Anti PCSK-9: Mecanismo de acción

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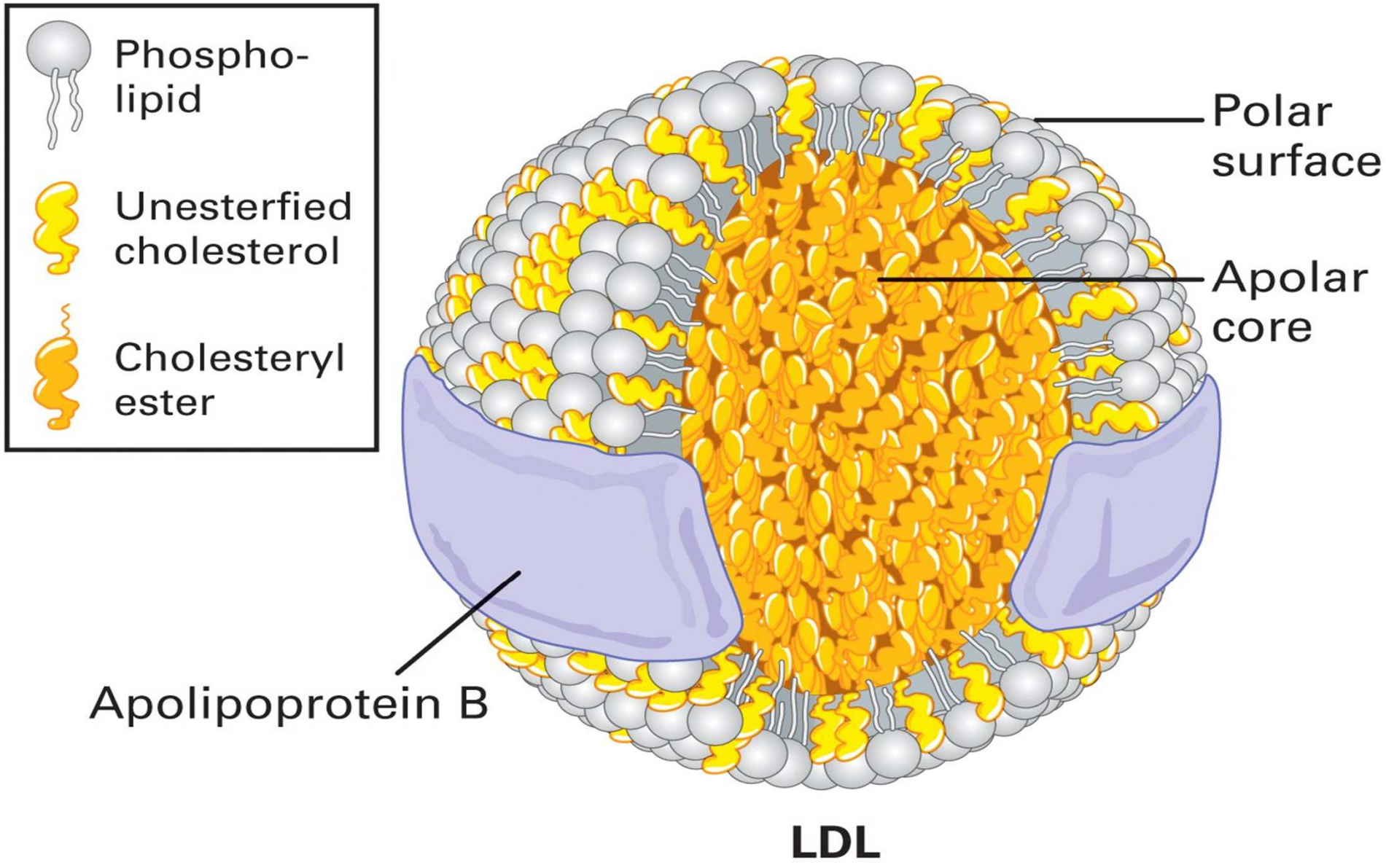
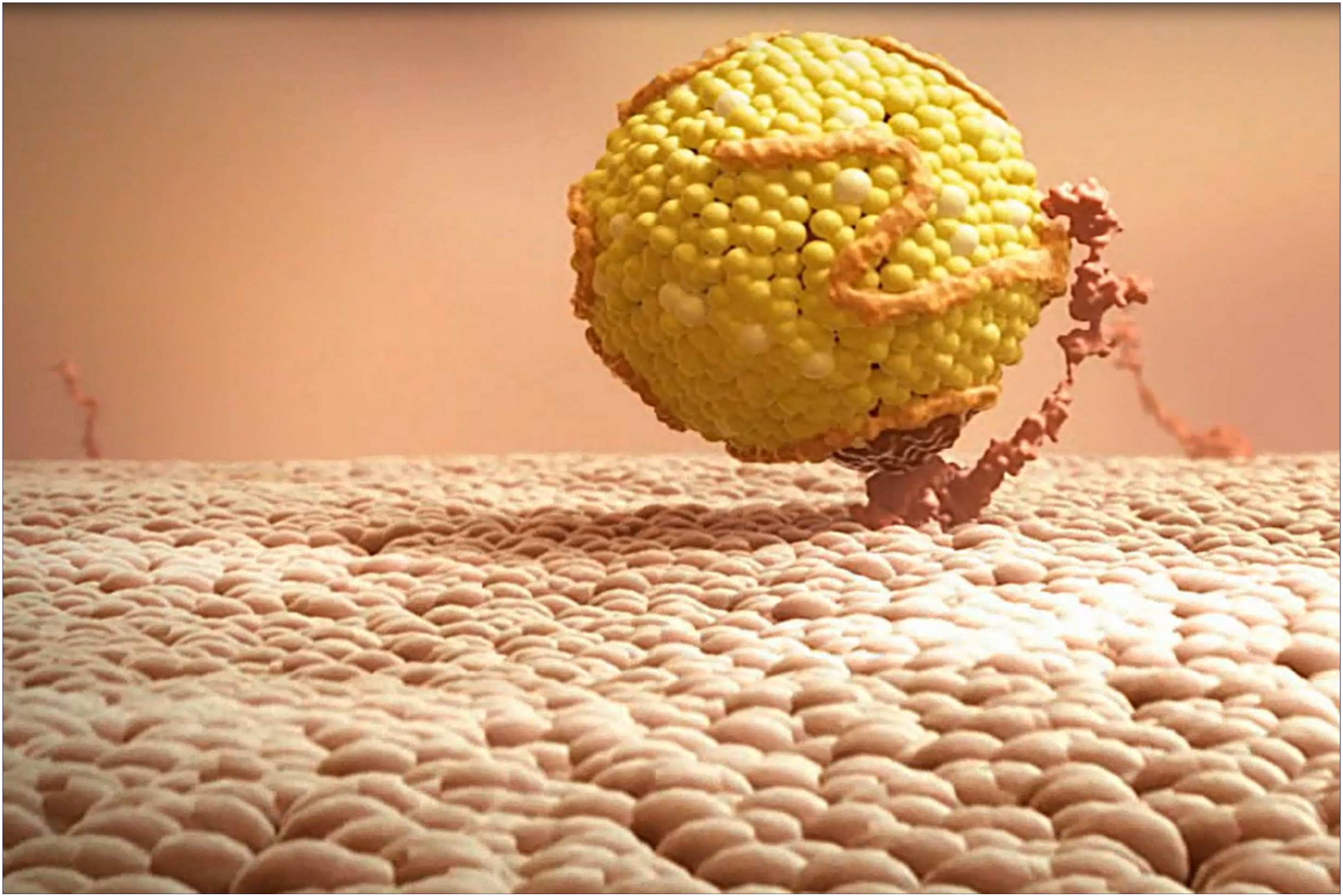
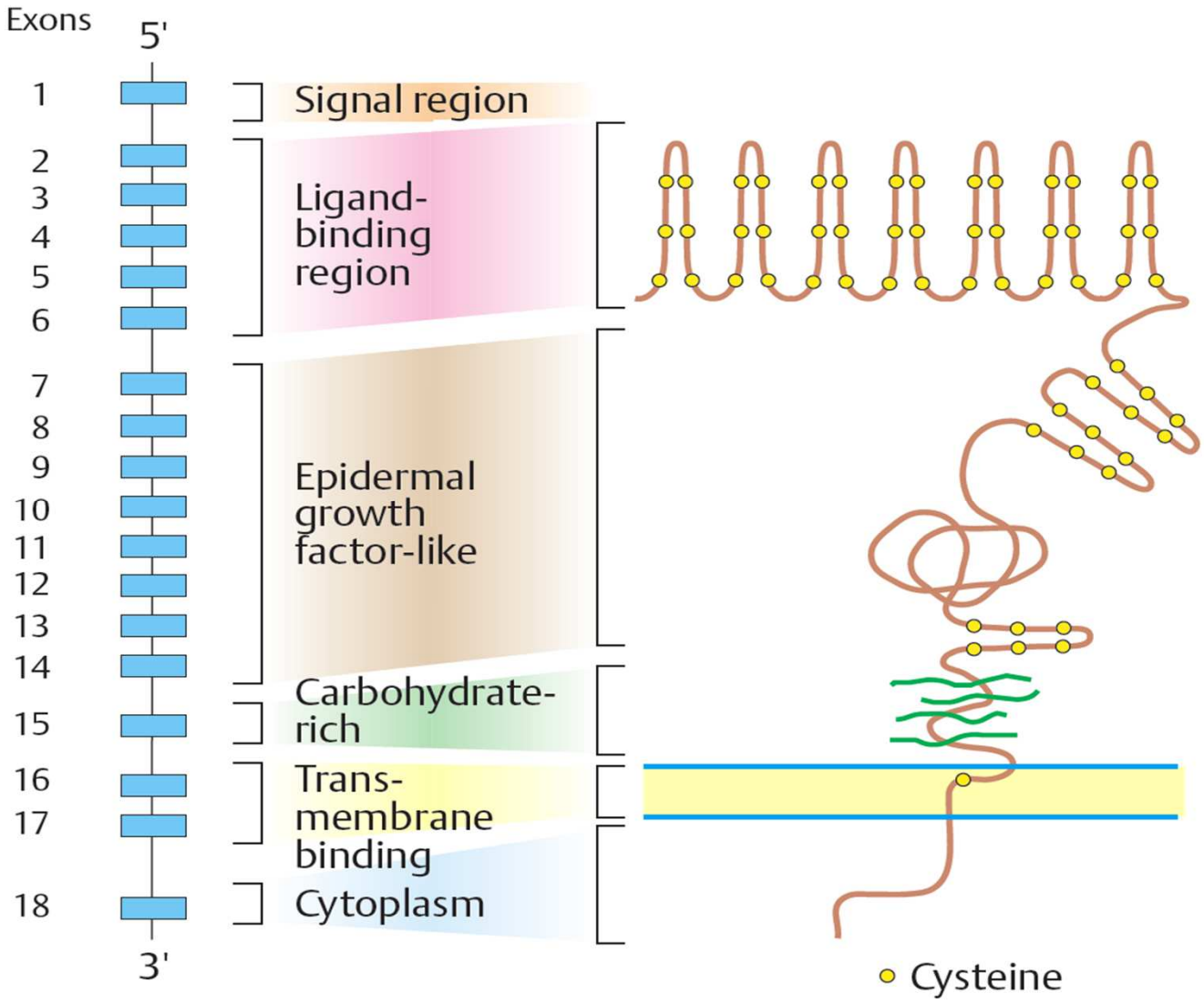
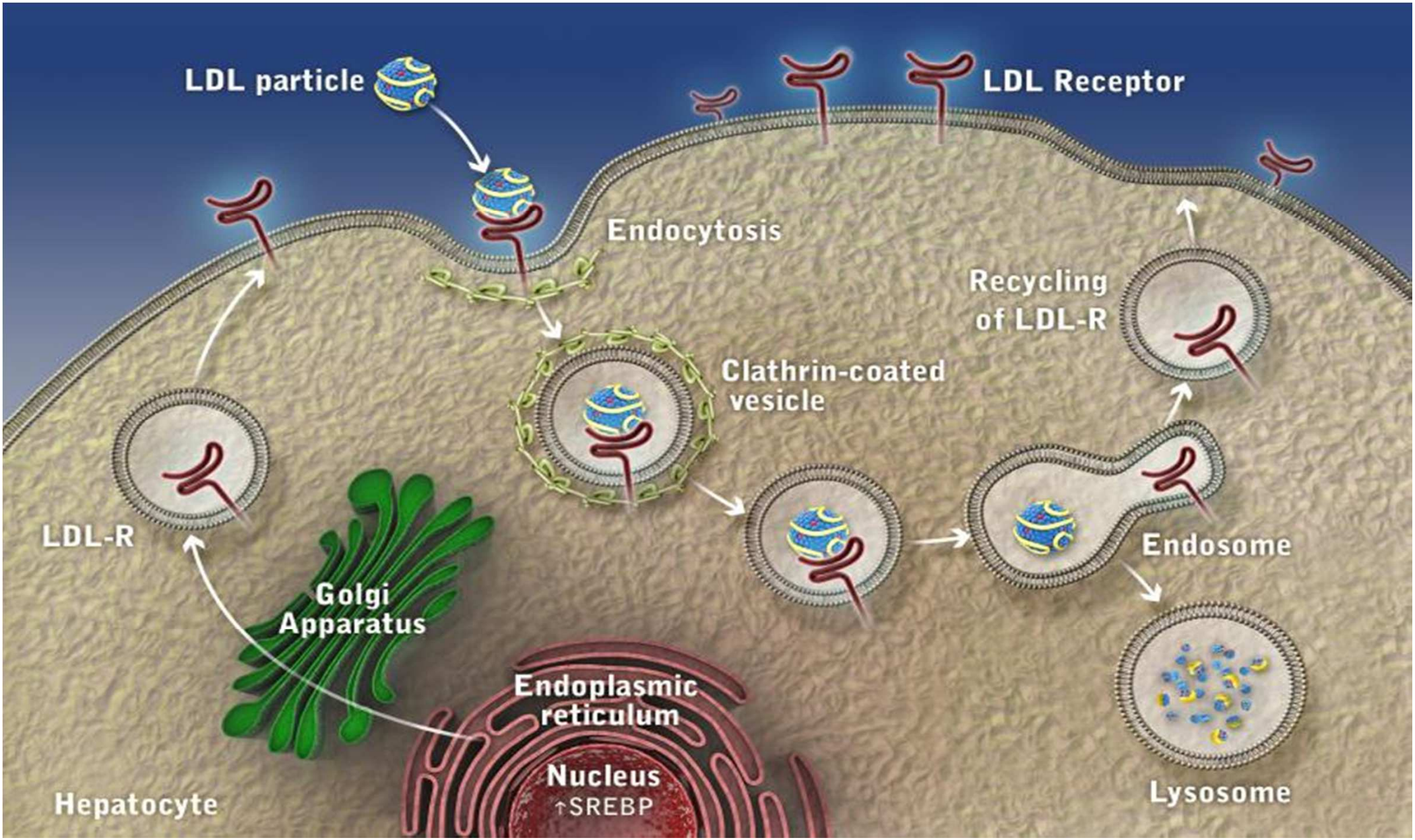

Phospho-
lipid
Unesterfied
cholesterol
Cholesteryl
ester
Polar
surface
Apolar
core
Apolipoprotein B
LDL

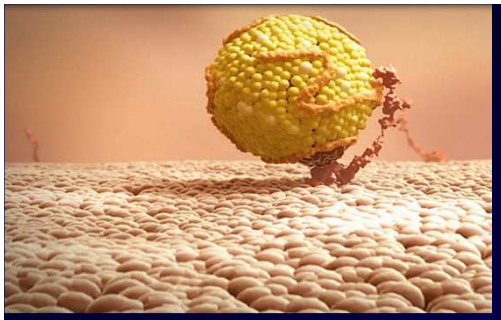


LDL receptor: a membrane-bound 160-kD Pr. of 839 AAs

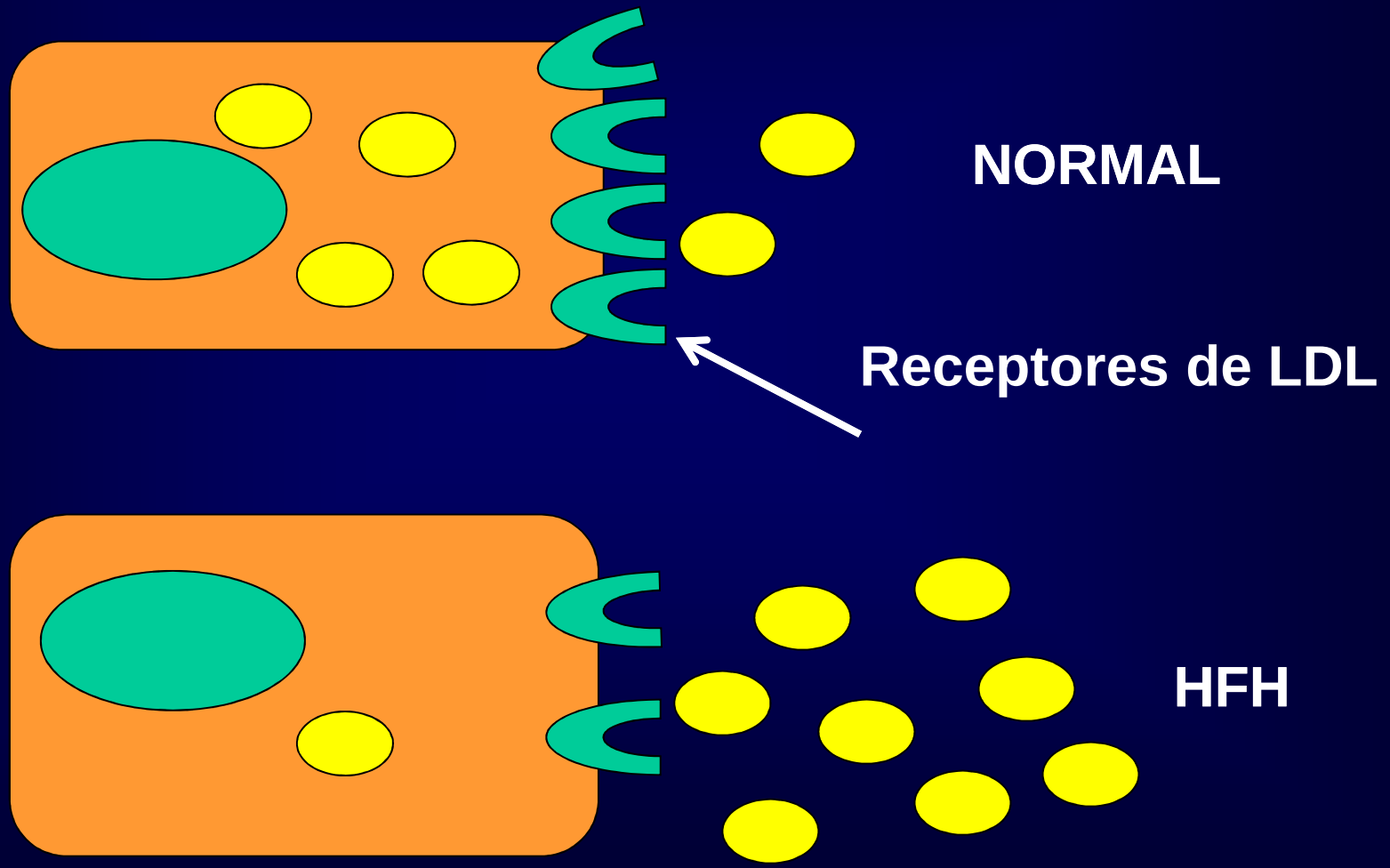


Función y reciclado del receptor de LDL

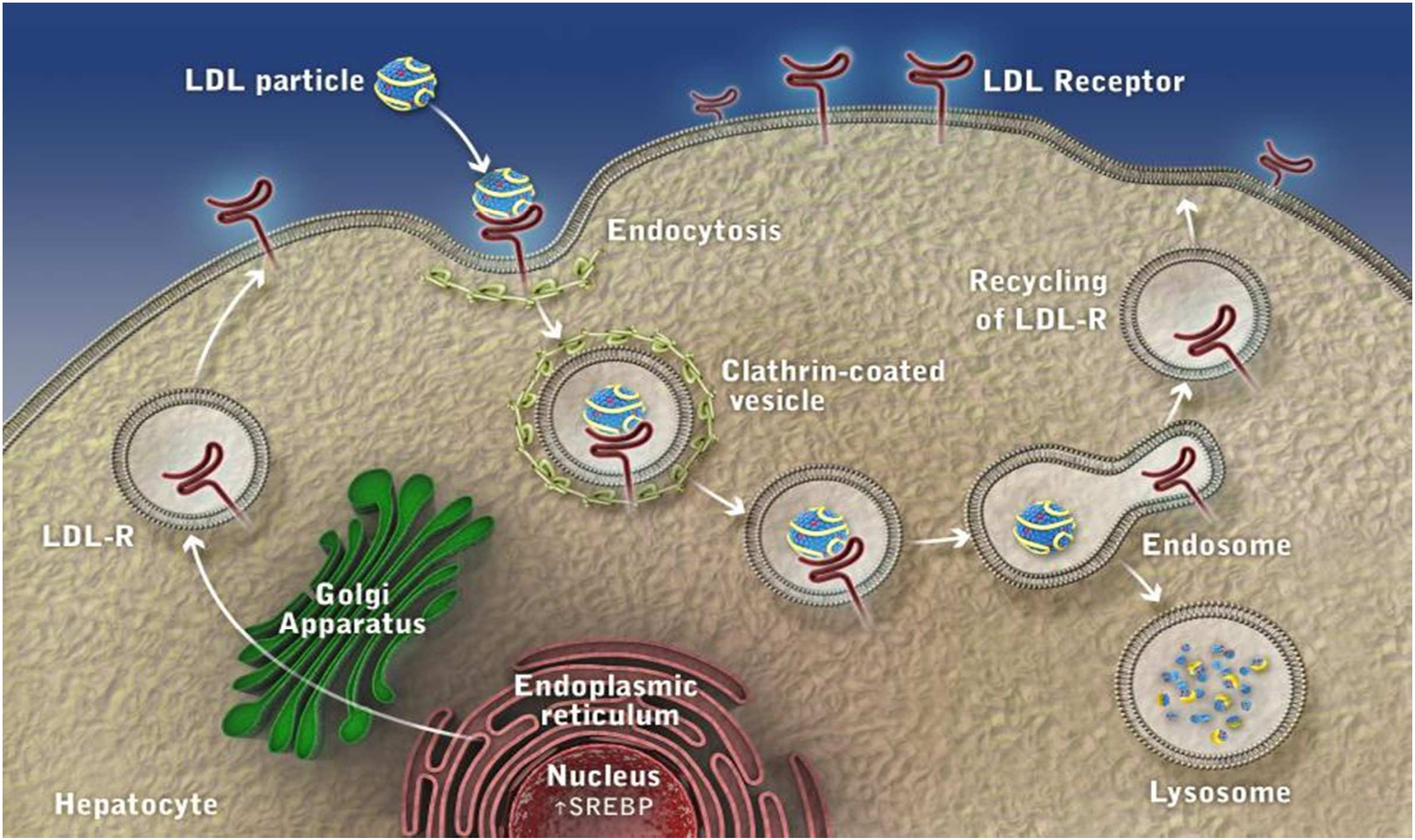


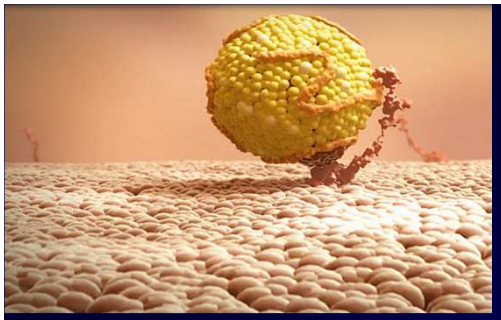


Hipercolesterolemia Familiar: Defecto del r-LDL

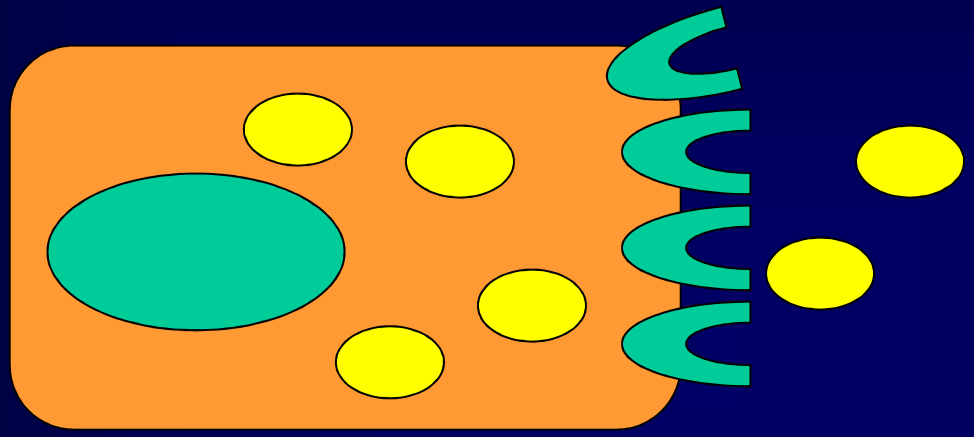


Función y reciclado del receptor de LDL

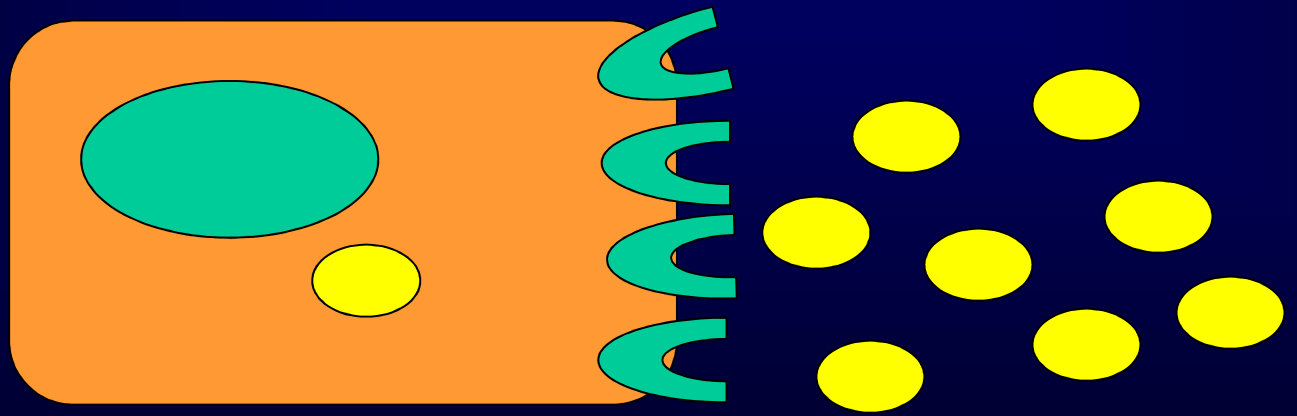




Hipercolesterolemia Familiar: Defecto de apoB



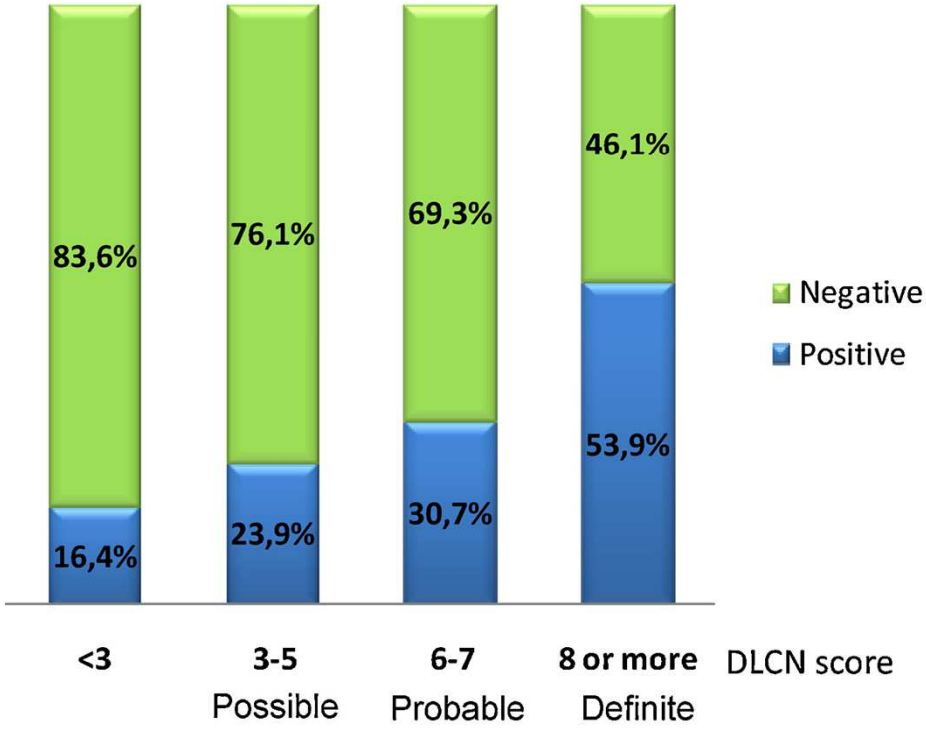
NORMAL



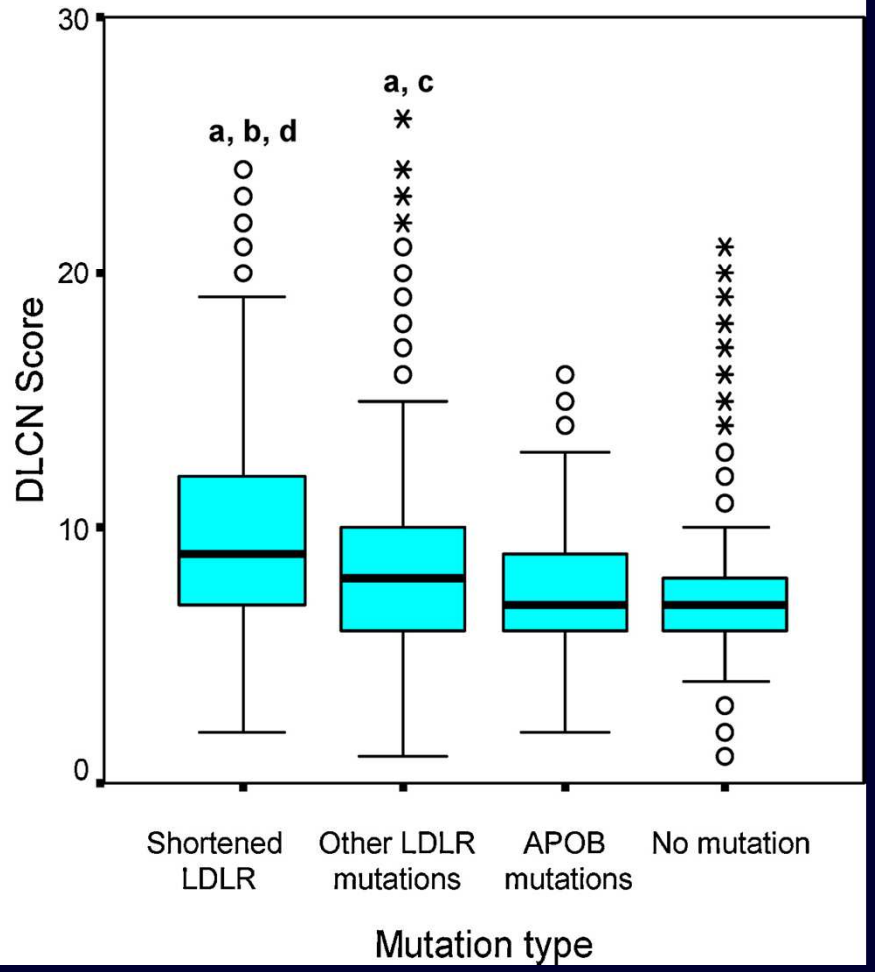
HFH

Prevalencia de mutaciones reconocidas en relación a la puntuación MedPed

A. Percentage of index cases were a mutation was found (positive cases), classified by DLCN score.



B. Comparison of the DLCN score by mutation type.



L Palacios et al. Atherosclerosis 2012; 221: 137-42.

Brief Communication

Nature Genetics **34**, 154 - 156 (2003)
Published online: 5 May 2003 | doi:10.1038/ng11

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4],

March 2004, Volume 114, Issue 4, pp 349-353

A mutation in *PCSK9* causing autosomal -dominant hypercholesterolemia in a Utah pedigree

Kirsten M. Timms, Susanne Wagner, Mark E. Samuels, Kristian Forbey, Howard Goldfine, Srikanth

Mutations in the *PCSK9* gene in Norwegian subjects with autosomal dominant hypercholesterolemia

TP Leren*

Article first published online: 17 MAR 2004

DOI: 10.1111/j.0009-9163.2004.0238.x

Issue

Clinical Genetics

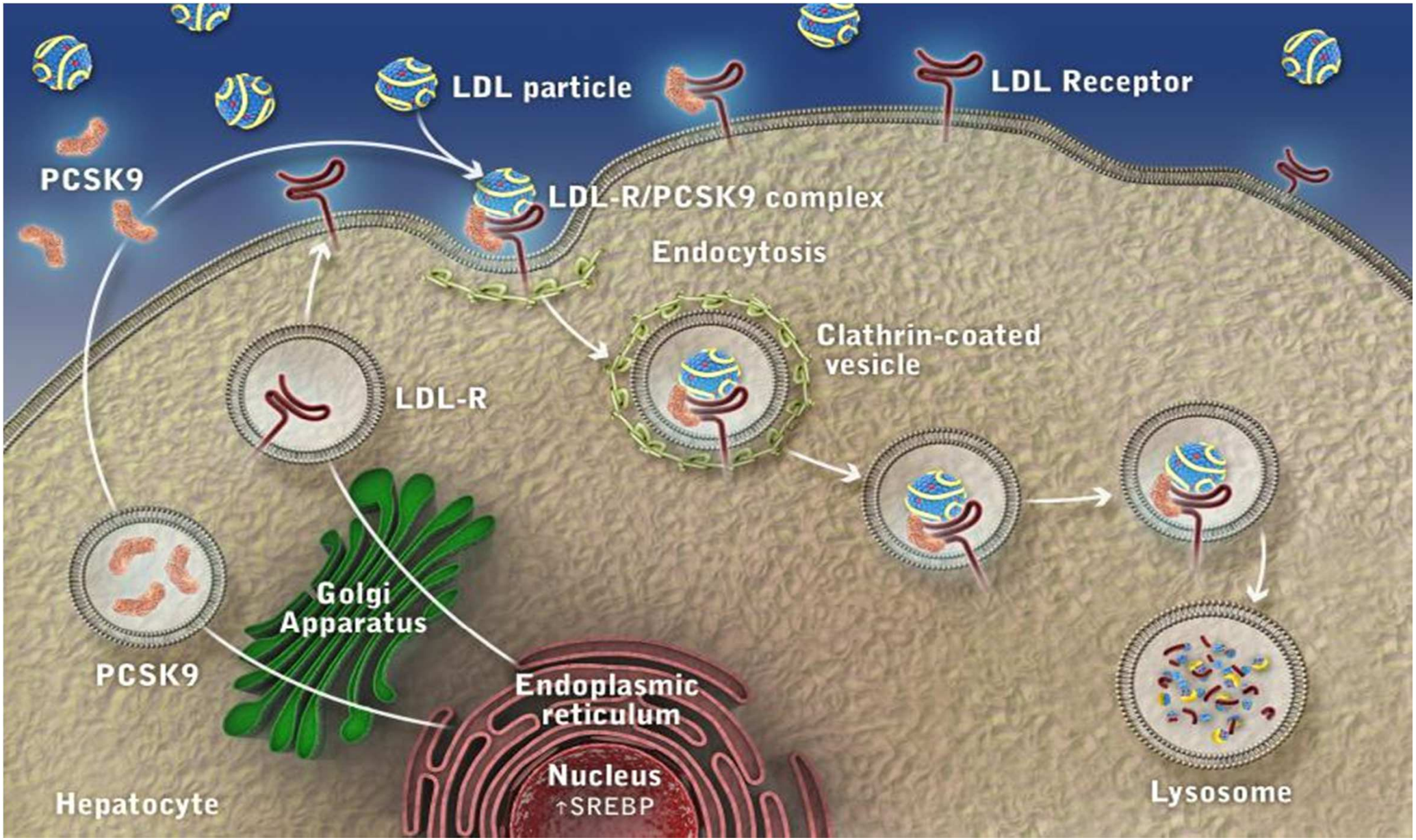
Volume 65, Issue 5, pages 419-422, May 2004

Mutaciones en PCSK9 que suponen un incremento de función (mutaciones de ganancia) y causan hipercolesterolemia autosómica dominante

Variante de PCSK9	Población	Características clínicas
D374Y	Familias británicas y noruegas, 1 familia de Utah	Enfermedad cardíaca prematura Xantomas en tendones Hipercolesterolemia severa
S127R	Familias francesas, sur africanas y noruegas	Xantomas en tendones; enfermedad cardiaca, IM temprano e ictus
R215H	Familia Noruega	Fallecimiento de un miembro a los 31 años por IM; historia familiar de enfermedad cardiovascular

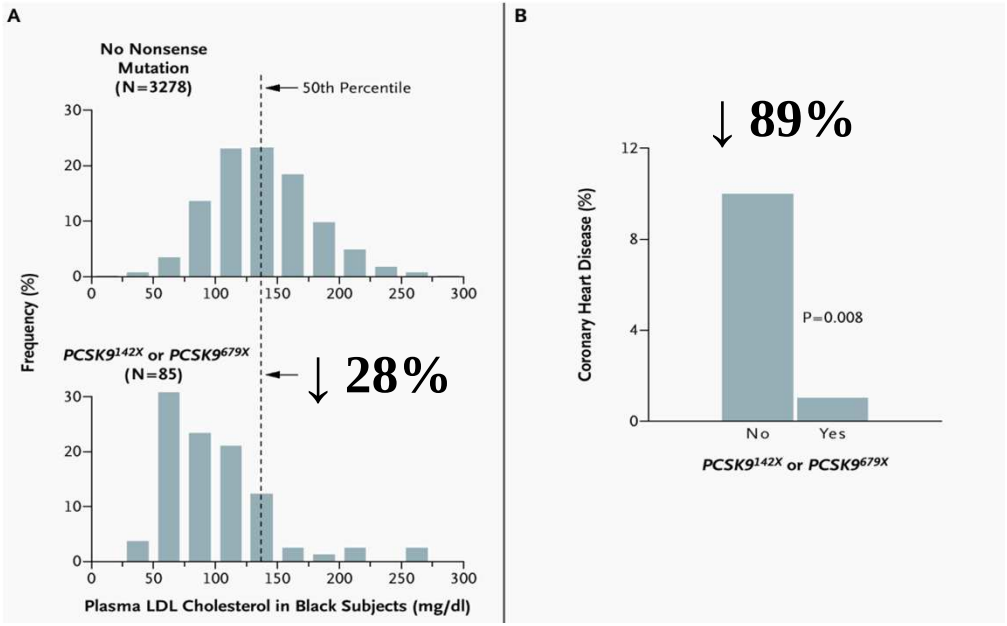
1. Abifadel M, et al. *Hum Gen*. 2009;30:520-529.
2. Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177.
3. Cameron J, et al. *Hum Mol Genet.* 2006;15:1551-1558.

Regulación del receptor de LDL por la PCSK9

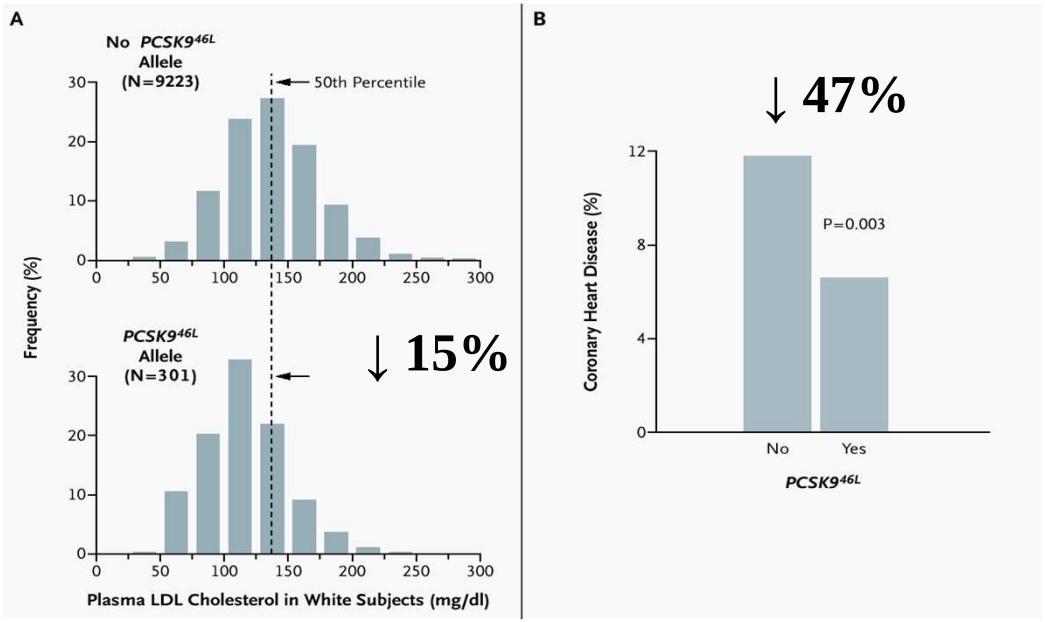


Distribución de colesterol-LDL e incidencia de enfermedad coronaria en función de la presencia o ausencia de mutaciones en el gen PCSK9 142X o PCSK9 679X

Población negra

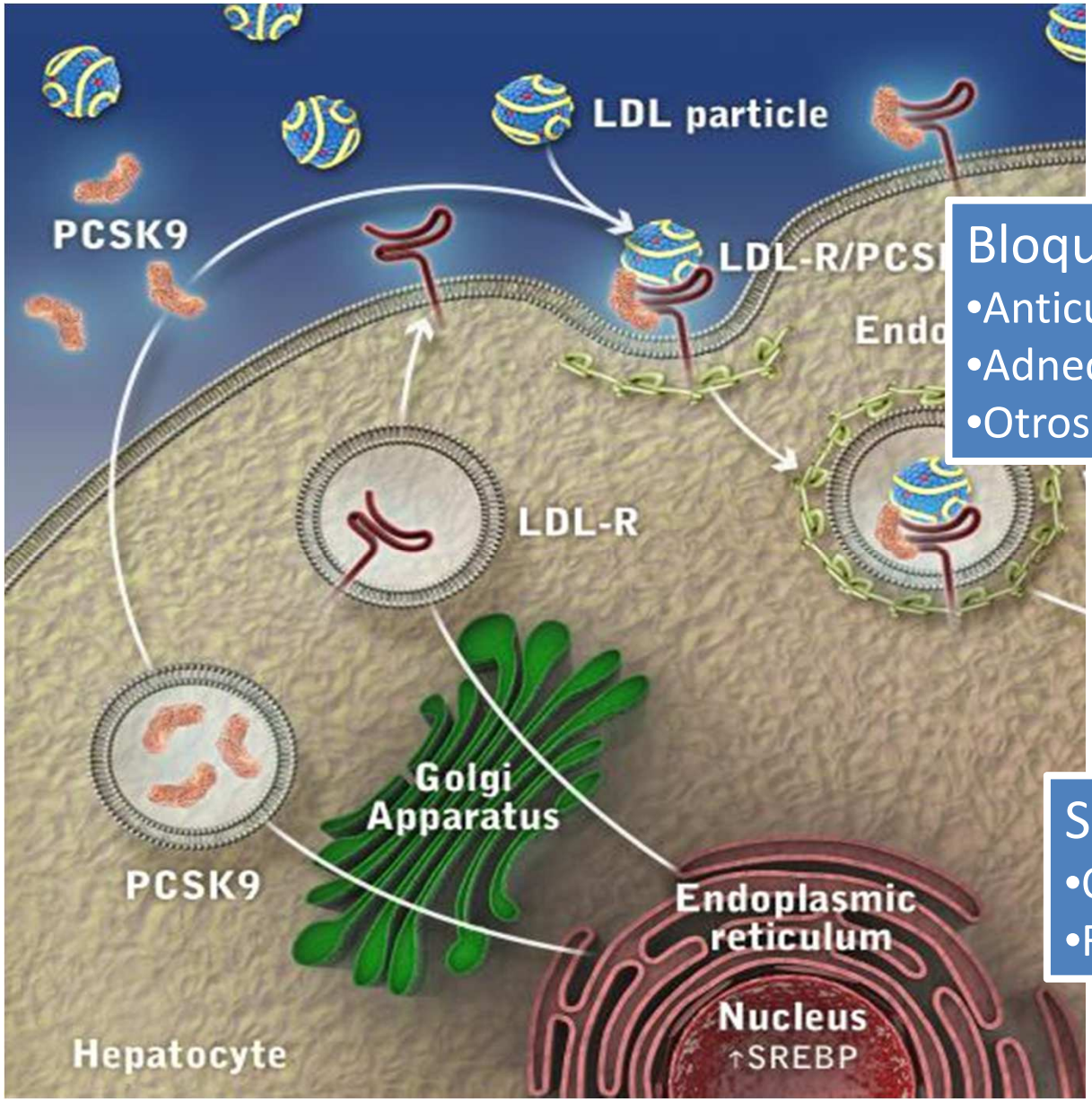


Población blanca



Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72

Lugares teóricos de inhibición de PCSK-9



Bloquear su unión al receptor:

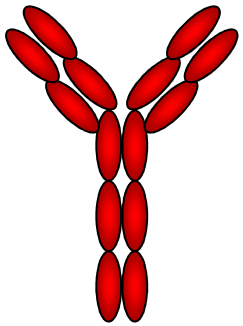
- Anticuerpos monoclonales
- Adnectinas
- Otros

Silenciar la síntesis:

- Oligonucleótidos antisentido
- RNA de interferencia

Anticuerpos monoclonales: Evolución

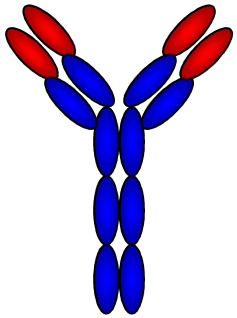
mouse mAb



- mouse variable
- mouse constant
- no repeated dosing

Quiméricos

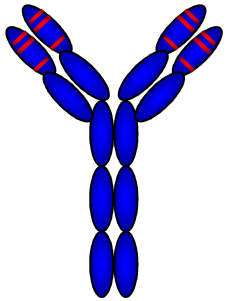
Rituximab
cetuximab



- all mouse variable
- human constant
- time-consuming to create

Humanizados

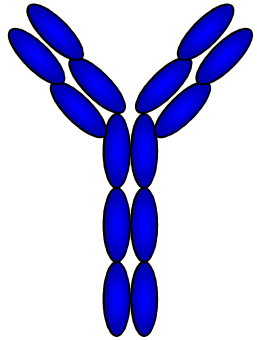
Trastuzumab
evacizumab



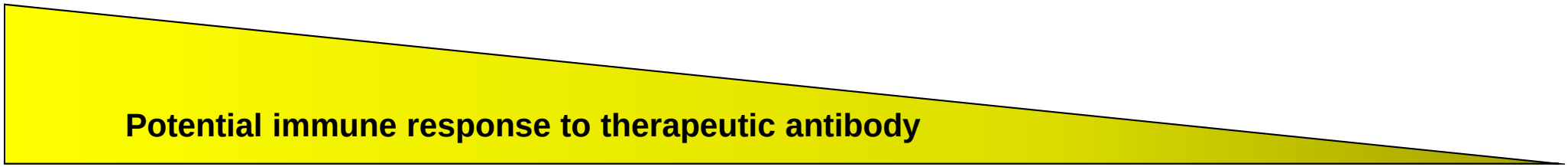
- part mouse variable
- human constant
- time-consuming to create

Humanos

Adalimumab
panitumumab



- human variable
- human constant
- repeated dosing possible



Déficit completo de PCSK-9

- Mujer de xx años