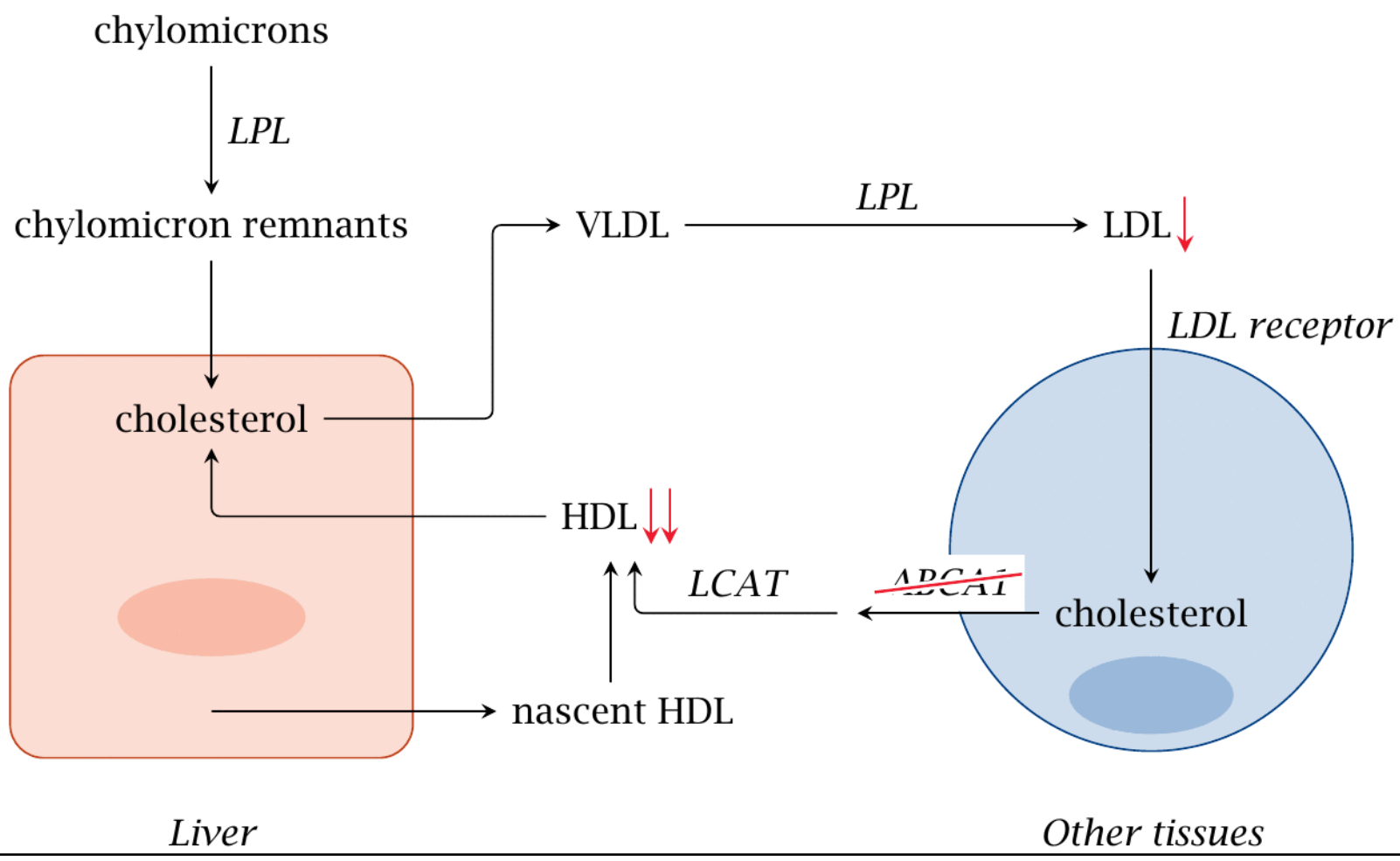


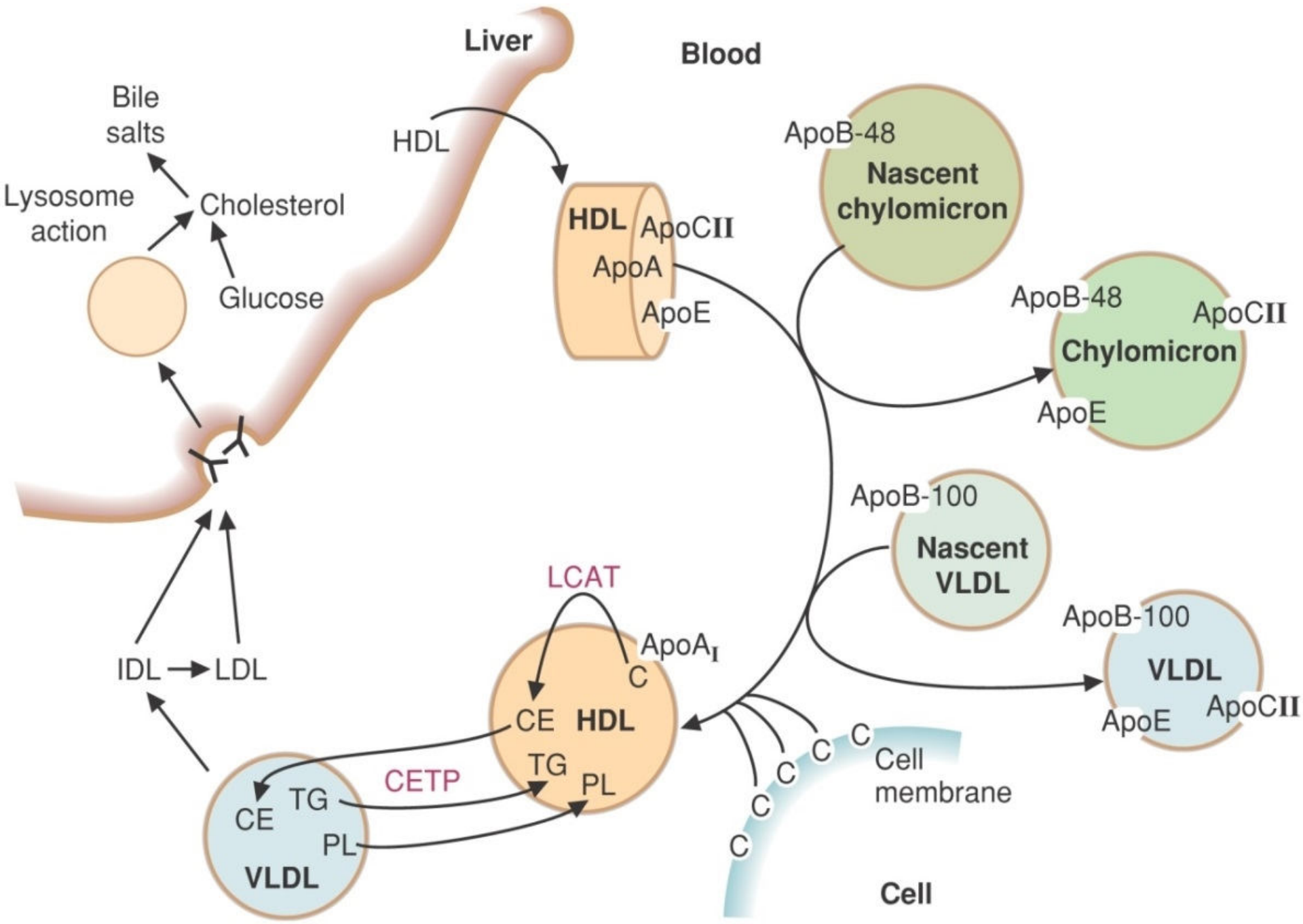
Cholesterol esters can be stored inside lipoprotein particles



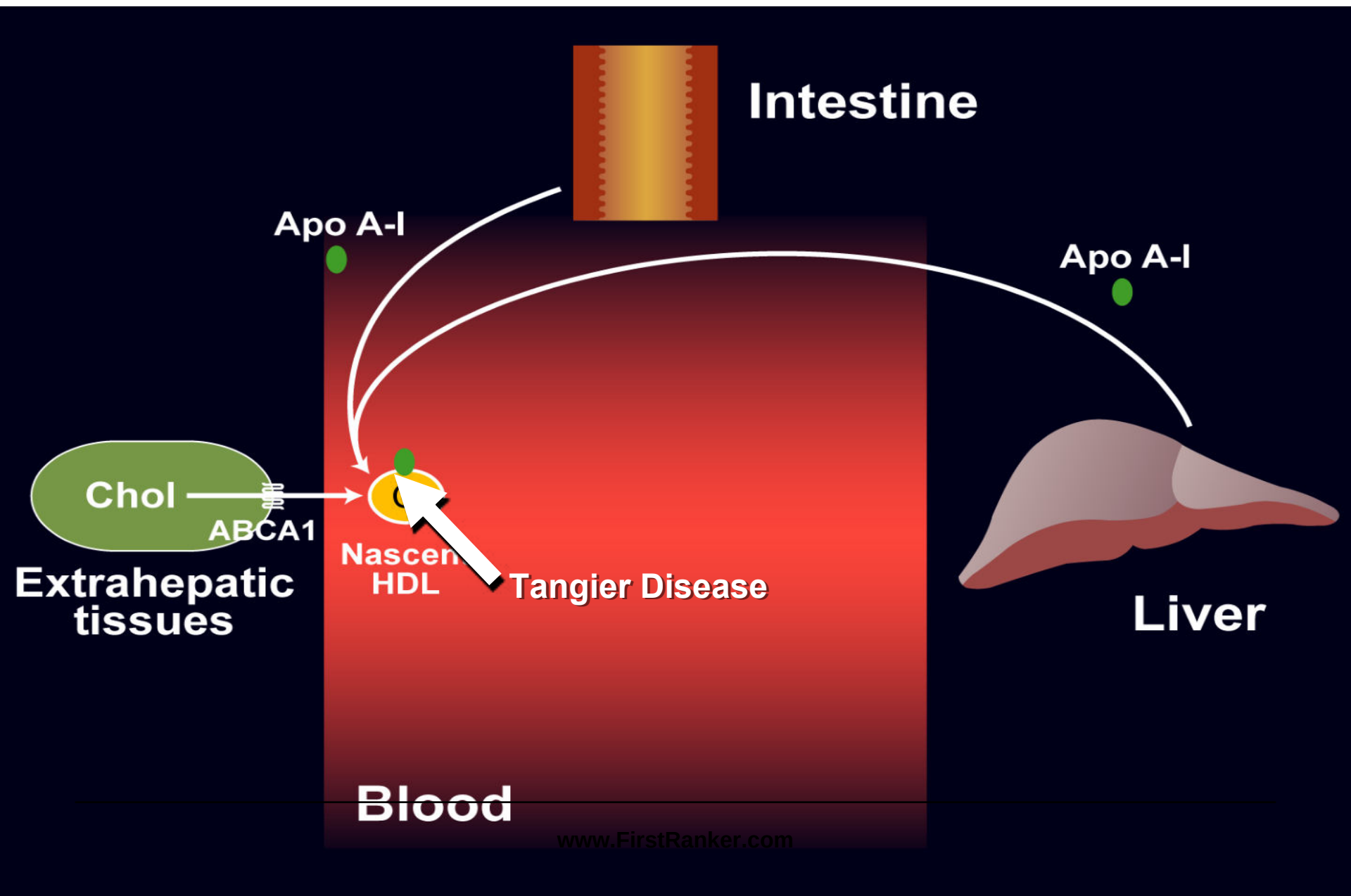
HDL Interactions with Other Particles

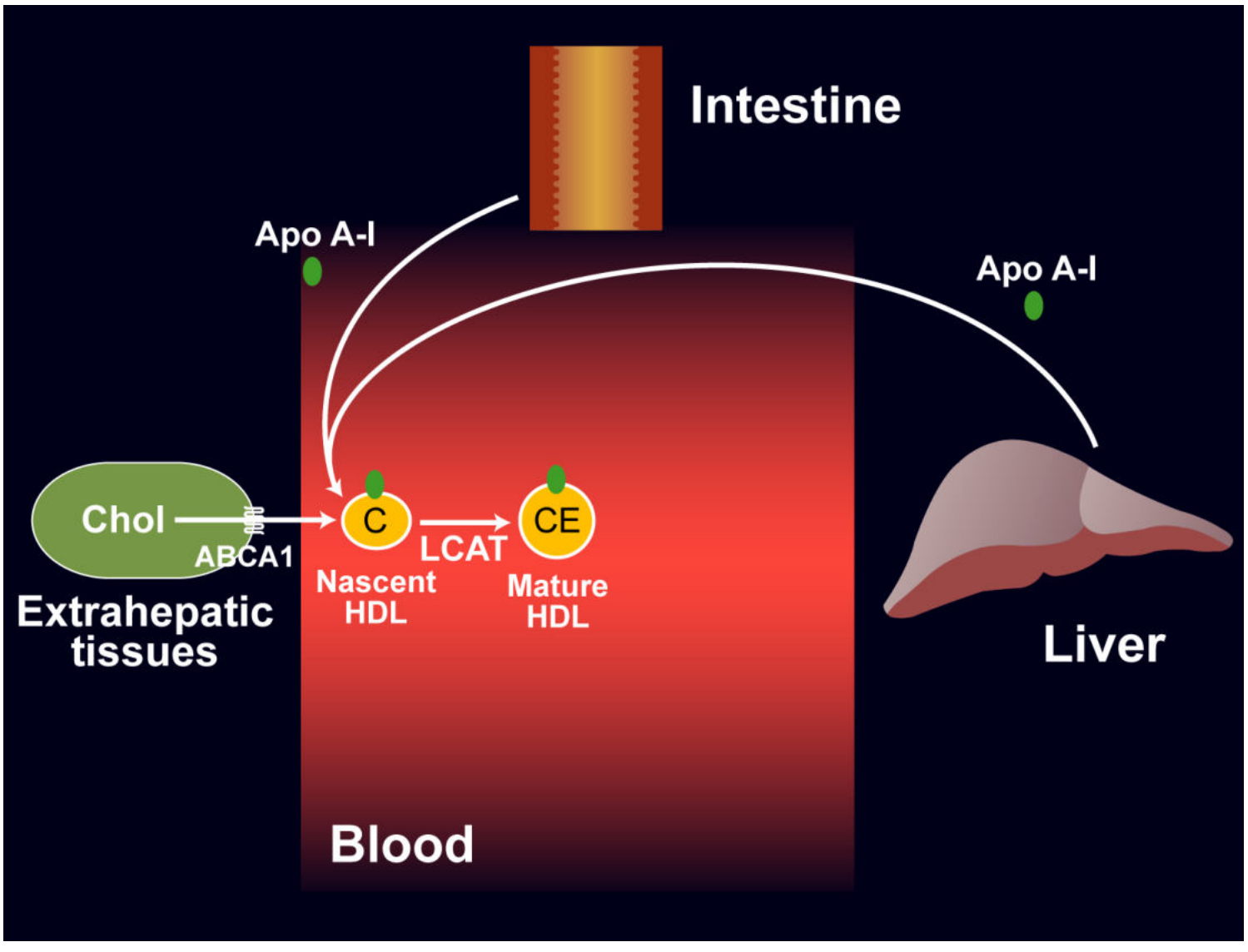
Tangier Disease: Disruption of Cholesterol Transfer to HDL

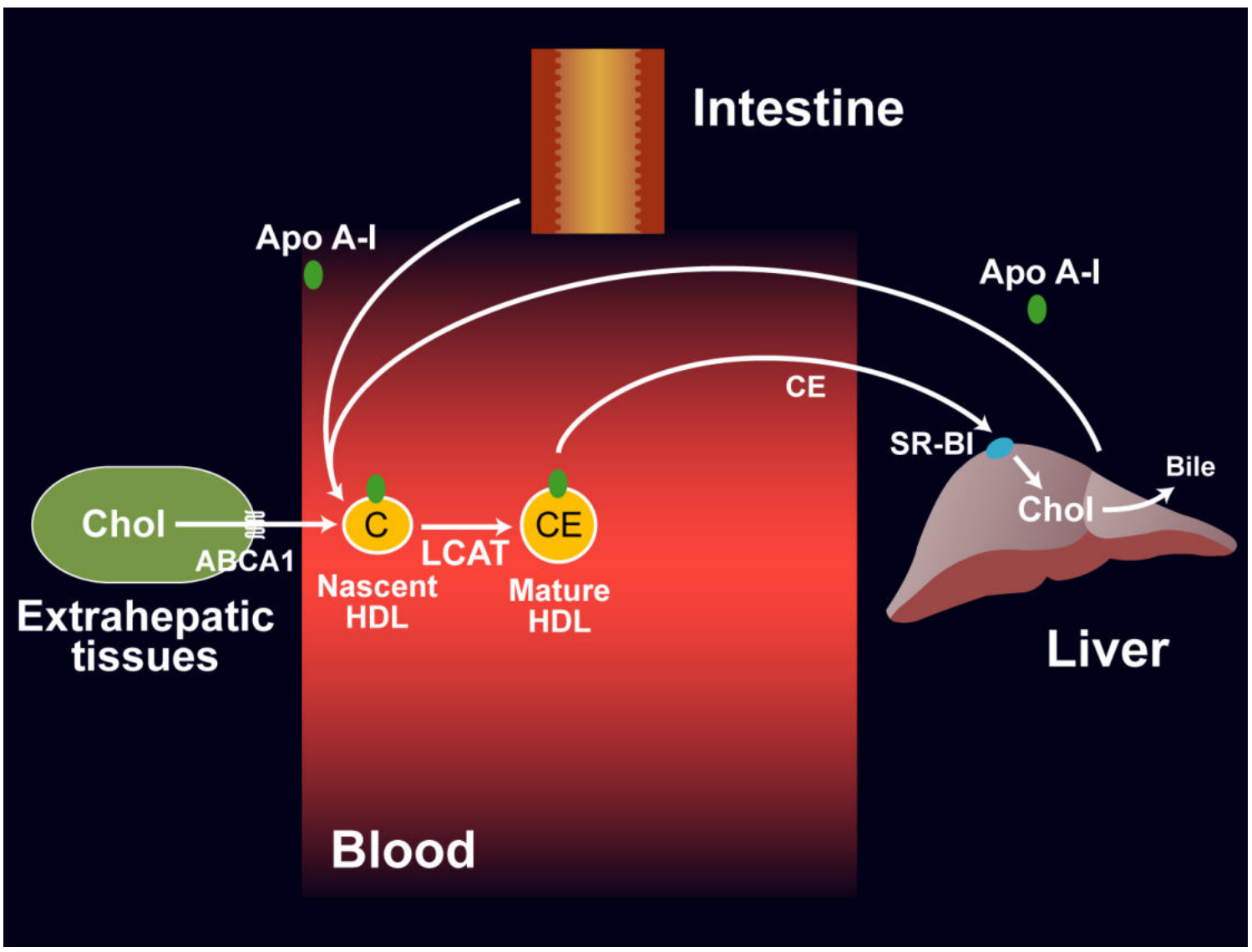


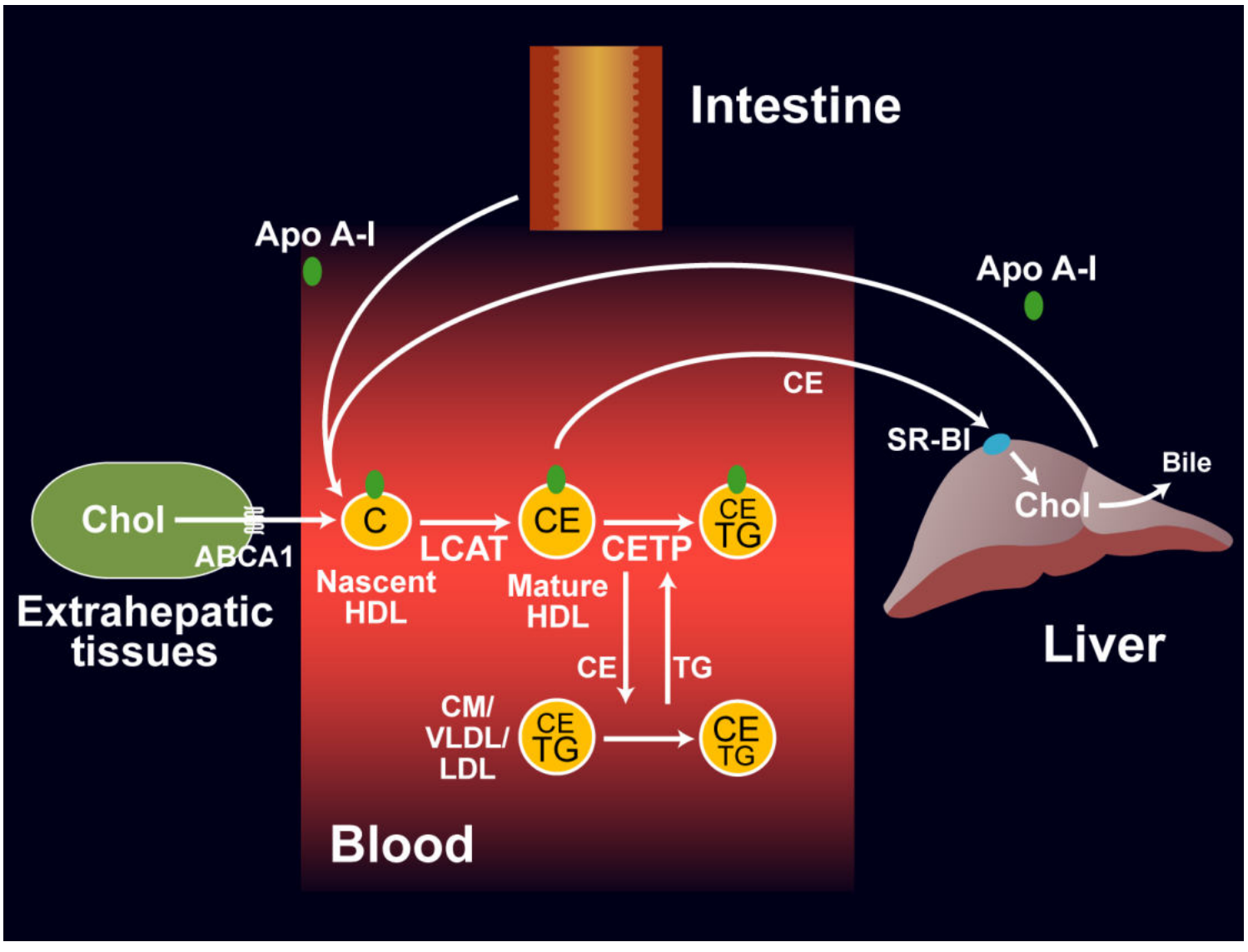


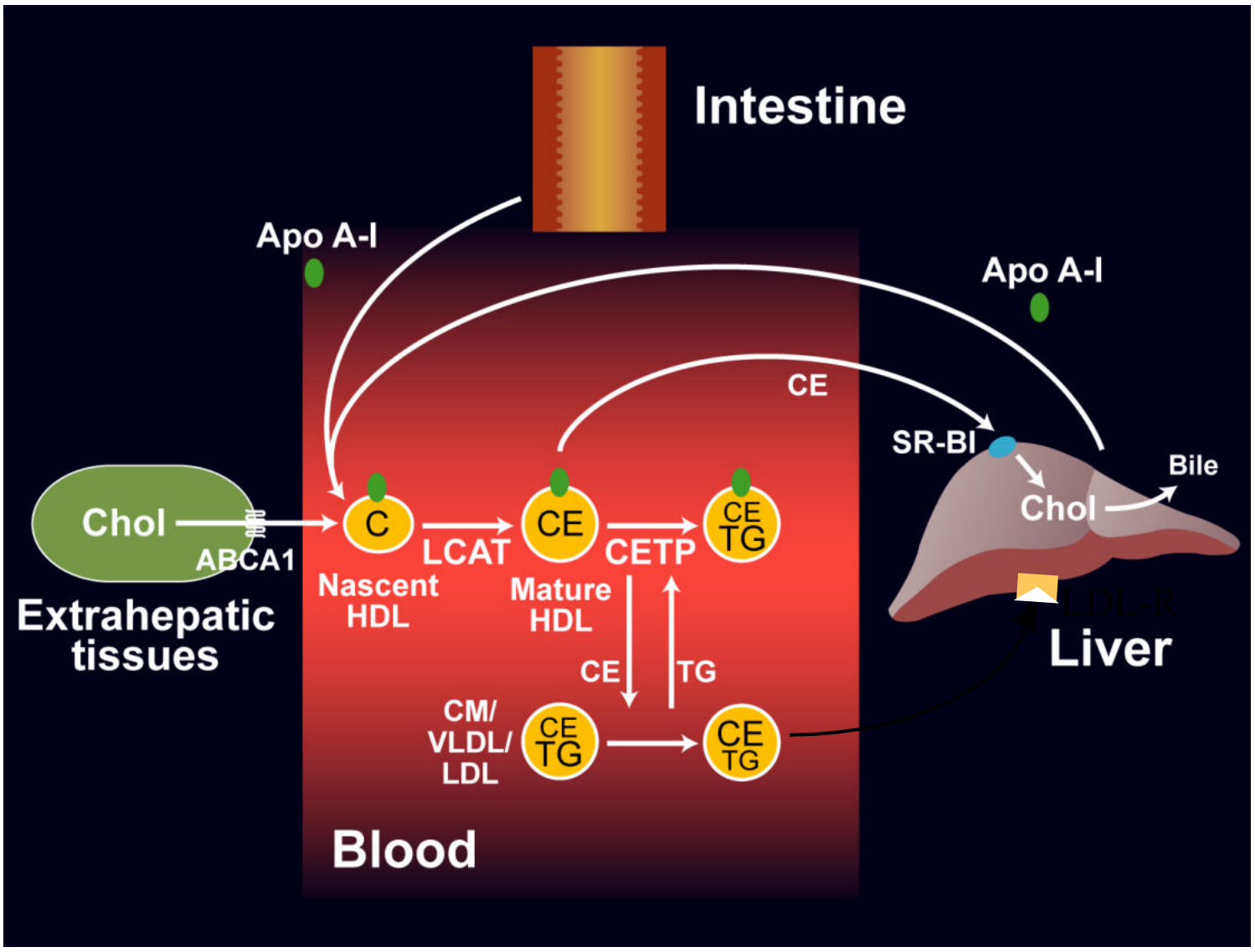
HDL and Reverse Cholesterol Transport

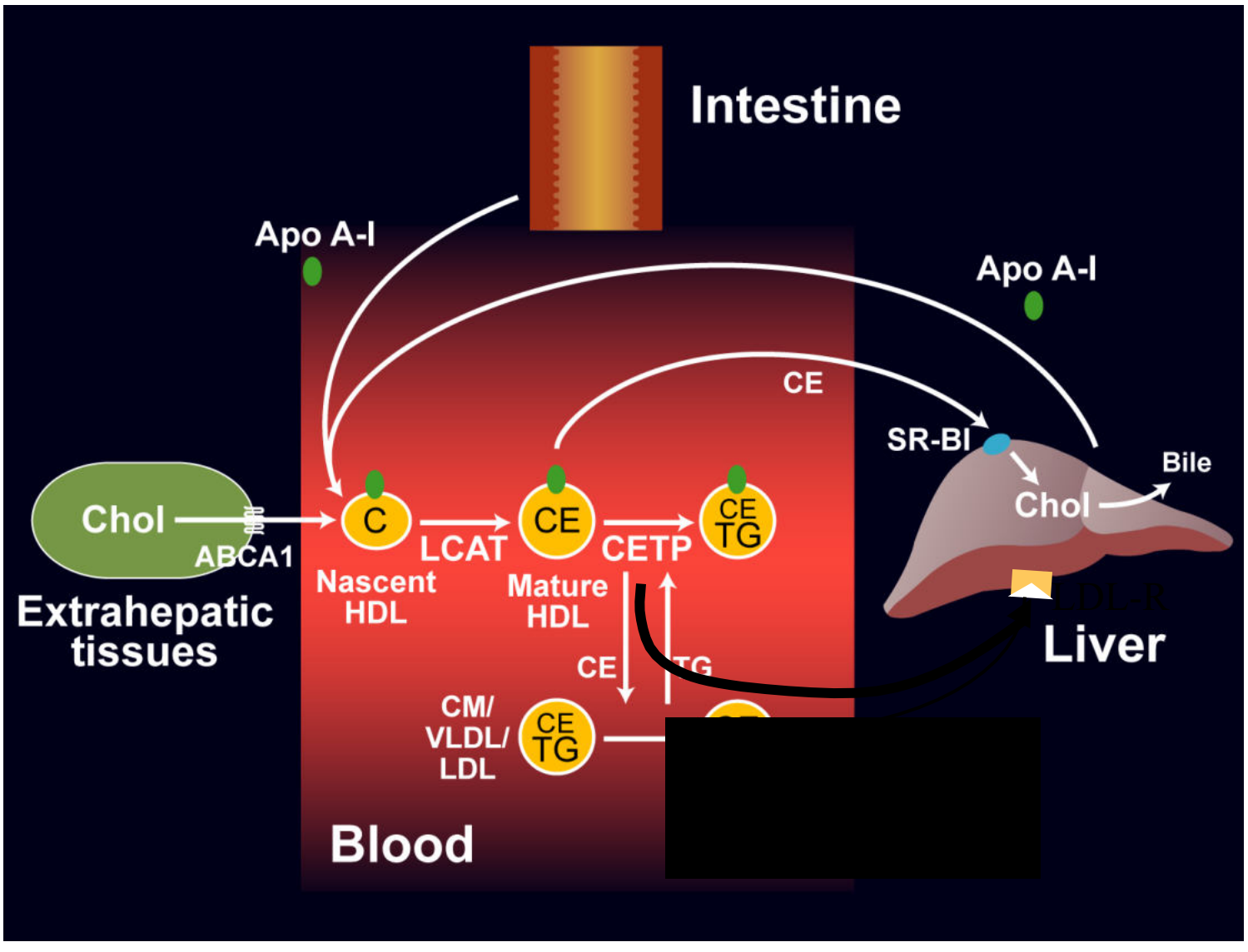












LDL/HDL Ratio and Cardiovascular Disease

- **LDL/HDL ratios are used as a diagnostic tool for signs of Cardiovascular disease**
- **A good LDL/HDL ratio is 3.5**

–LDL above normal range =

"Bad Cholesterol"

–HDL within normal range =

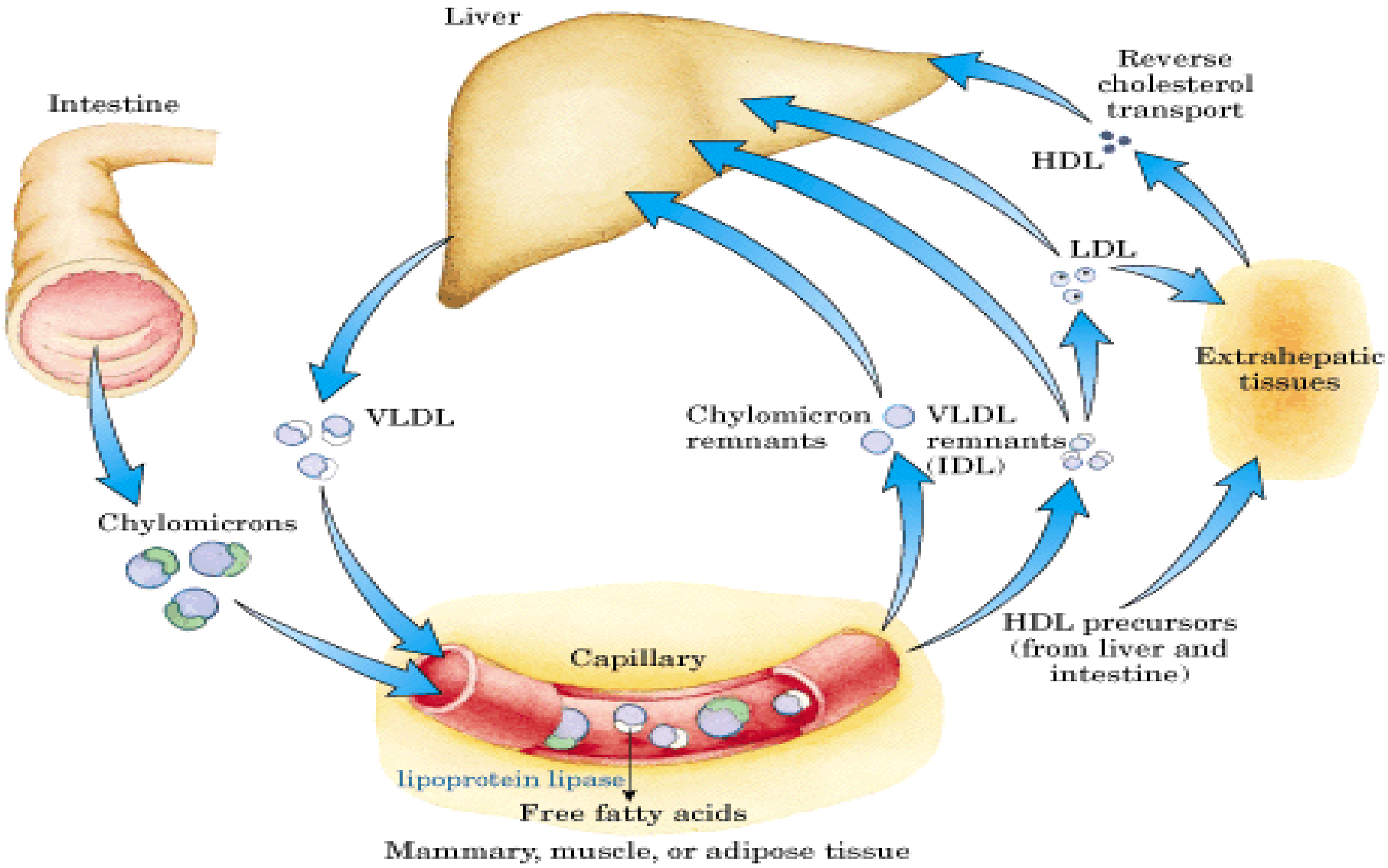
"Good Cholesterol"

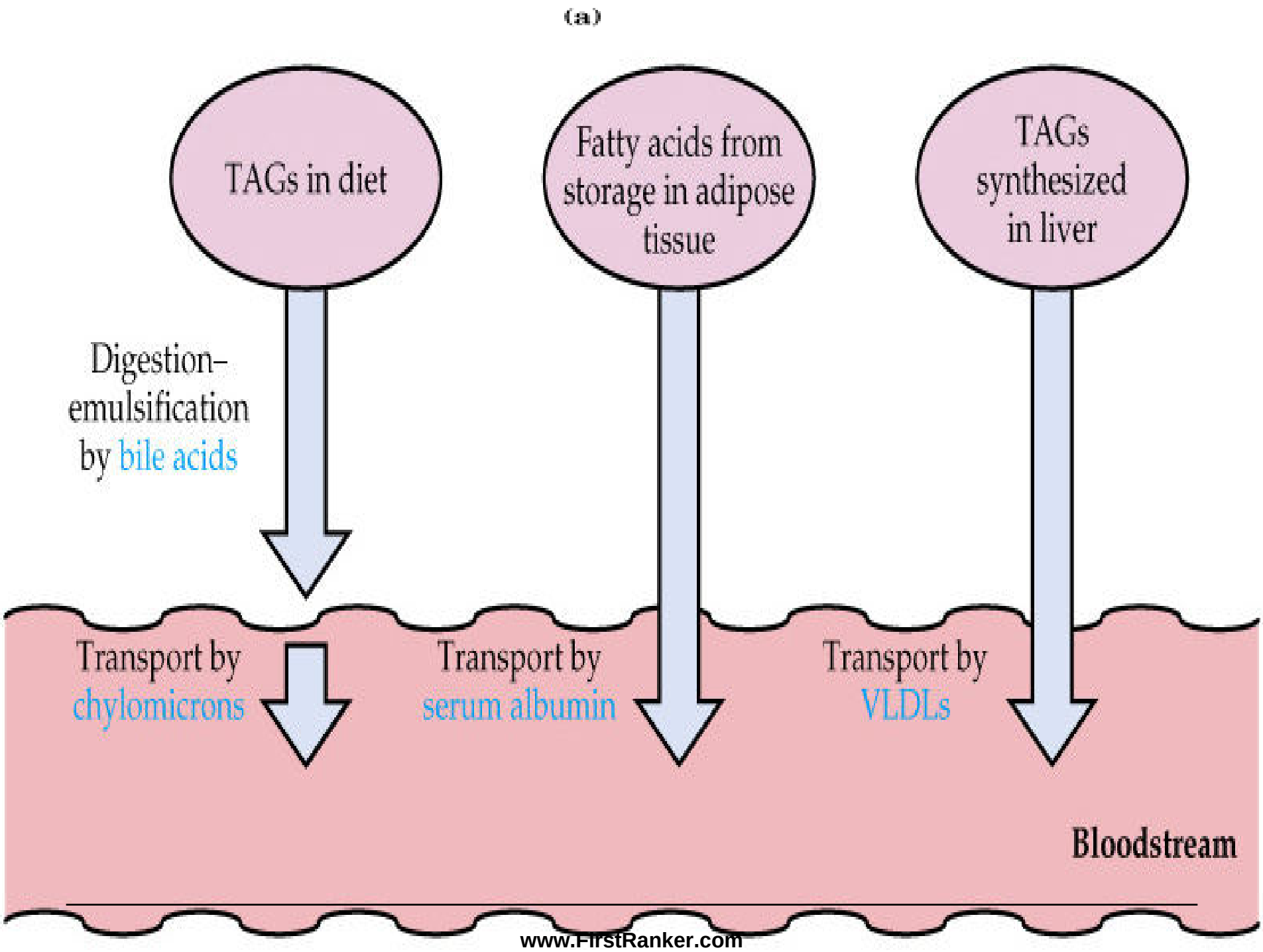
-HDL above normal range =

"Bad Cholesterol"

- **Protective role of HDL is not very clear.**
  - **An esterase that breaks down oxidized lipids is associated with HDL.**
  - **It is possible (but not proven) that this enzyme helps to destroy oxidized LDL**

Lipoproteins Facilitate Lipid Transport





Effects Of Normal Lipoprotein Metabolism

Normal LP Metabolism

- **Maintains Normal levels of Lipoproteins in the blood circulation by:**
  - **Normal Formation of LP** by specific tissues
  - **Normal Transformation and Transport of LP** in blood
  - **Normal Uptake of LP by** specific tissues

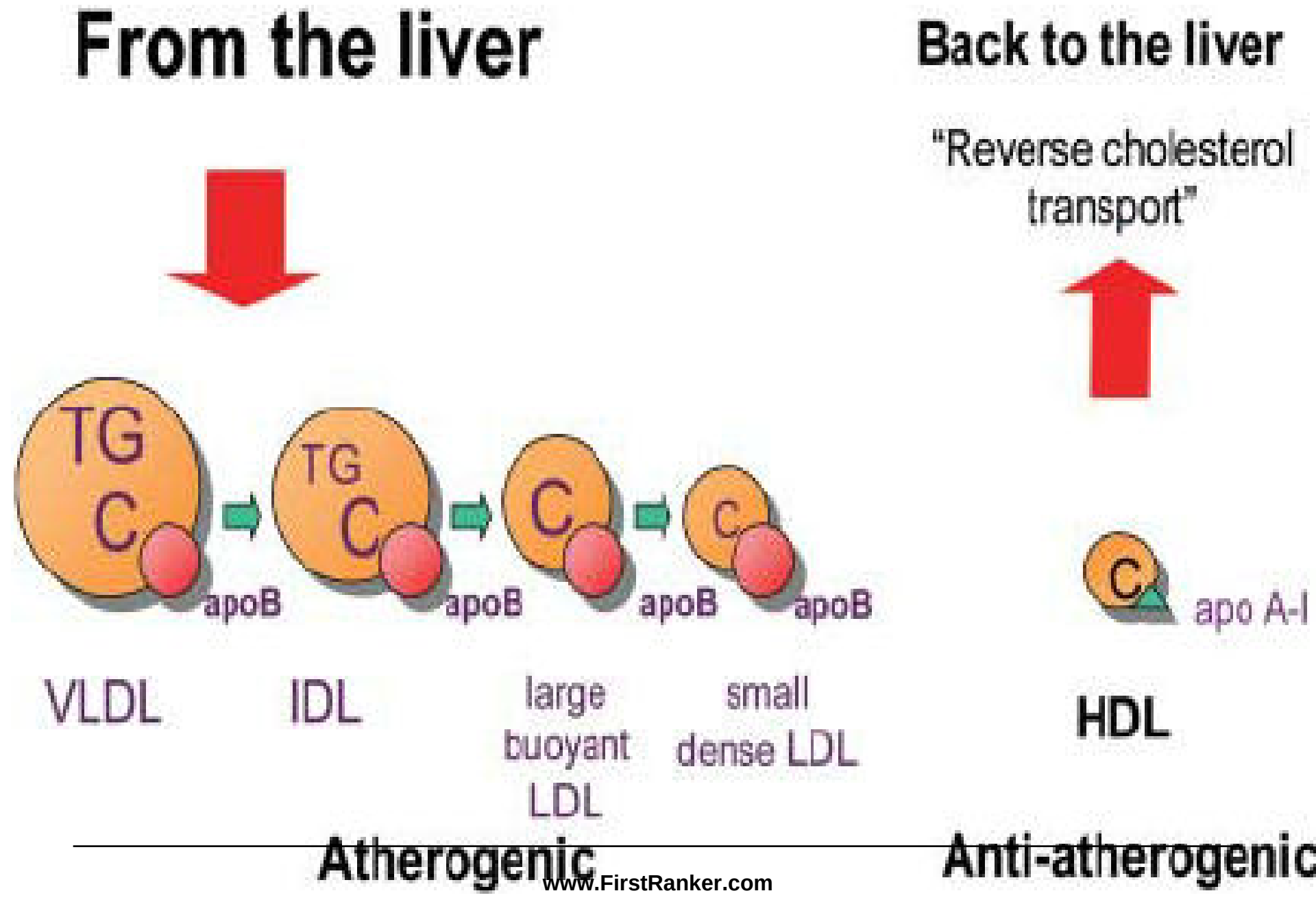
- **Normal Lipoprotein Metabolism Reduces the risk of:**
  - –Atherosclerosis
  - –Myocardial Infarction
  - –Stroke

Lipoprotein Population Distributions

- Serum Lipoprotein concentrations **differ between adult men and women**.
- Primarily as a result of **differences in sex hormone levels.**

- Women having, on average, higher HDL cholesterol levels and lower total Cholesterol and TAG levels than men.

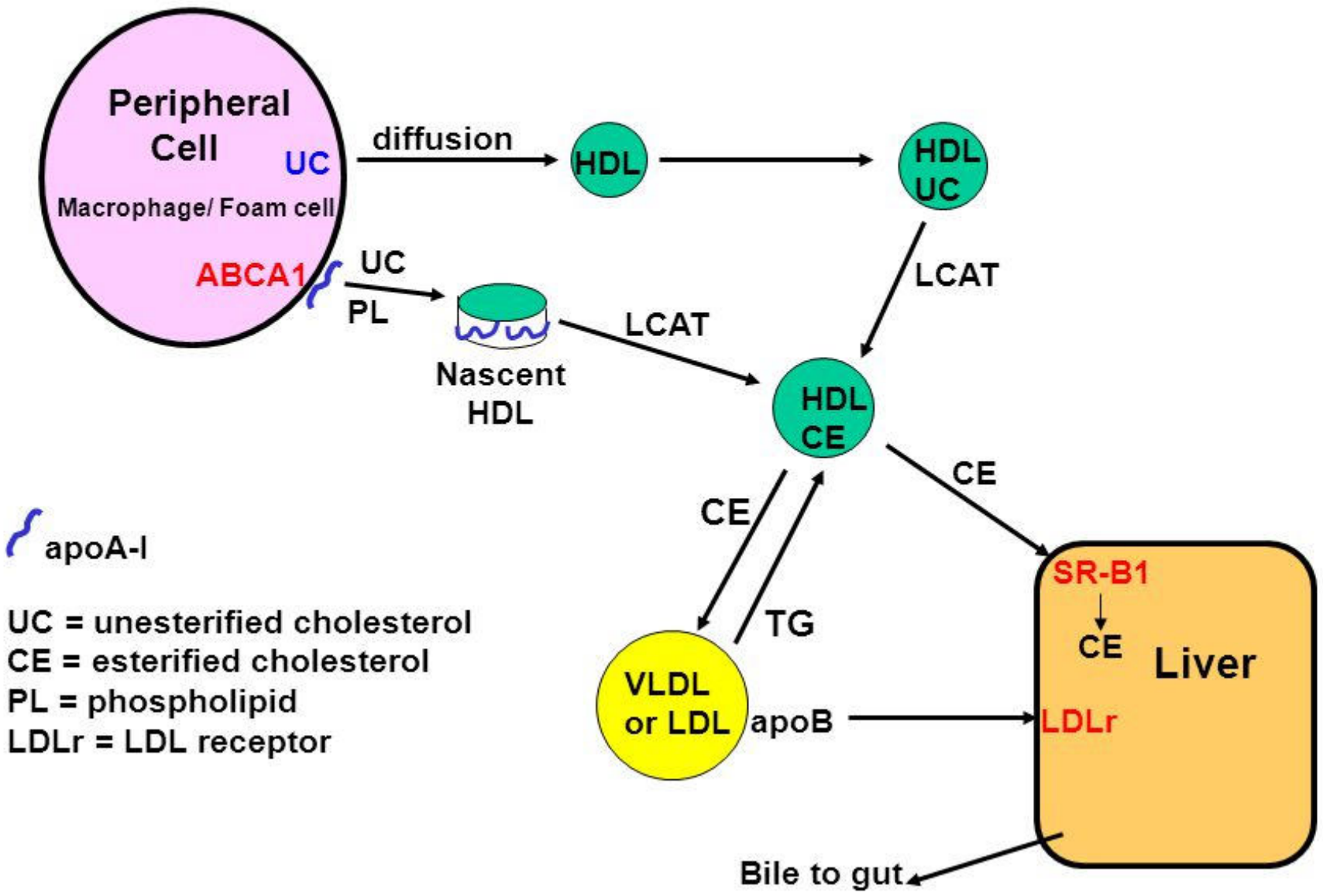
- The difference in total cholesterol, however, disappears in **post menopause** as **Estrogen decreases and use of Cholesterol is reduced.**

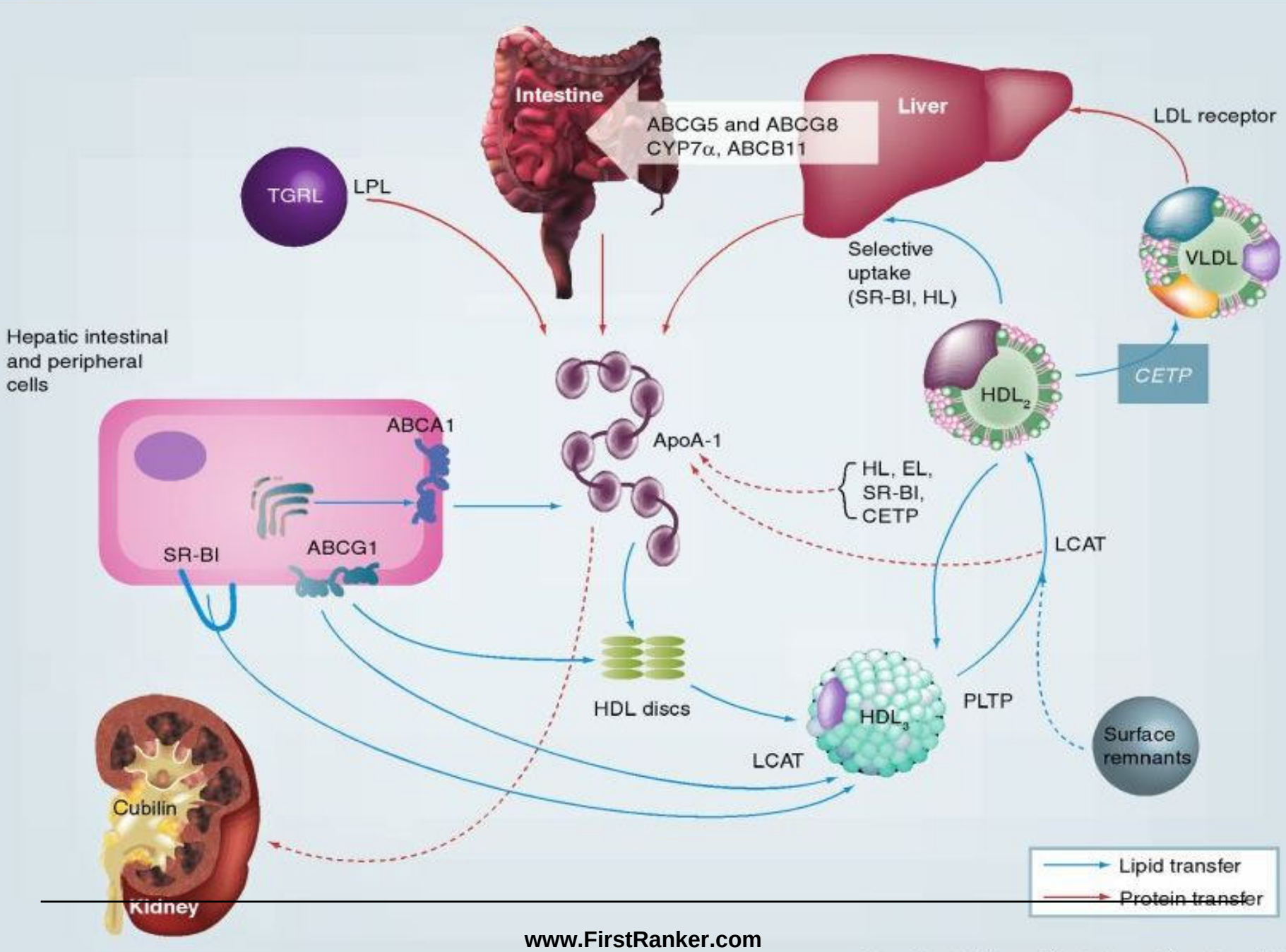


Reverse Cholesterol Transport

Delivery of peripheral tissue cholesterol to the liver for catabolism

Requires HDL, apoA-I and LCAT





Expert Rev. Cardiovasc. Ther. © Future Science Group (2010)

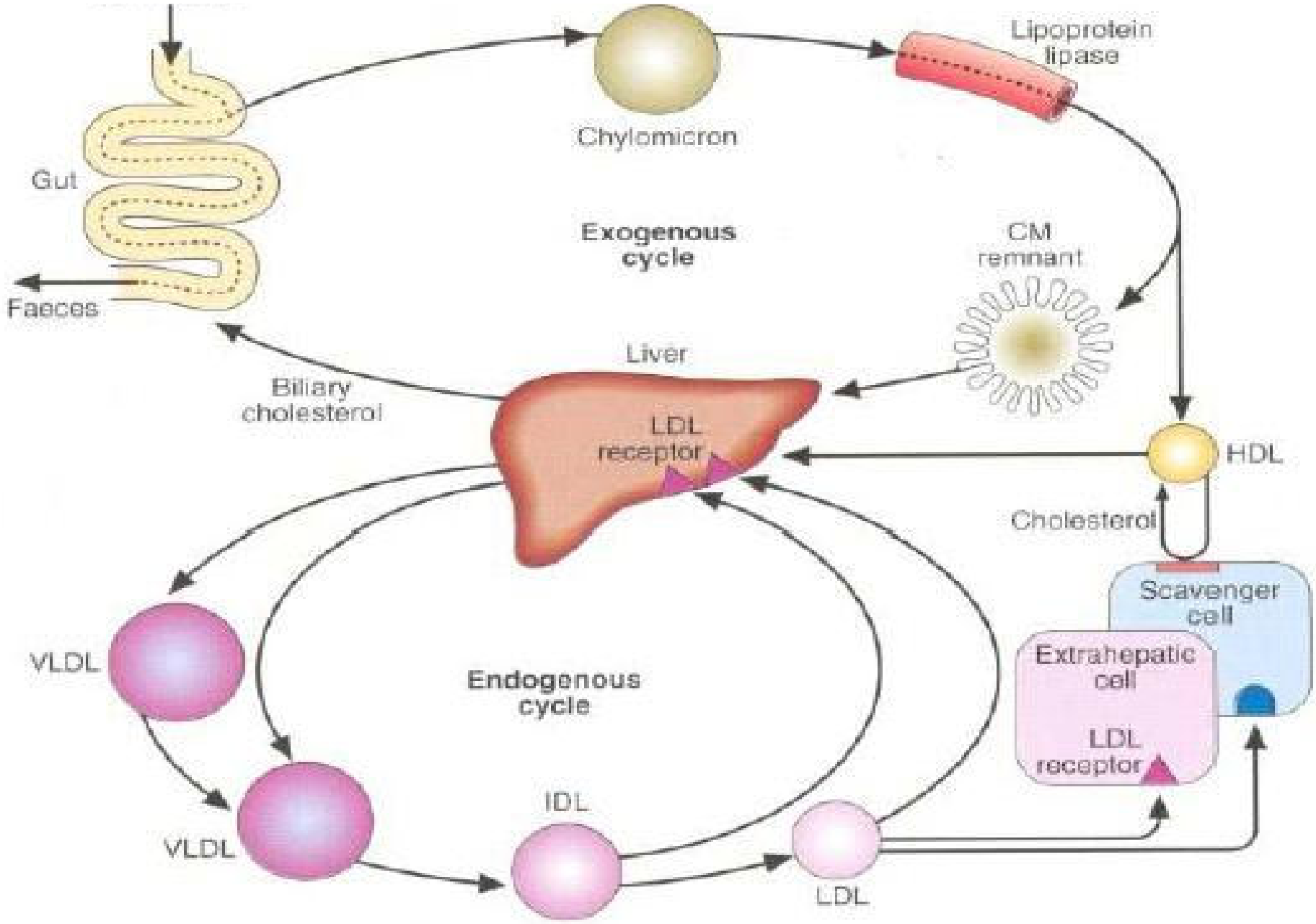
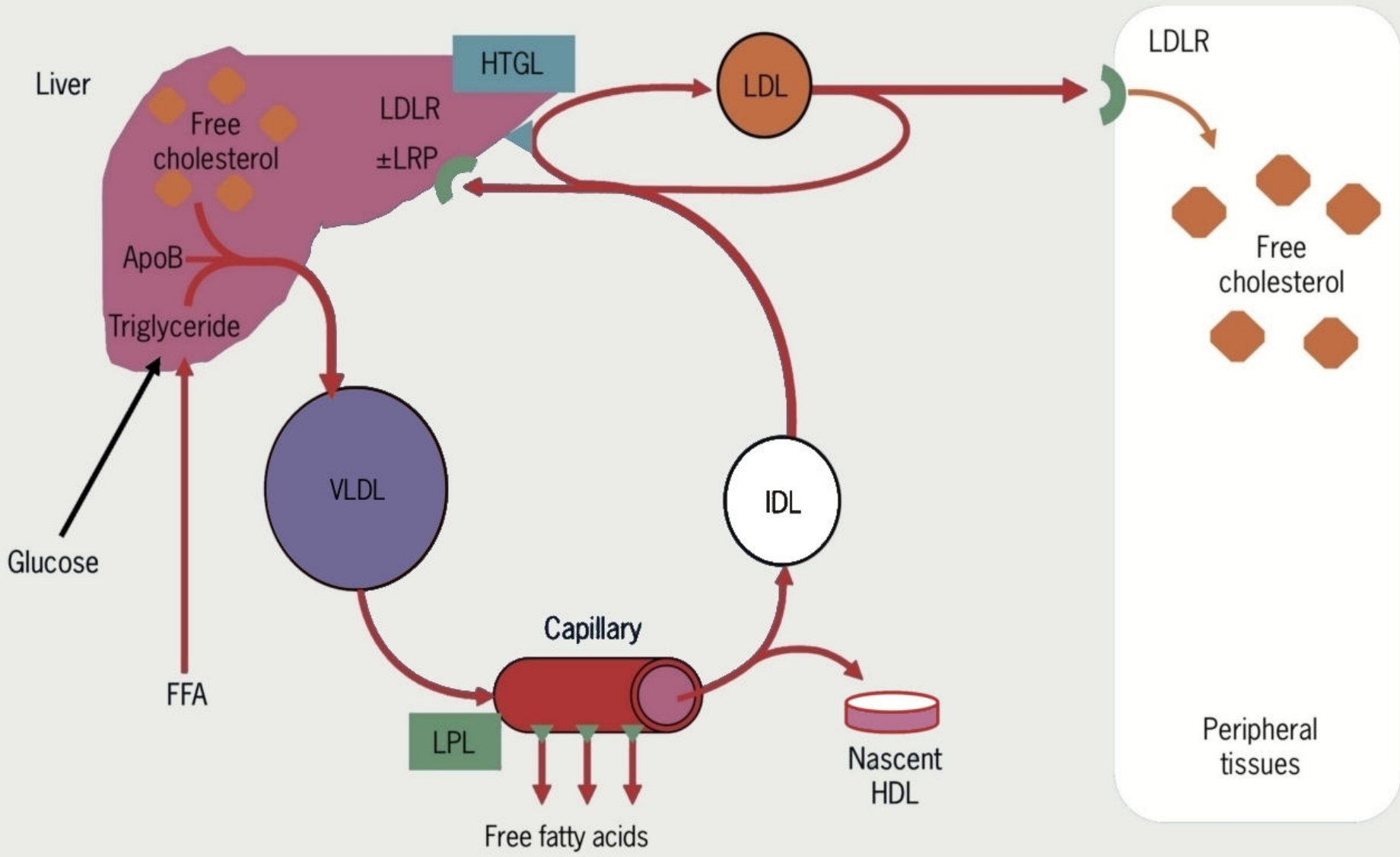


Fig. 2 Lipoprotein metabolism.



Key: ApoB = apolipoprotein B; FFA = free fatty acids; HDL = high-density lipoprotein cholesterol; HTGL = hepatic triglyceride lipase; IDL = intermediate-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; LPL = lipoprotein lipase; LRP = LDL receptor-related protein; VLDL = very low-density lipoprotein cholesterol

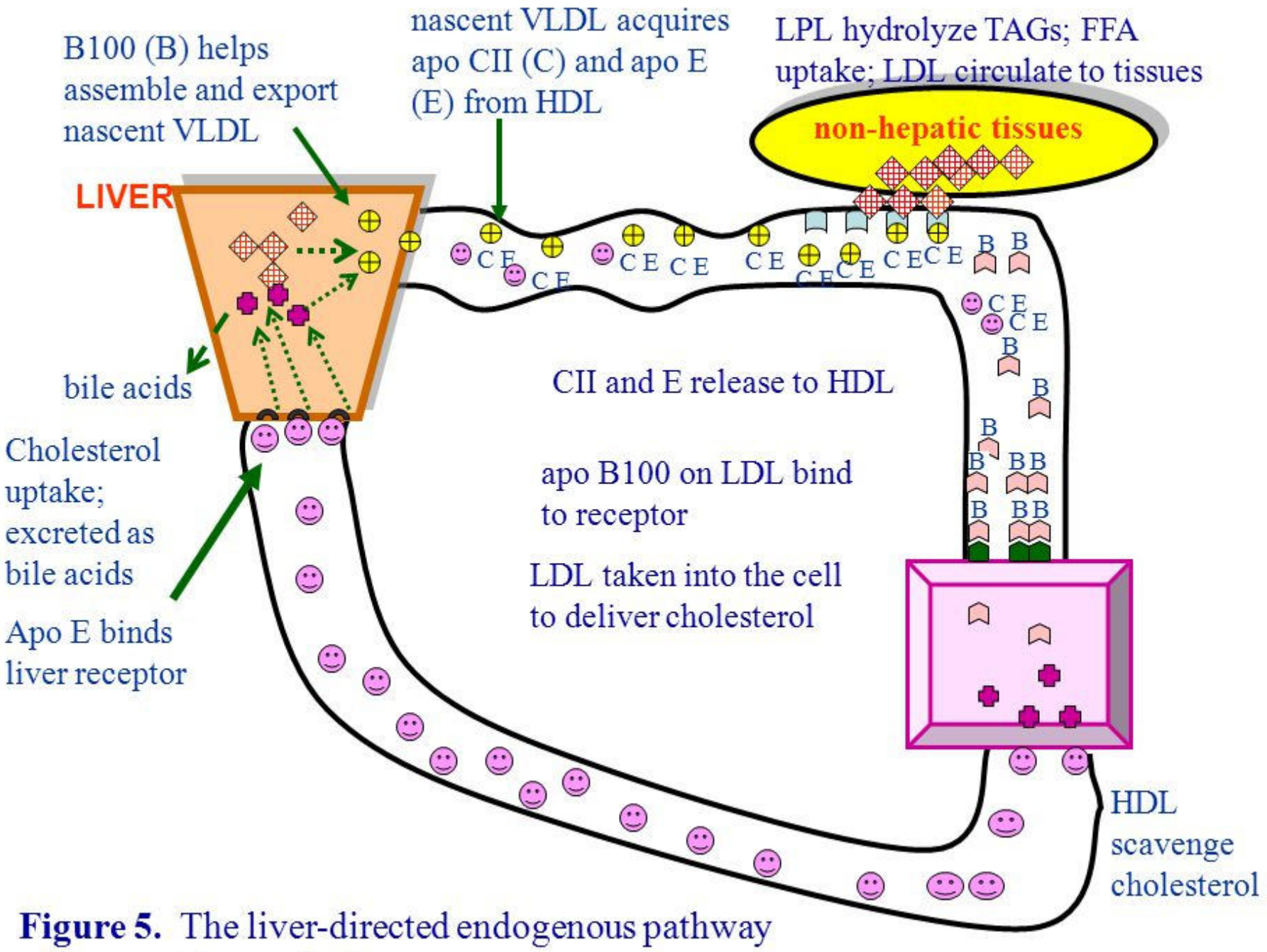
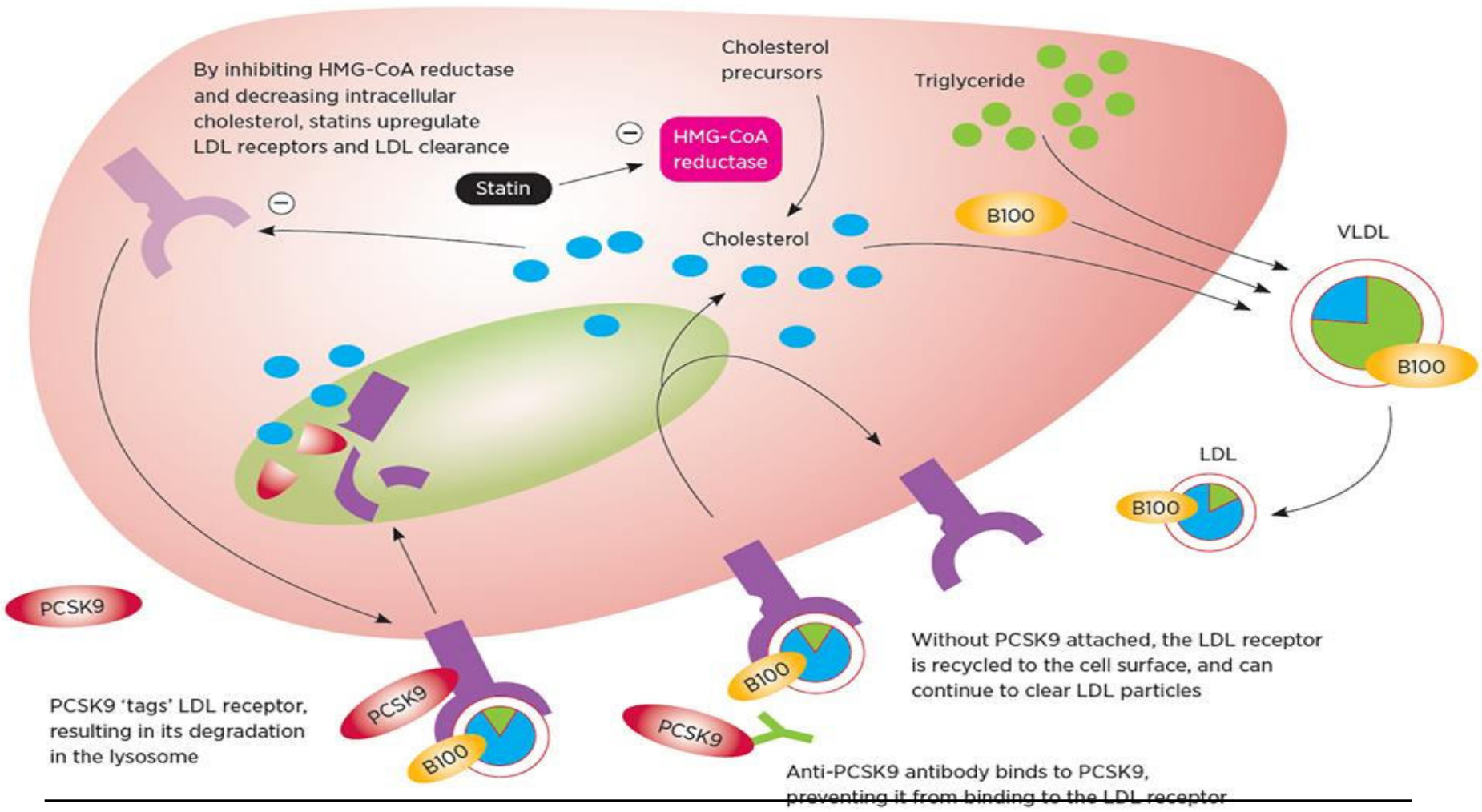


Figure 5. The liver-directed endogenous pathway of lipoprotein metabolism.

PCSK9
Proprotein Convertase Subtilisin /Kexin type 9



B100 apolipoprotein-B100 PCSK9 proprotein convertase subtilisin/kexin type 9 LDL low-density lipoprotein VLDL very low-density lipoprotein

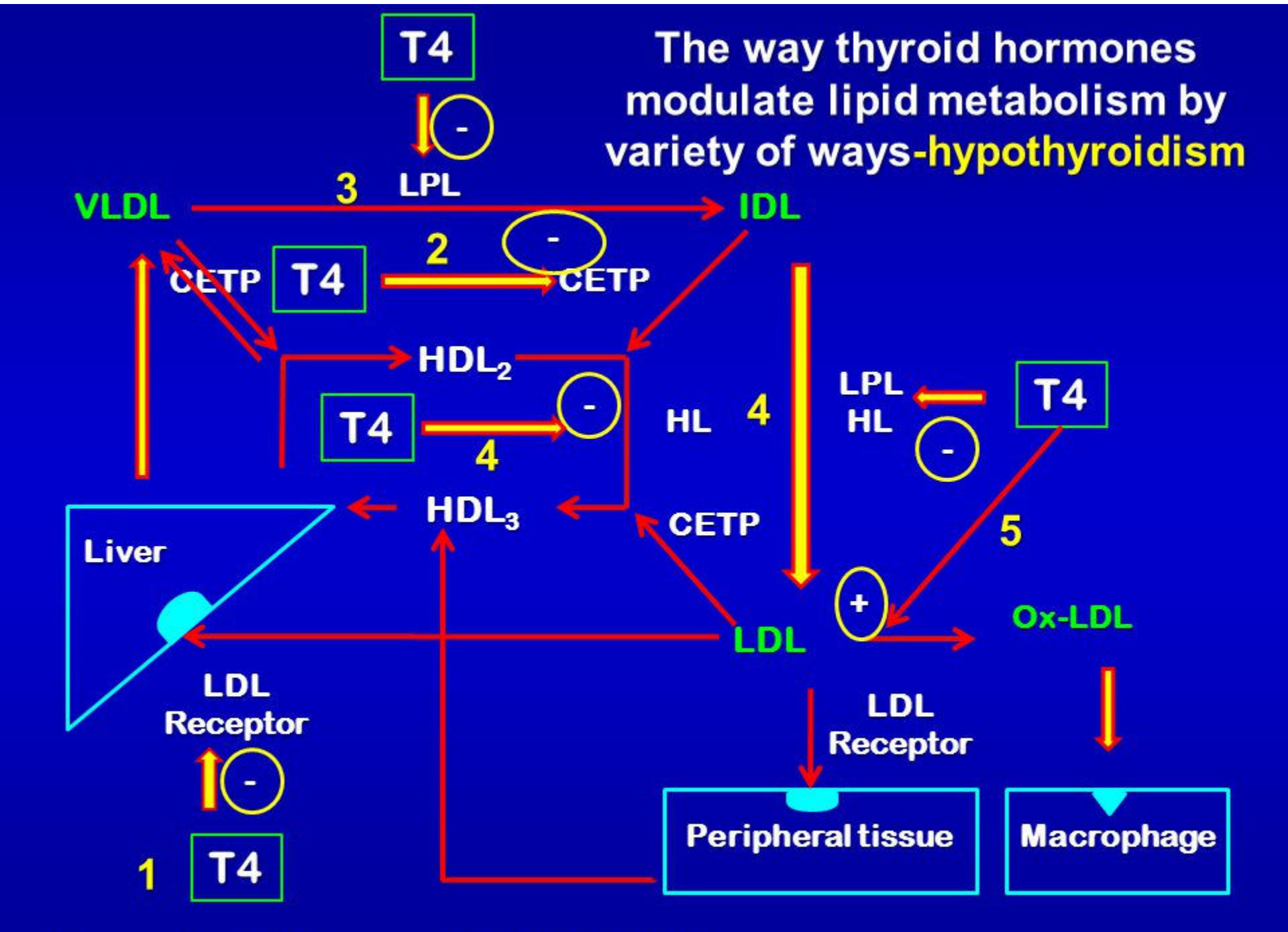
PCSK9 - Mechanisms of Action

- **PCSK9** is a **Proprotein Convertase responsible for**
- **Degradation of low-density lipoprotein (LDL) receptors** in Liver.
- **Mutations in PCSK9 gene cause familial Hypercholesterolemia**
- Due to reduced number of LDL receptors on surface of hepatocytes.
- Decreases their ability to clear LDL cholesterol from plasma.

PCSK9 inhibitors – Mechanisms of Action

- **Conversely other PCSK9 mutations** result in
- Unusually low concentrations of plasma LDL cholesterol and a reduced risk of atherosclerotic disease.
- **Blocking activity of PCSK9 with monoclonal antibodies** reduces degradation of LDL receptors
- **An injection of PCSK9-specific antibody suppresses** LDL-cholesterol concentrations.

- Increases clearance of LDL cholesterol



Liberopoulos EN. Hormones 2002, 1(14): 218-223