"FARMACI INNOVATIVI, BIOTECNOLOGICI E TERAPIE STAMINALI: FARMACOLOGIA, FARMACOTERAPIA E NORMATIVE"

Roma, 14 aprile 2015

Appropriatezza ed innovazione: le sfide della ricerca

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ELENCO FARMACI INNOVATIVI
Data aggiornamento: luglio 2014

PRINCIPI ATTIVI CLASSIFICATI IN FASCIA A

ATC4	PRINCIPIO ATTIVO	CLASSE	INNOVATIVITÀ	DATA DECISIONE CTS	DATA G.U.*	DATA SCADENZA**
L04AA	FINGOLIMOD	A	POTENZIALE	30/05/11	07/12/2011	06/12/2014

PRINCIPI ATTIVI CLASSIFICATI IN FASCIA H

ATC4	PRINCIPIO ATTIVO	CLASSE	INNOVATIVITÀ	DATA DECISIONE CTS	DATA G.U.*	DATA SCADENZA**
L03AX	plerixafor	H	POTENZIALE	03/05/2011	09/12/2011	08/12/2014
L01XC	ipilimumab	H	IMPORTANTE	30/10/2012	09/03/2013	08/03/2016
L02BX	abiraterone	H	POTENZIALE	15/11/2012	06/04/2013	05/04/2016
M09AB	collagenasi di clostridium histolyticum	H	POTENZIALE	06/03/2013	14/03/2013	13/03/2016
L01XC	brentuximab vedotin	H	POTENZIALE	02/12/2013	08/07/2014	07/07/2017
L01XC	pertuzumab	H	IMPORTANTE	02/12/2013	08/07/2014	07/07/2017

APPROPRIATEZZA

- ✓ note AIFA
- ✓ registri
- ✓ linee guida

INNOVAZIONE

- ✓ oncologia
- ✓ epatite
- ✓ …… ipercolesterolemia

Farmaci innovativi in ambito cardiovascolare

STATINE	Prevenzione primaria Prevenzione secondaria Sono considerate la terapia di prima scelta ma un significativo rischio residuo rimane anche dopo
STATINE + EZETIMIBE	Doppia inibizione a livello epatico ed intestinale
PCSK9	Per i pazienti che necessitano di una ulteriore riduzione di LDL-C

Evolocumab

(anticorpo monoclonale completamente umano anti-PCSK9)

nella riduzione del LDL-C e del rischio di malattie cardiovascolari

1953 1961-1965 1973 1975 1977 1982 1983 1998 2000+

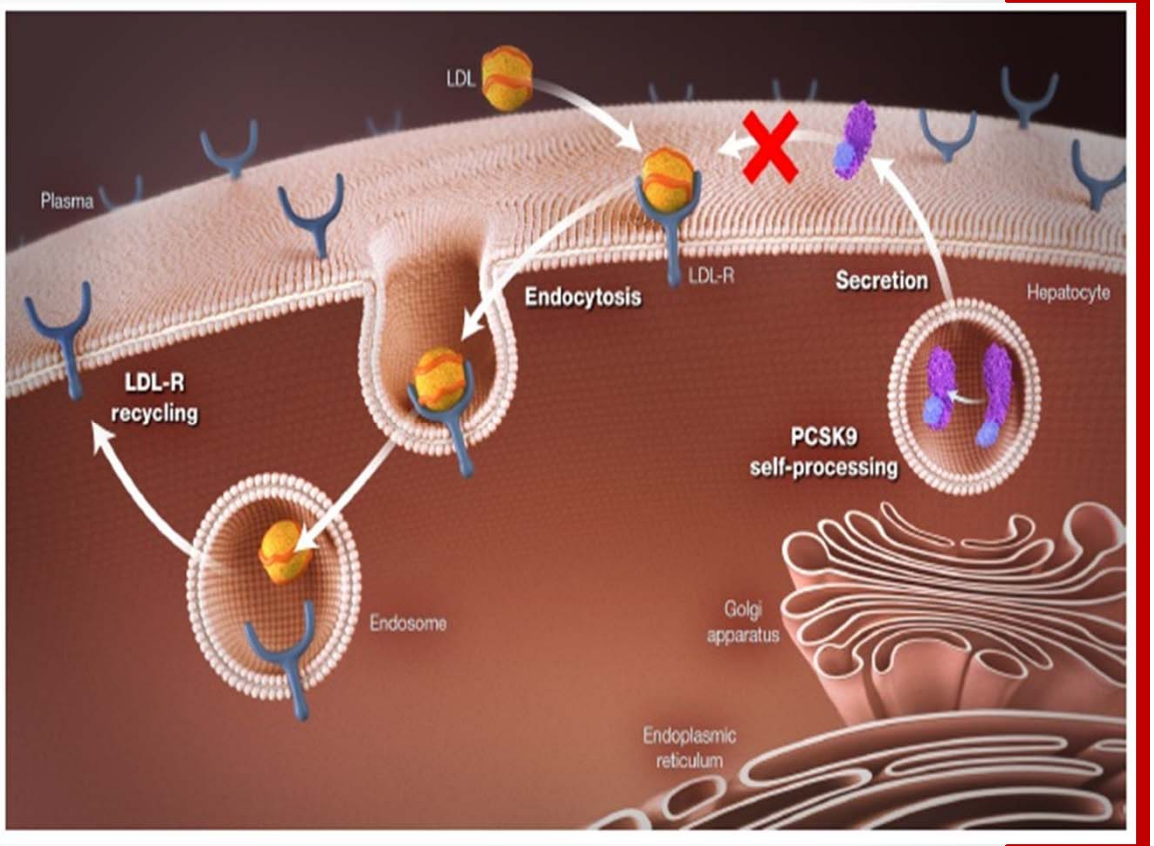
Proprotein Convertase Subtilisin-like/kexin Type 9 (PCSK9)

Evolocumab

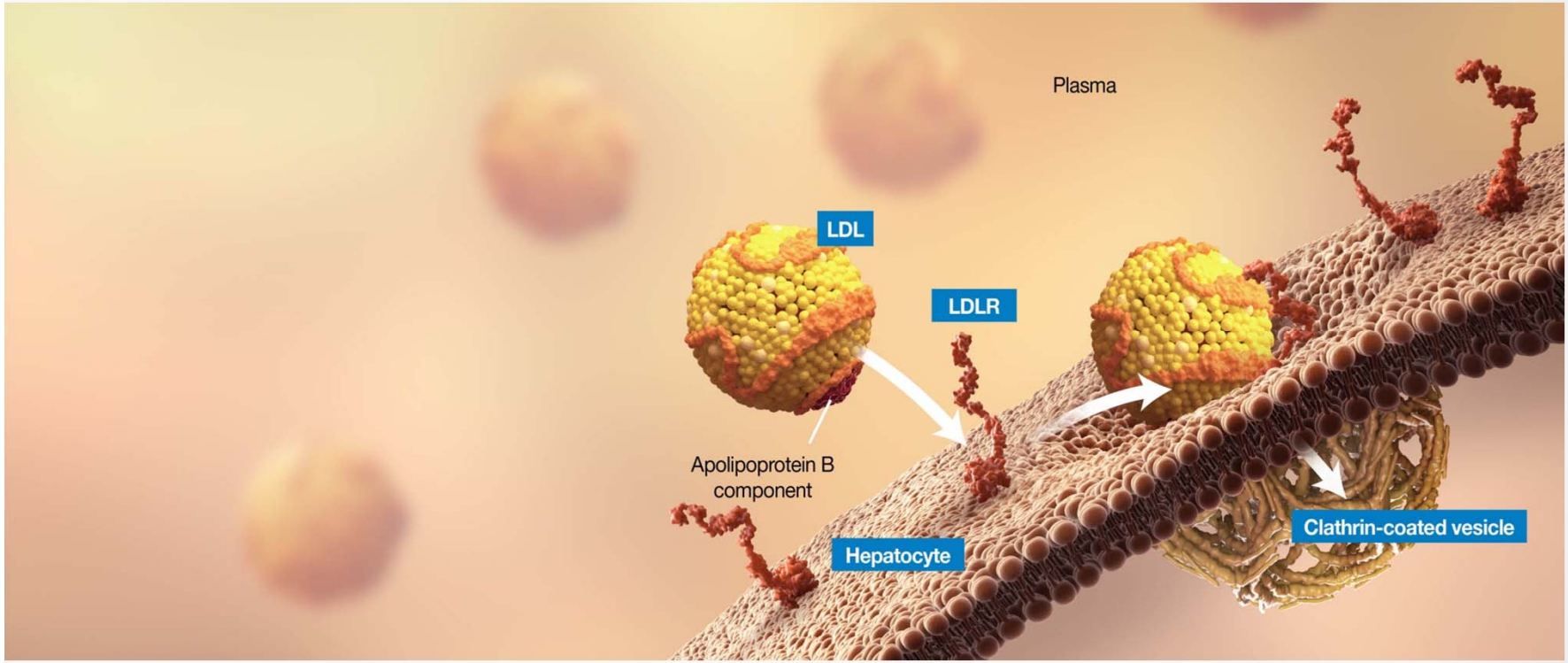
E’ un anticorpo totalmente umano che inibisce la Proproteina convertasi subtilisina/kexina di tipo 9, una proproteina che riduce la capacità del fegato di rimuovere il colesterolo LDL dal sangue

Quando al legame tra Ldl e recettore si aggiunge anche il legame della PCSK9 si ha la degradazione a livello lisosomiale anche del recettore che dunque non è più disponibile sulla superficie cellulare

Inibendo l’attività del PCSK9 si riduce il colesterolo LDL in quanto aumenta l’espressione dei recettori Ldl

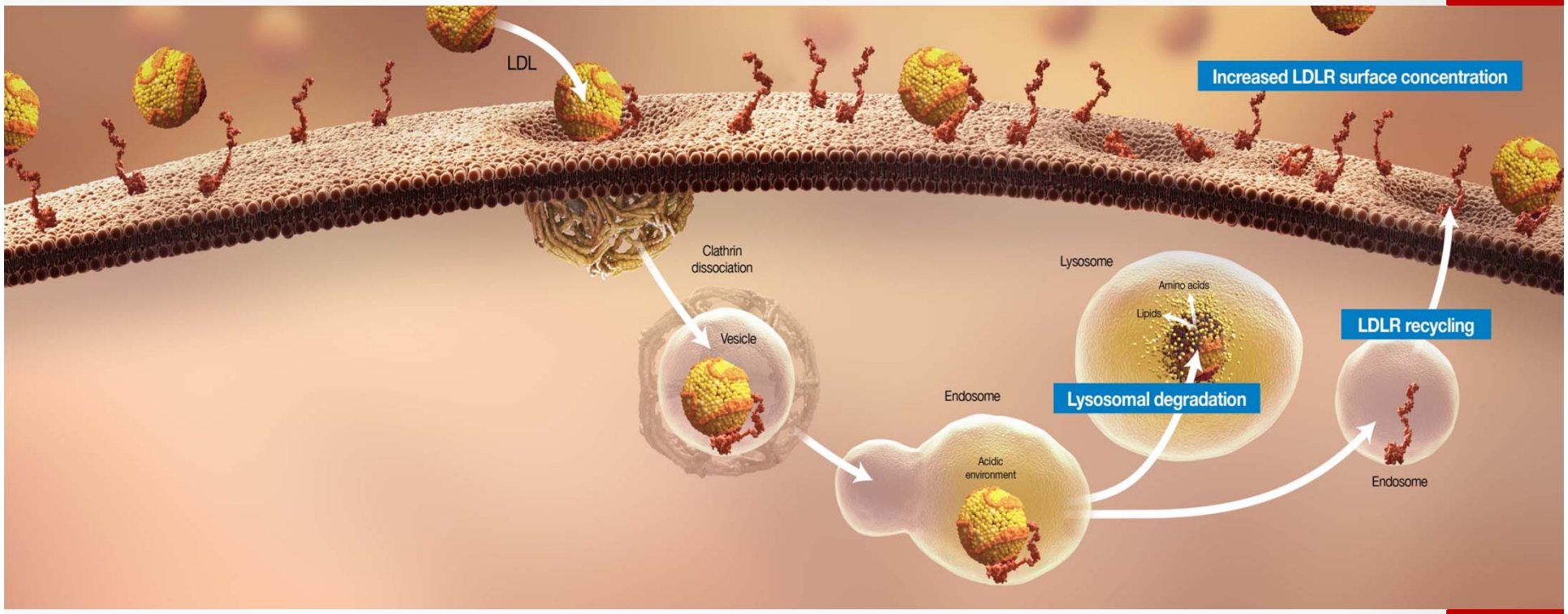


Hepatic LDLRs Play a Central Role in Cholesterol Homeostasis



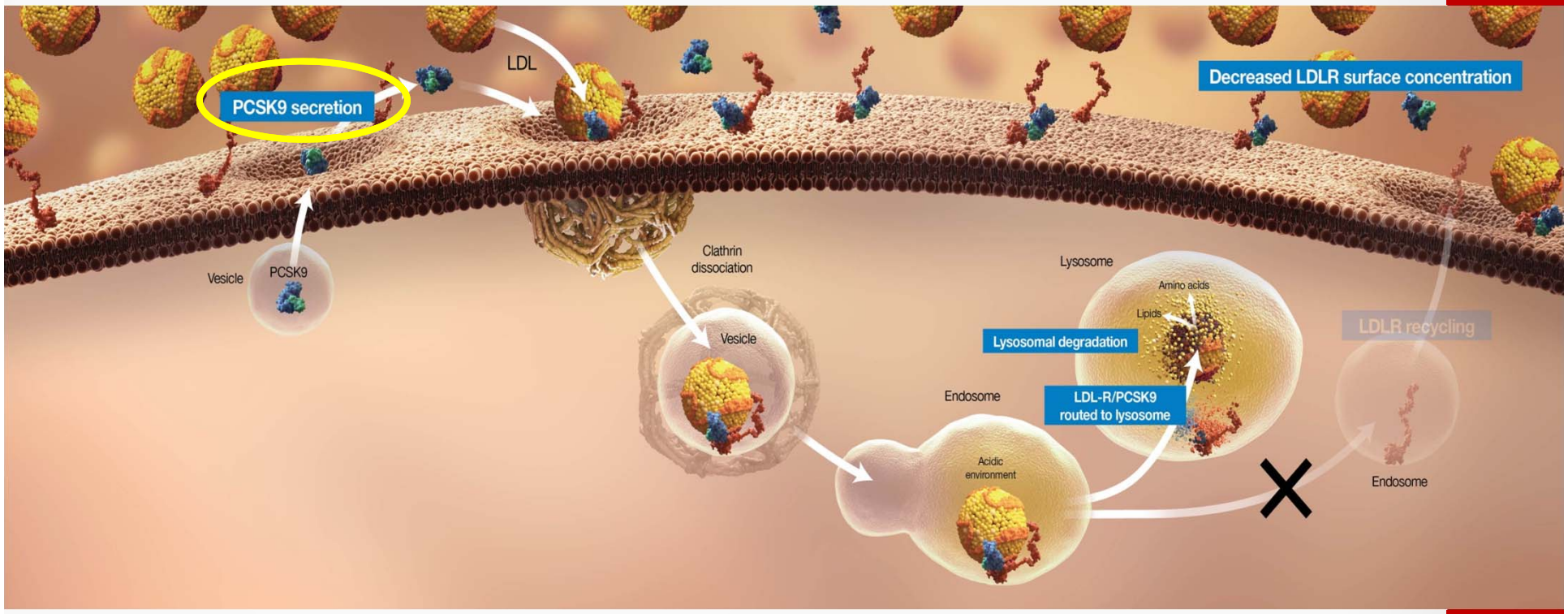
Elaborated from 1. Brown MS, et al. *Proc Natl Acad Sci* 1979;76:3330-3337.
Elaborated from 2. Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
Elaborated from 3. Steinberg D, et al. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.

Recycling of LDLRs Enables Efficient Clearance of LDL-C Particles



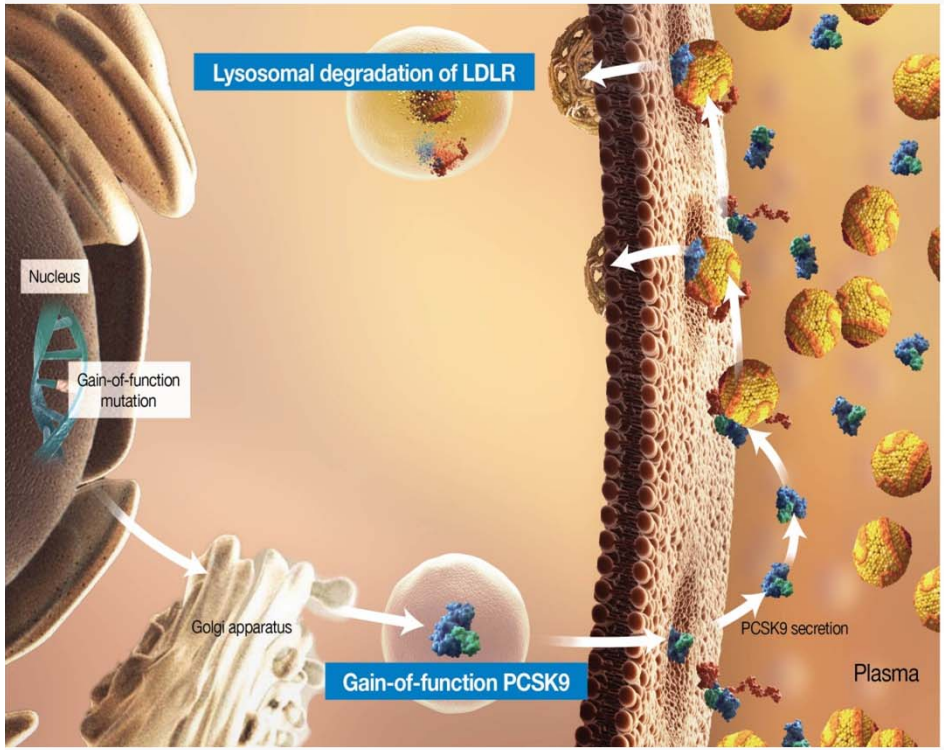
Elaborated from 1. Brown MS, et al. *Proc Natl Acad Sci U S A*. 1979;76:3330-3337.
Elaborated from 2. Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.
Elaborated from 3. Goldstein JL, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.

PCSK9 Regulates the Surface Expression of LDLRs by Targeting for Lysosomal Degradation

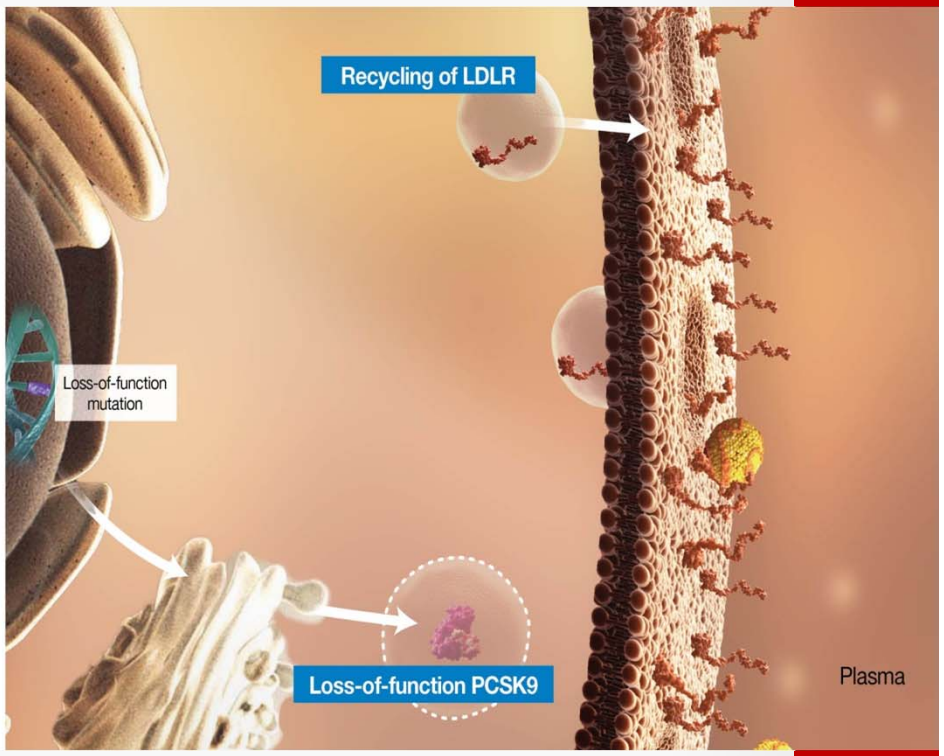


Elaborated from 1. Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
Elaborated from 2. Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177.
Elaborated from 3. Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels

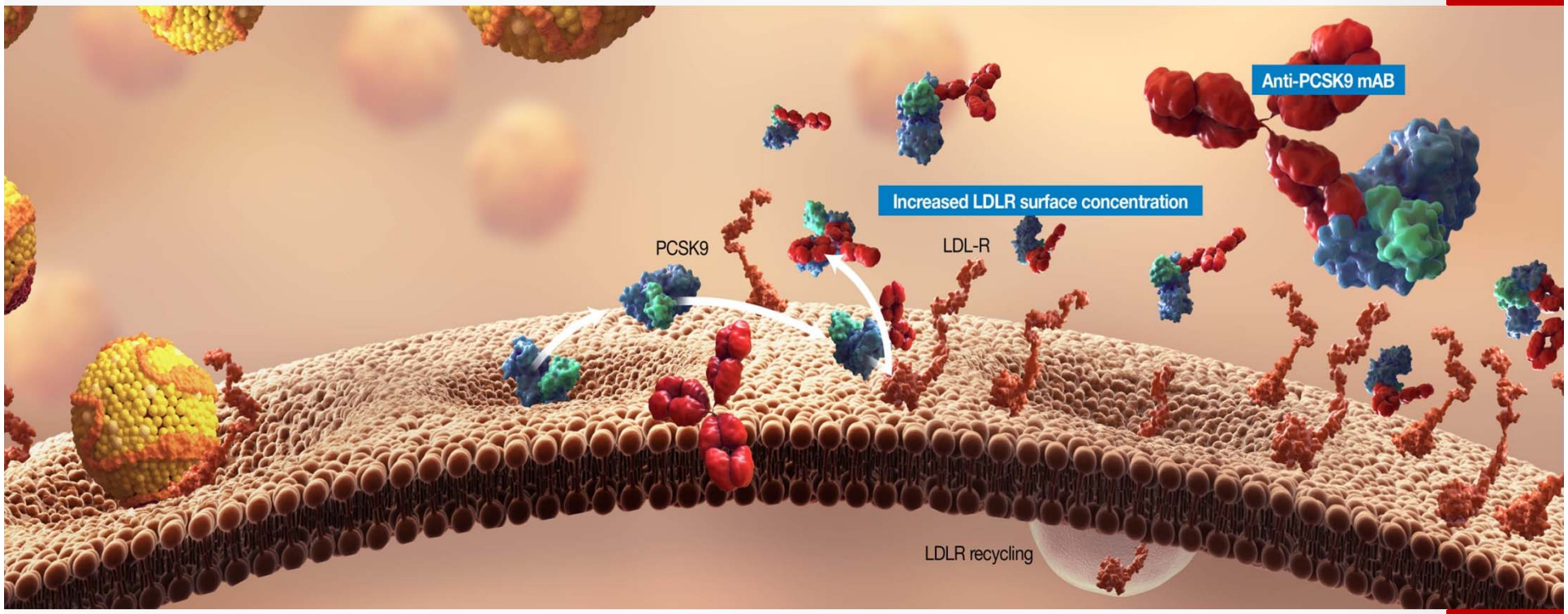


PCSK9 Gain of Function = Less LDLRs



PCSK9 Loss of Function = More LDLRs

Blockade of PCSK9/LDLR Interaction May Lower LDL Levels



Elaborated from 1. Chan JC, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825.

PROFICIO

Program to

Reduce LDL-C and Cardiovascular

Outcomes

Following

Inhibition of

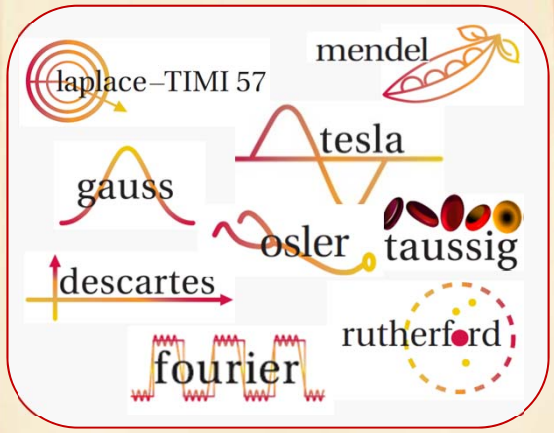
P***C***SK9

In Different

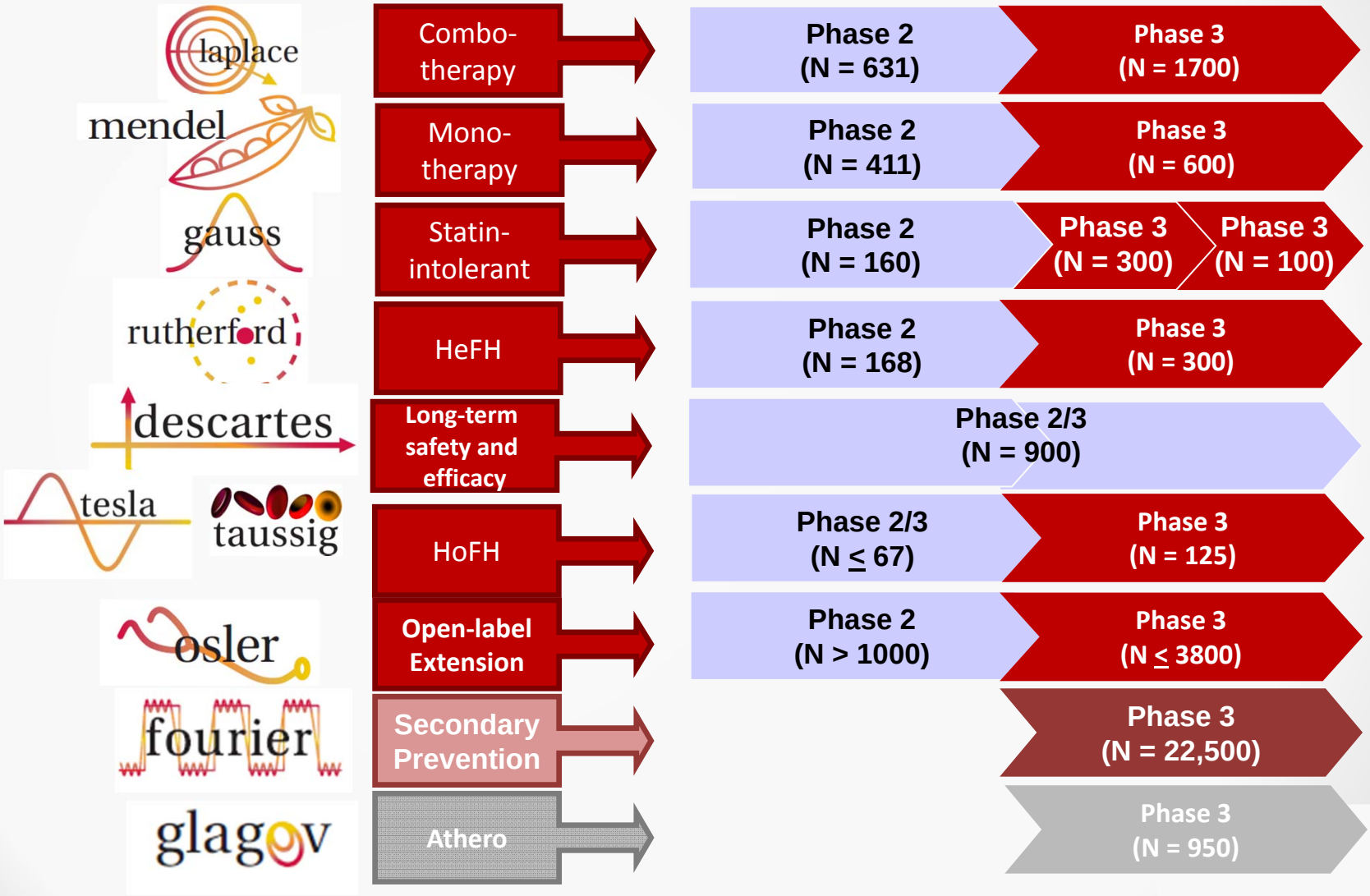
P***o***pulations

(Latin):

- *To advance*
- *To make progress*



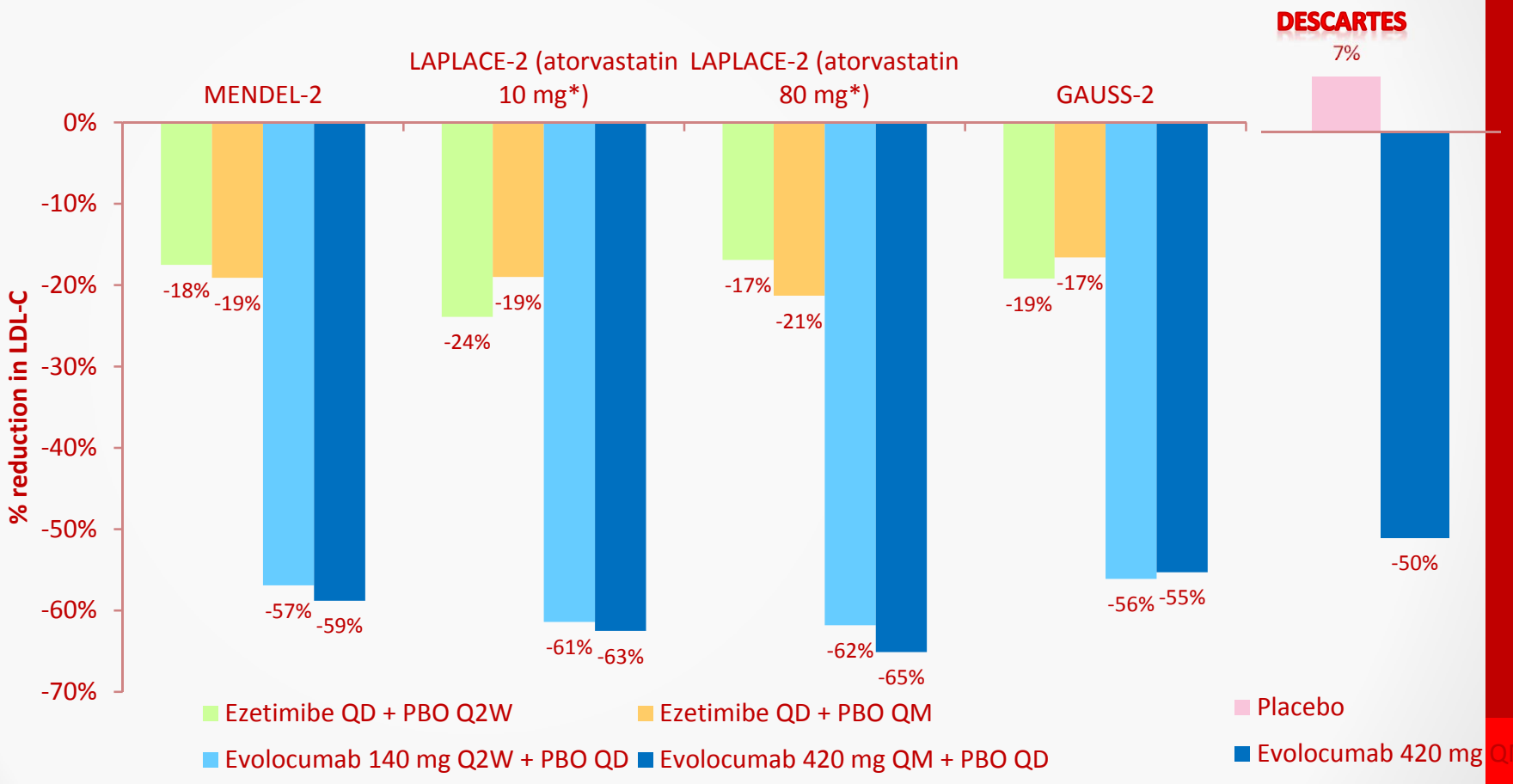
….10 studi clinici di fase III



Overview - AMG 145 Phase 3 Studies

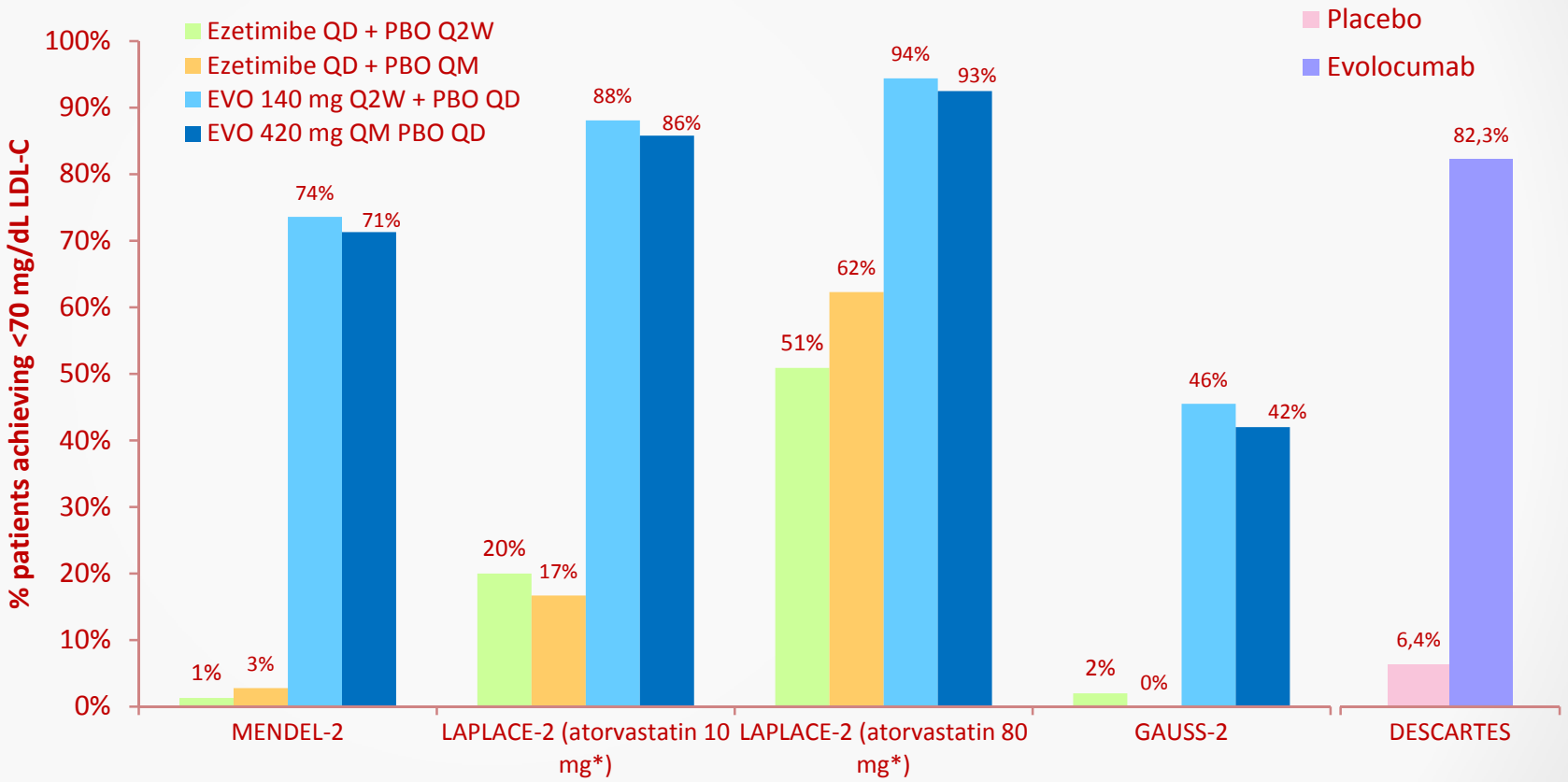
Study	M mendel	Combo laplace–TIMI 57	He ruthferford)	Statin-int gauss	Outcome fourier	HoF tesla 3)
Acronym						
N	600	1700	300	300 + 100	22500	57-67
Background lipid lowering therapy	None	One of 3 statins at various doses	Statin +/- all allowed LLT (stable)	No statin or low dose statin	Atorvastatin ± ezetimibe	Statin +/- ezetimibe
Treatment Duration	12 wks	12 wks	12 wks	12 wks	~ 5 years	• Part A 12 wks • Part B 12 wks
Comparator(s)	• Q2W: placebo • QM: placebo • ezetimibe	• Q2W: placebo • QM: placebo • ± ezetimibe	• Q2W: placebo • QM: placebo	• Ezetimibe	• Q2W: placebo • QM: placebo	• Part A: open-label • Part B: placebo Q4W
AMG 145 doses	• Q2W: 140mg • QM : 420mg	• Q2W : 140mg • QM : 420mg	• Q2W: 140mg • QM: 420mg	• Q2W: 140mg • Q4W: 420mg	• Q2W: 140mg • Q4W: 420mg	• QM: 420 mg
Follow-up	30d s/p osler	30d s/p osler	30d s/p last I taussig osler	30d s/p last I taussig osler	none	30d s/p l taussig
Extension options	138	138	110 or 271	110 or 271	NA	

Phase III Evolocumab Trial Summary – Reduction in LDL-C



*Only 2 statin dose groups are shown for the LAPLACE-2 study; these indicate the level of LDL-C reductions seen with moderate intensity (atorvastatin 10 mg) and high intensity (atorvastatin 80 mg) statin
Percentage reduction in LDL-C for each trial at mean of Week 10 and Week 12; DESCARTES reduction at Week 52.
LAPLACE-2 patients are grouped by moderate- or high-intensity statin combination therapy.

Phase III Evolocumab Trial Summary – LDL-C Goal Fulfilment

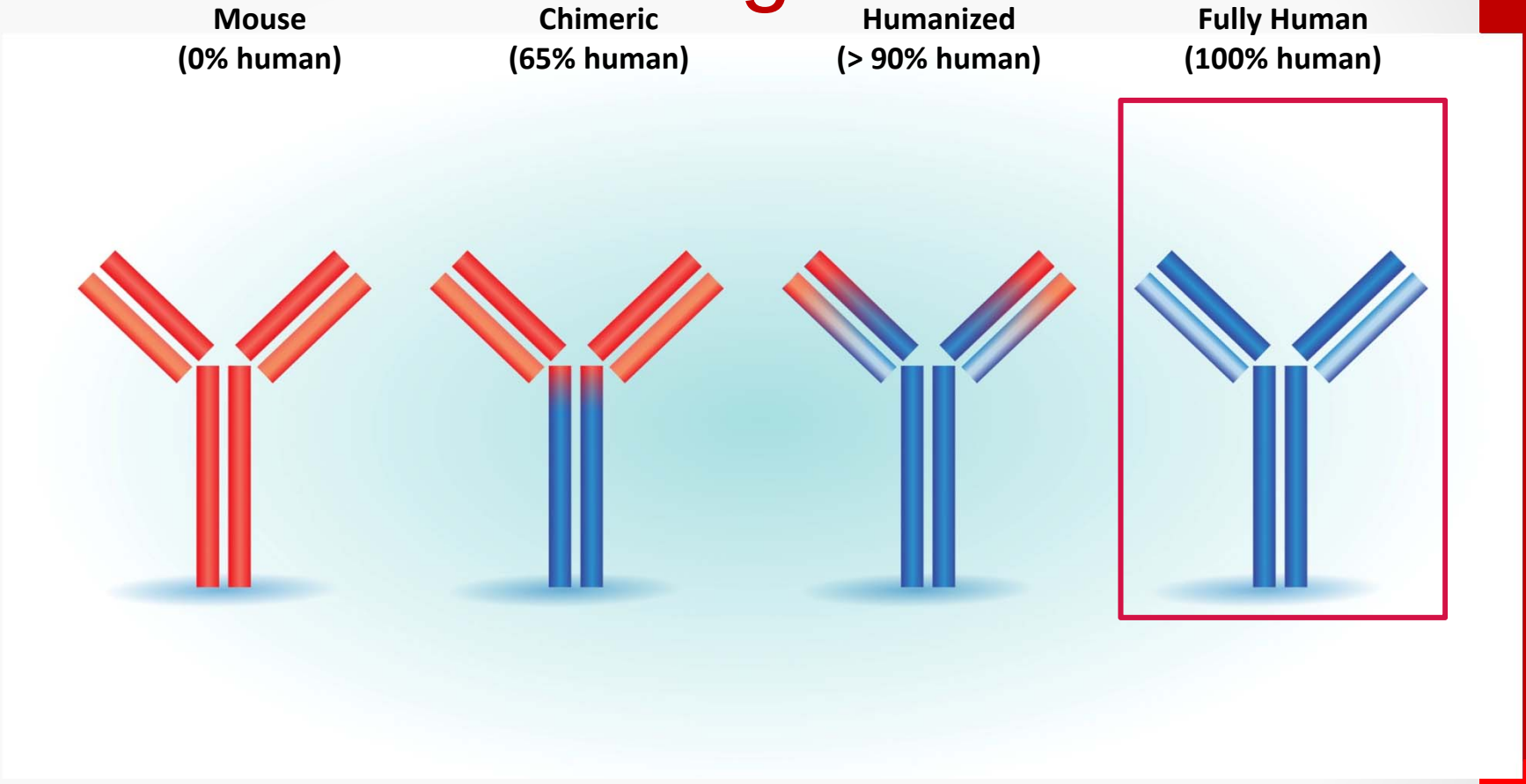


*Only 2 statin dose groups are shown for the LAPLACE-2 study; these indicate the level of LDL-C goal fulfilment seen with moderate intensity (atorvastatin 10 mg) and high intensity (atorvastatin 80 mg) statin

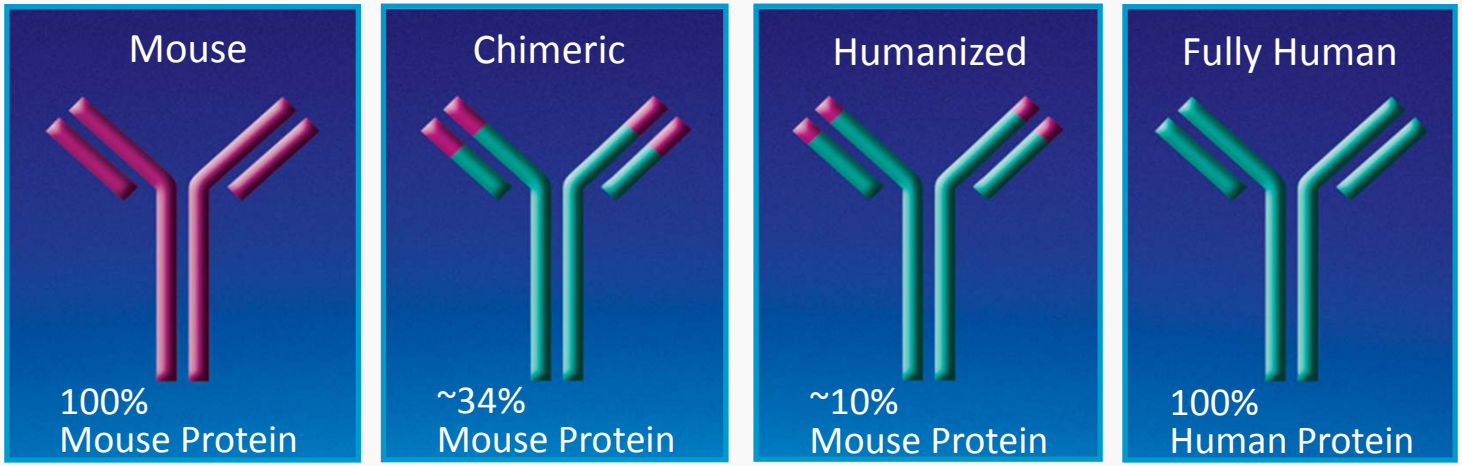
Percentage of patients achieving LDL-C treatment goal of <70 mg/dL at a mean of Weeks 10 and 12; DESCARTES patients at Week 52.

LAPLACE-2 patients are grouped by moderate- or high-intensity statin combination therapy

Sicurezza : Gli anticorpi umani riducono l'immunogenicità



Lo sviluppo degli anticorpi monoclonali



cetuximab
rituximab

bevacizumab

evolocumab
panitumumab

La sfida…….

- Abbiamo bisogno solo di più innovazione?
- Abbiamo bisogno solo di più ricerca?
- Abbiamo bisogno solo di più dati?

- ...o, più semplicemente di migliorare l'uso delle risorse per ricerca e innovazione e l'uso dei risultati?

Il cambiamento

Non e' la specie piu' intelligente a sopravvivere e nemmeno quella piu' forte. E' quella piu' predisposta ai cambiamenti

[Charles Darwin]