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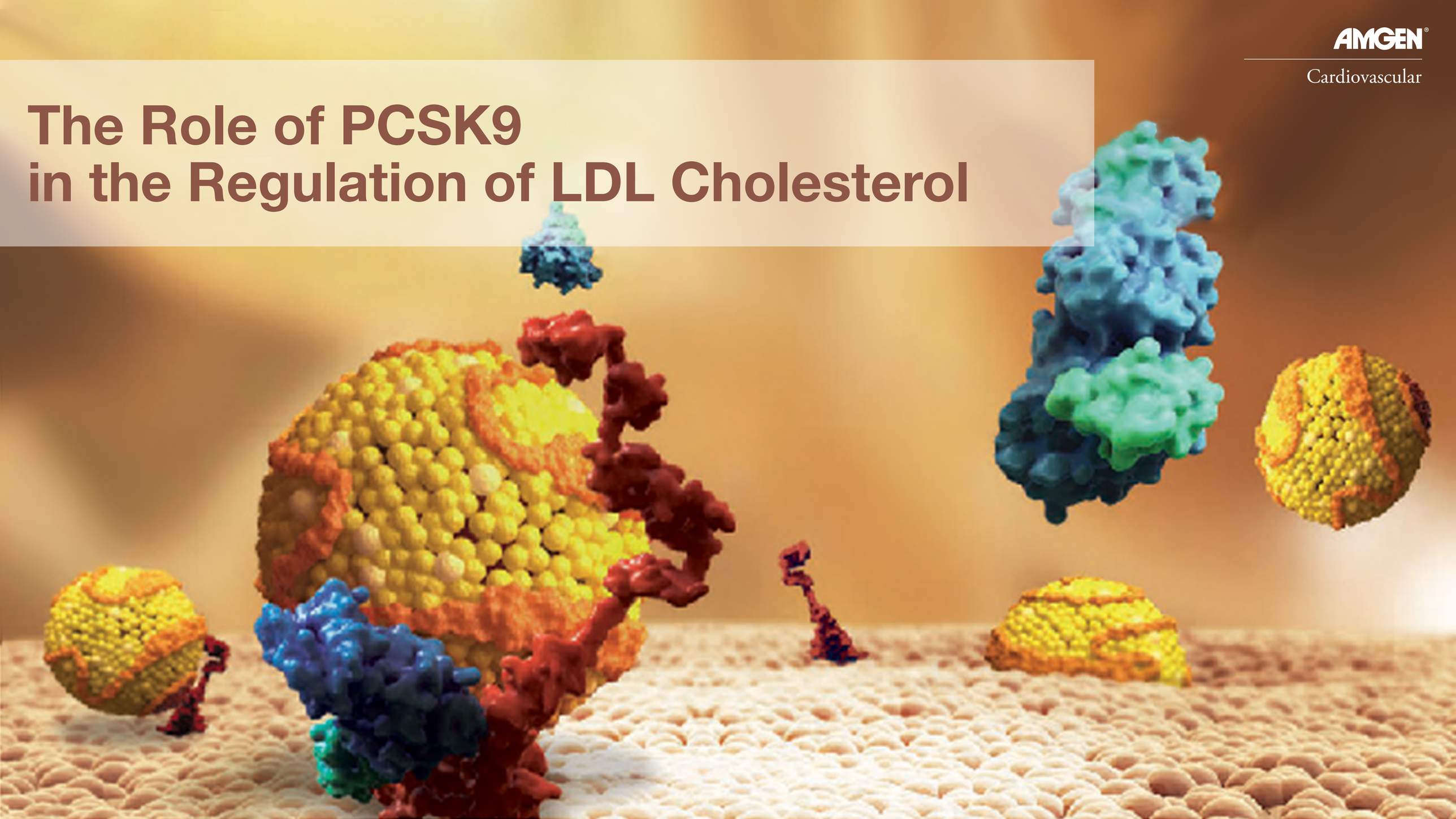
Cardiovascular

The Role of PCSK9 in the Regulation of LDL Cholesterol

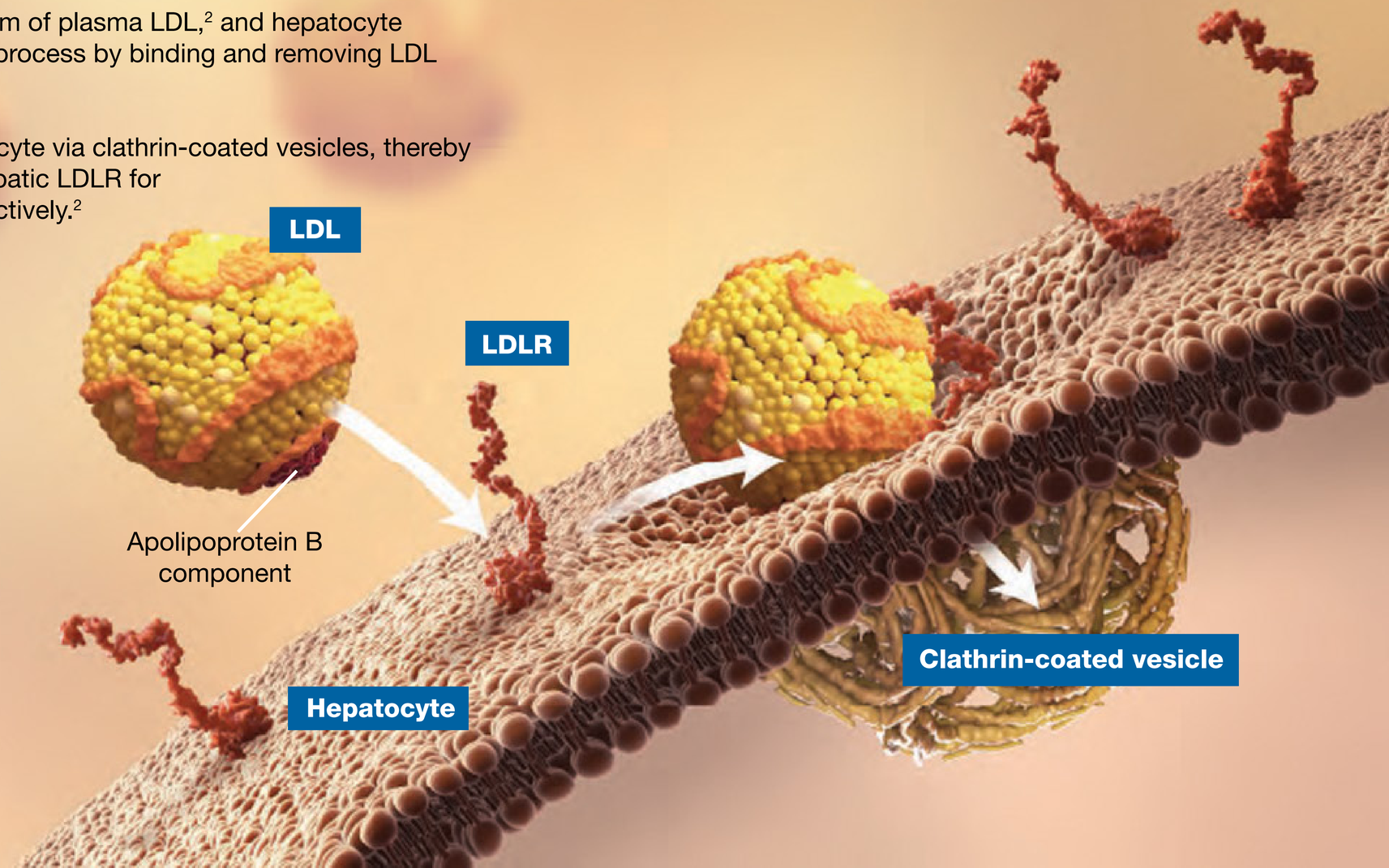


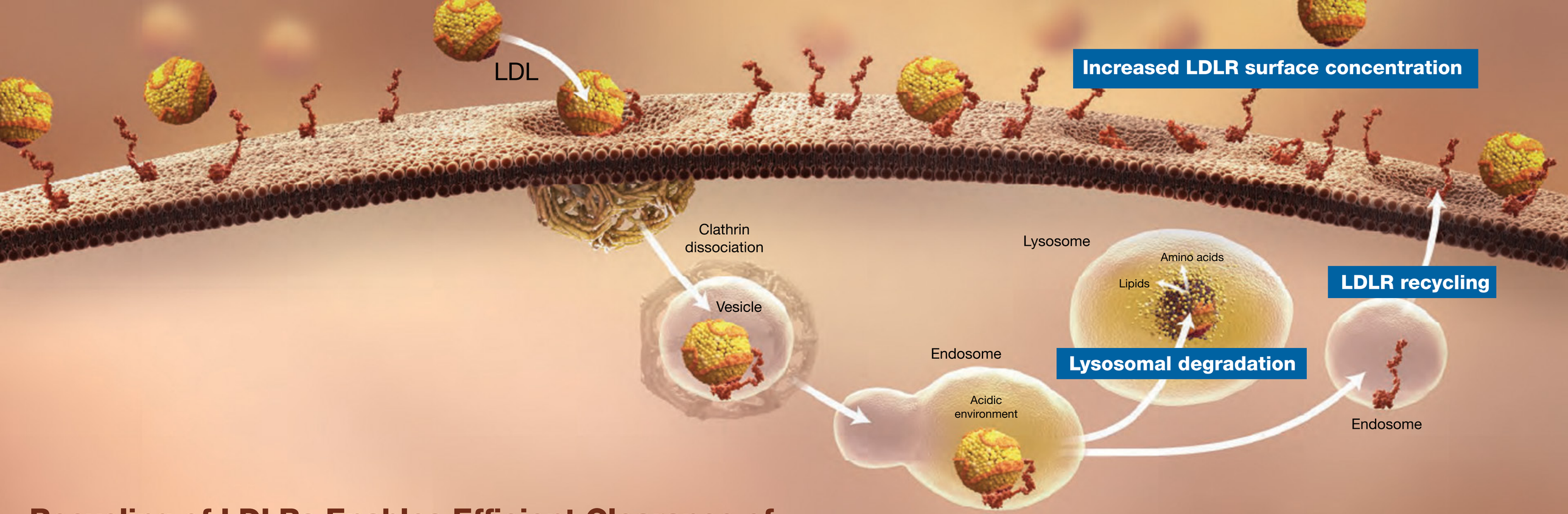
Hepatic Low-Density Lipoprotein Receptors (LDLRs) Play a Central Role in Cholesterol Homeostasis

- Low-density lipoprotein (LDL) particles consist mostly of cholesteryl esters packaged with a protein moiety called apolipoprotein B (apoB), with 1 apoB molecule in each LDL particle.[1,2] LDL particles are the primary carriers of plasma cholesterol in humans,[1] and high LDL levels have a strong and direct relationship with the development of atherosclerosis.[3]

- The liver is responsible for the clearance and catabolism of plasma LDL,[2] and hepatocyte expression of LDL receptors (LDLRs) is central to this process by binding and removing LDL from the plasma.[4,5]

- The LDL/LDLR complex is internalized into the hepatocyte via clathrin-coated vesicles, thereby removing LDL from the blood.[1,5,6] The affinity of the hepatic LDLR for apoB on LDL enables LDLRs to clear plasma LDL effectively.[2]



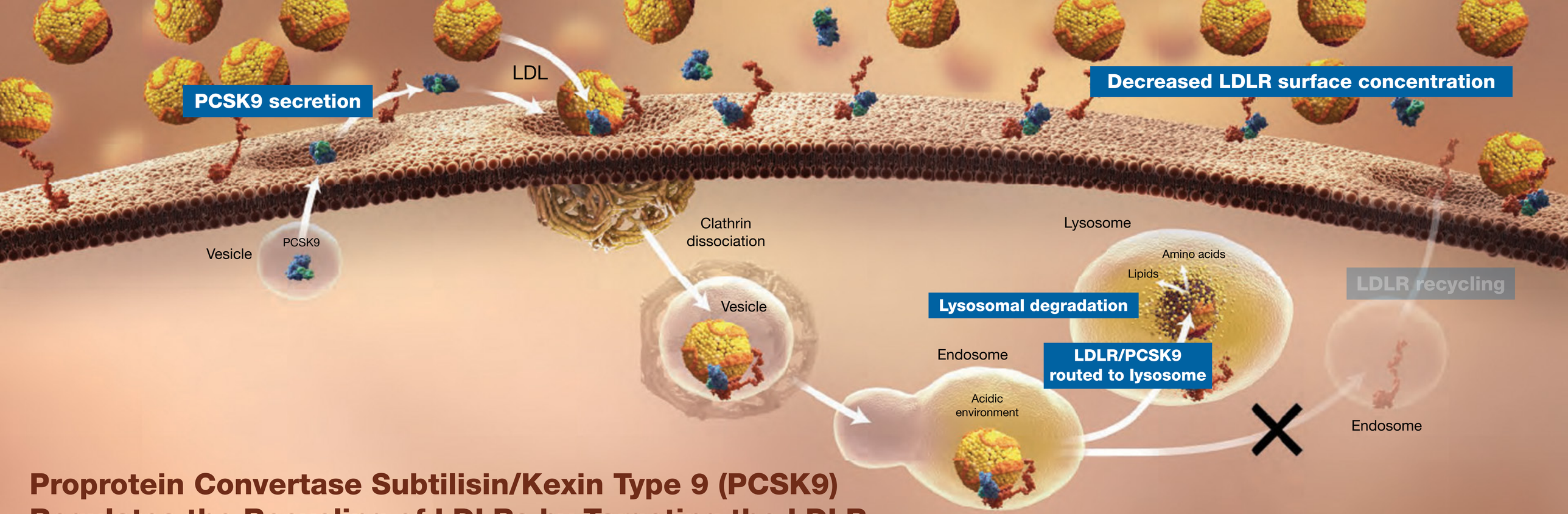


Recycling of LDLRs Enables Efficient Clearance of LDL Particles

- Clathrin-coated vesicles containing internalized LDL/LDLR complexes fuse with endosomes, resulting in dissociation of the LDL particles from the LDLRs due to the acidic environment.[5] The free LDLRs then recycle back to the surface of the hepatocyte to bind and clear additional LDL from the blood.[5]

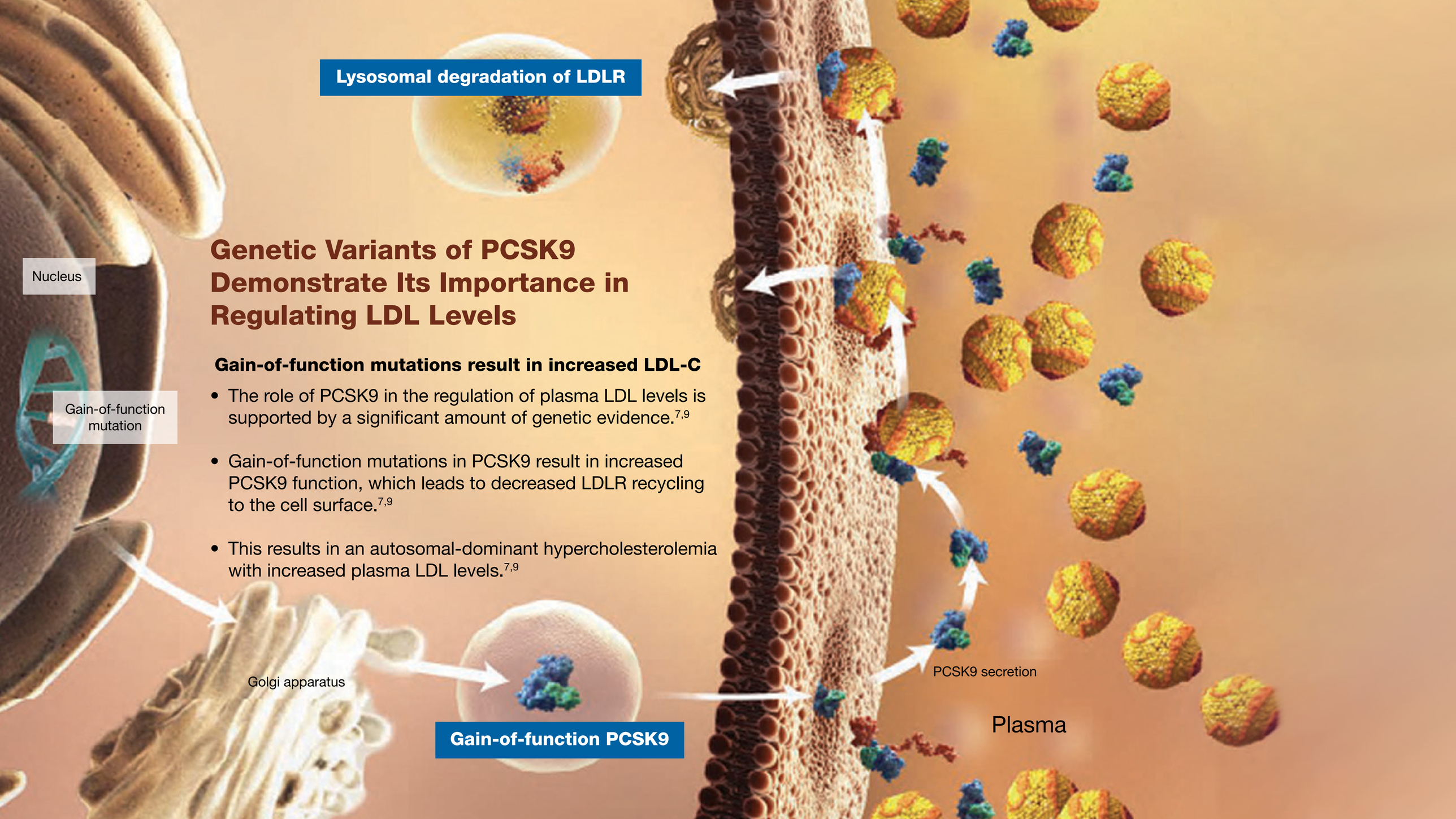
- Free LDL particles in the endosomes are transported to the lysosomes and degraded into lipids and amino acids.[1]

- The ability of hepatic LDLRs to be recycled is a key determinant of hepatic efficacy in lowering plasma LDL levels.



Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Regulates the Recycling of LDLRs by Targeting the LDLR for Degradation

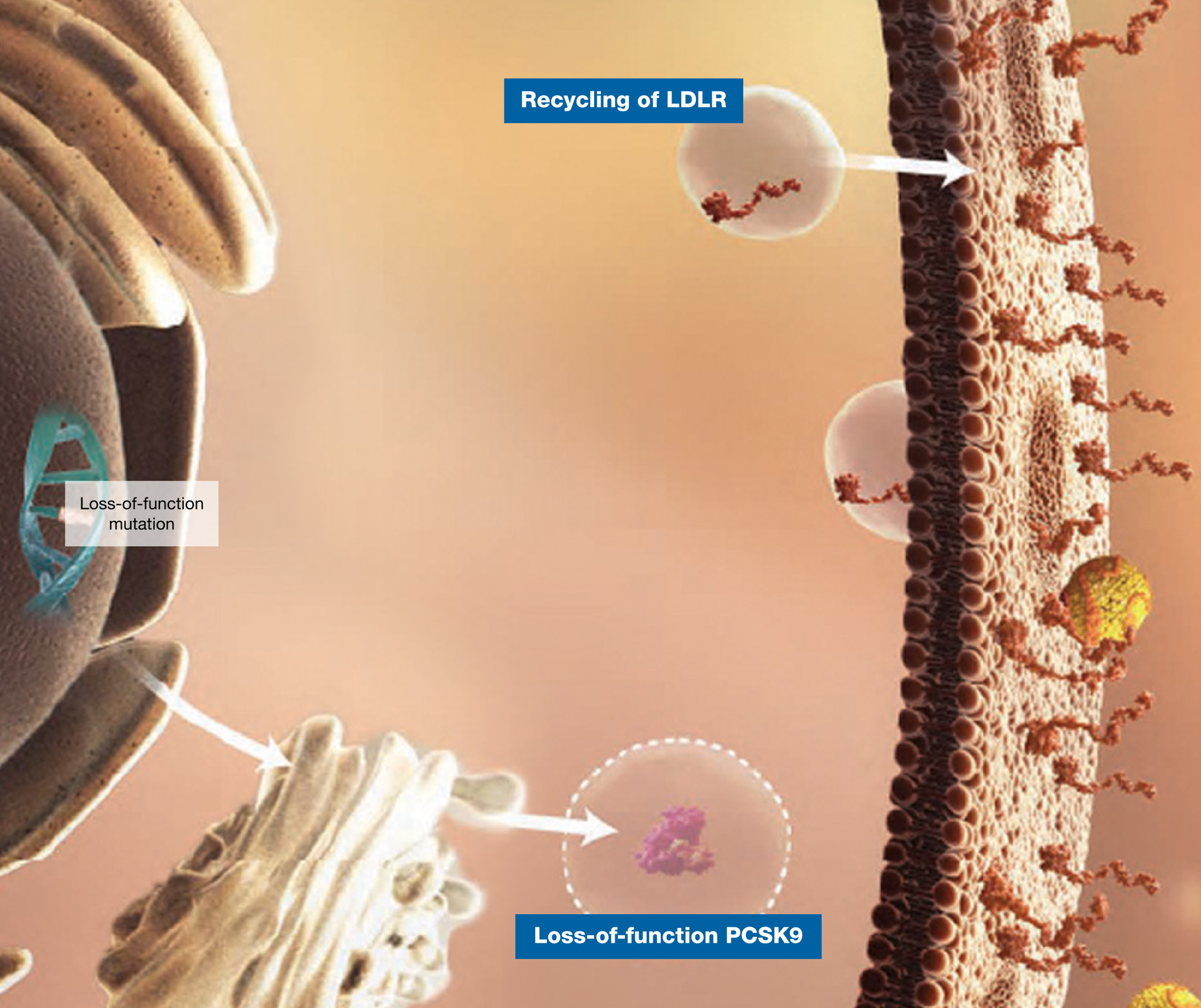
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proprotein produced in hepatocytes and secreted into the plasma as functional PCSK9.[7] Extracellular PCSK9 binds to the LDLR on the surface of the hepatocyte and is internalized within the endosome.[8]
- The LDLR/PCSK9 complex is then routed to the lysosome for degradation, thereby preventing the recycling of LDLR back to the hepatocyte surface.[3,8]
- By preventing LDLRs from recycling back to the surface, PCSK9 reduces the concentration of LDLRs on the surface of the hepatocytes, resulting in a lower LDL clearance rate and elevated levels of plasma LDL.[3]



Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels

Gain-of-function mutations result in increased LDL-C

- The role of PCSK9 in the regulation of plasma LDL levels is supported by a significant amount of genetic evidence.[7,9]
- Gain-of-function mutations in PCSK9 result in increased PCSK9 function, which leads to decreased LDLR recycling to the cell surface.[7,9]
- This results in an autosomal-dominant hypercholesterolemia with increased plasma LDL levels.[7,9]



Loss-of-function mutations are associated with decreased LDL-C[11]

- Mutations in the human PCSK9 gene that lead to a loss of PCSK9 function are found in 1% to 3% of the representative populations.[10,11]
- These loss-of-function mutations have been associated with lower levels of circulating PCSK9,[12] lower plasma LDL levels.[10]

List of References

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