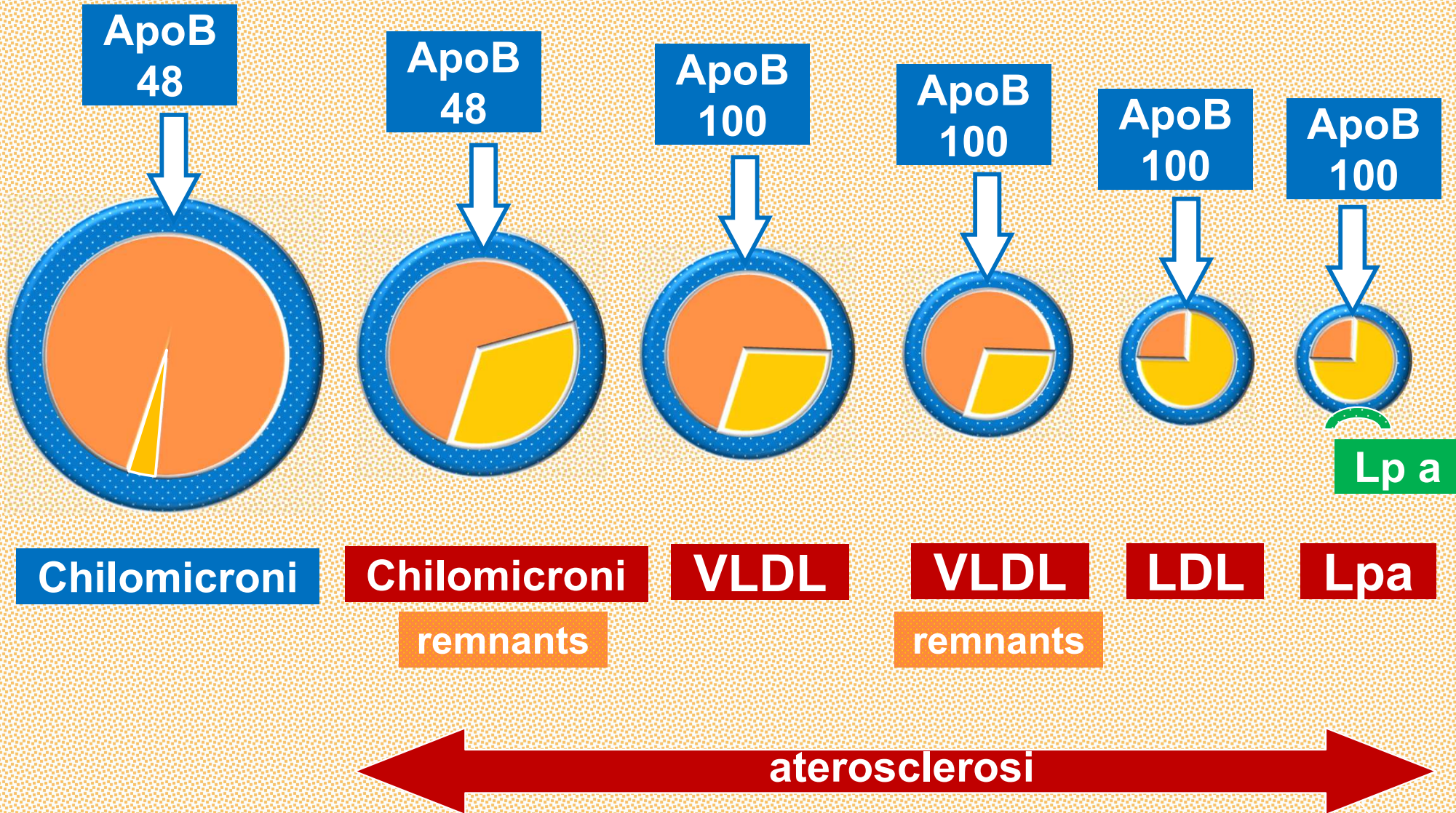


# TERAPIA GENICA

- la svolta innovativa nel controllo del metabolismo lipidico -

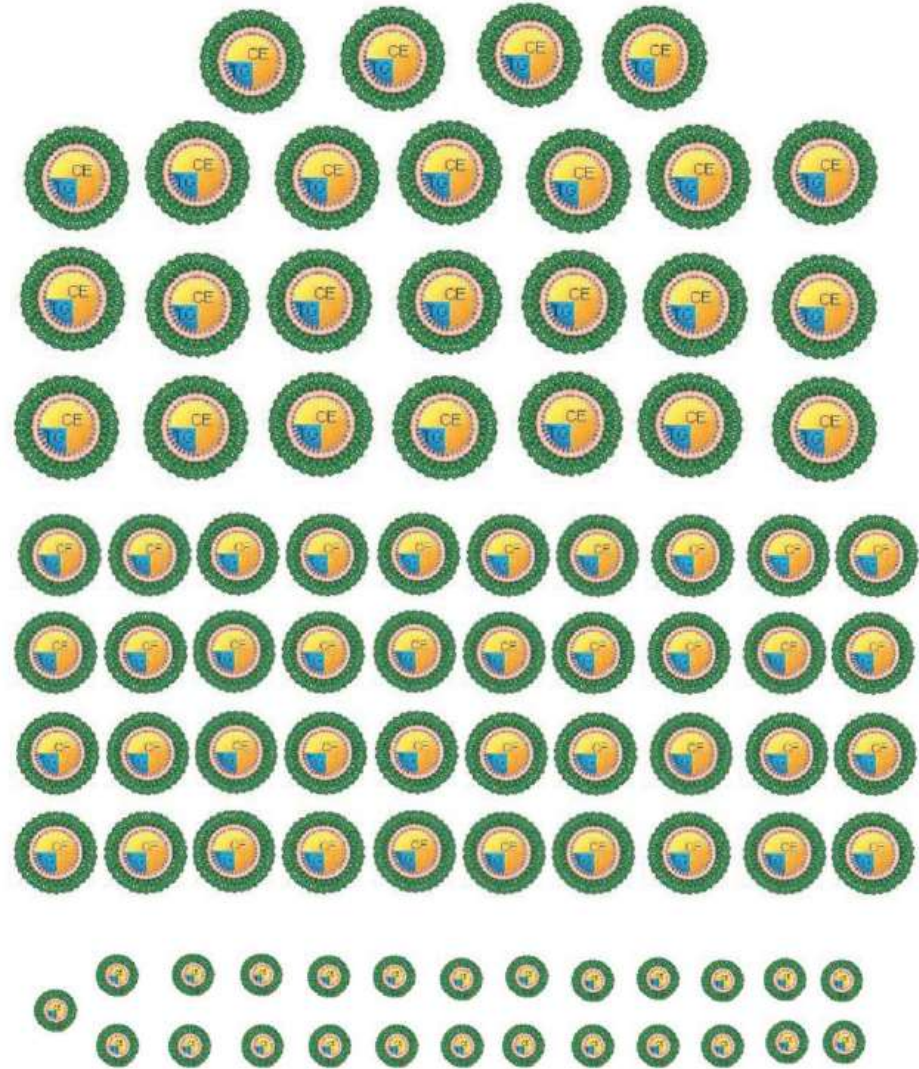
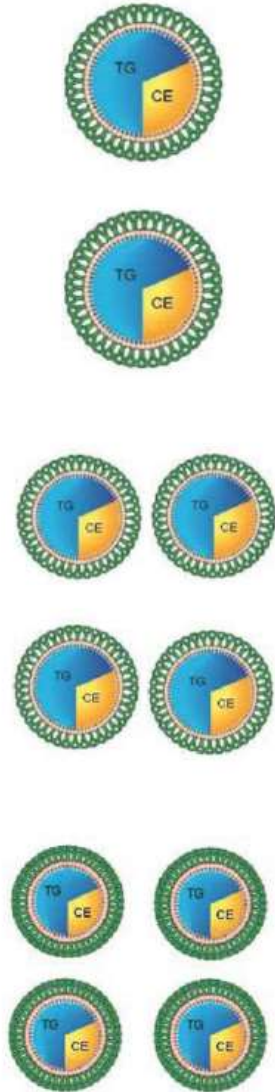
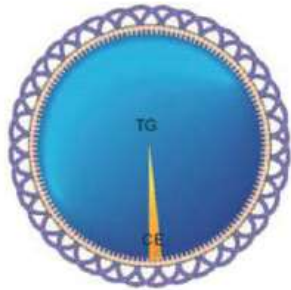
# Lipoproteine Plasmatiche



**VLDL**

**LDL**

**Chilomicroni / remnants**



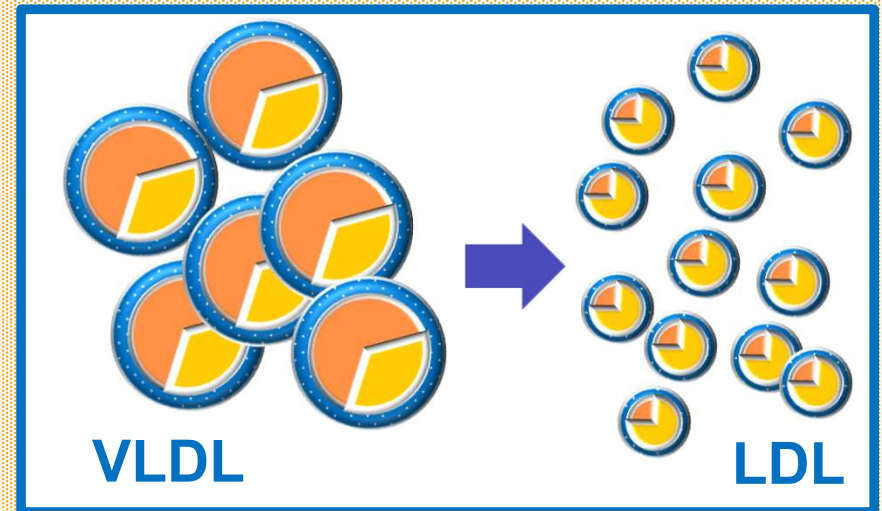
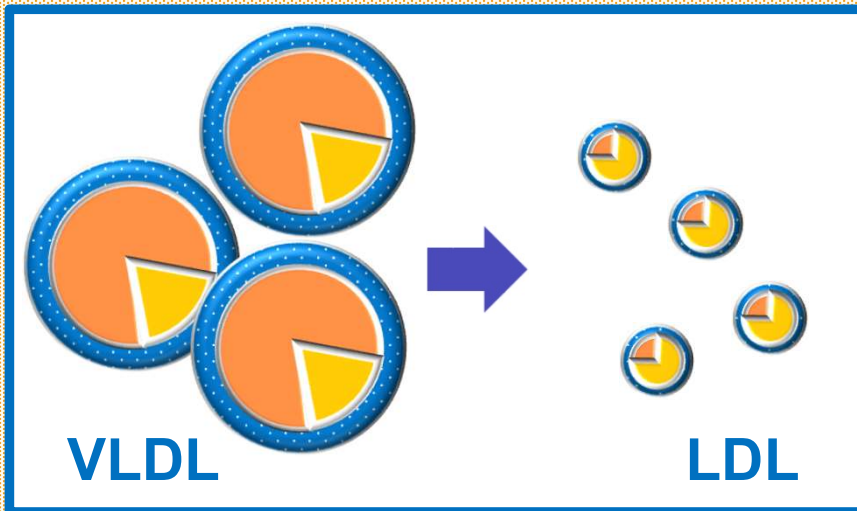
**LDL piccole dense**

**Trigliceridi  
> 250 mg/dl**



**Iper TGL poligenica**

**Iperlipemia fam. combinata**



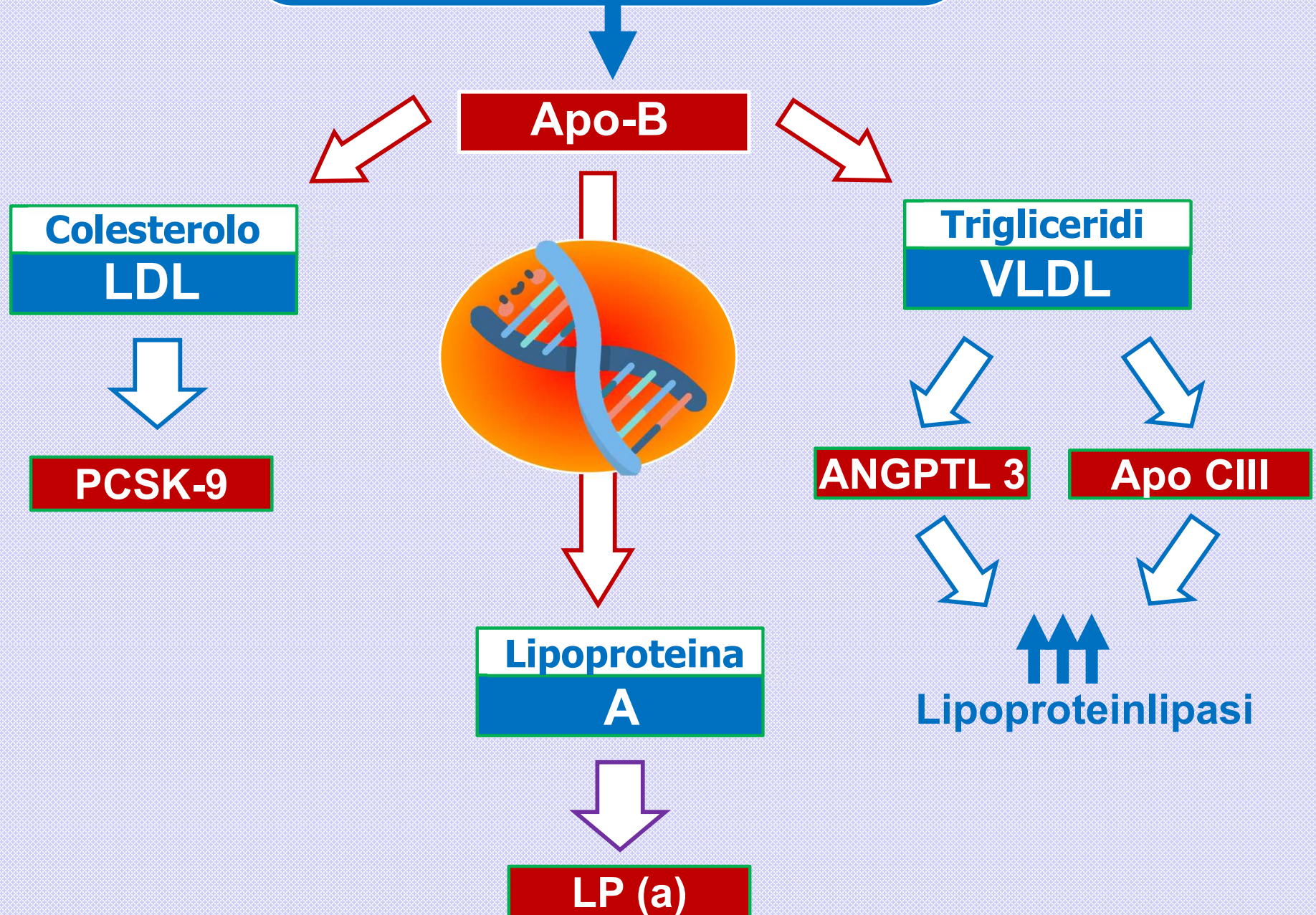
**Rischio medio-basso**

**Rischio Alto**



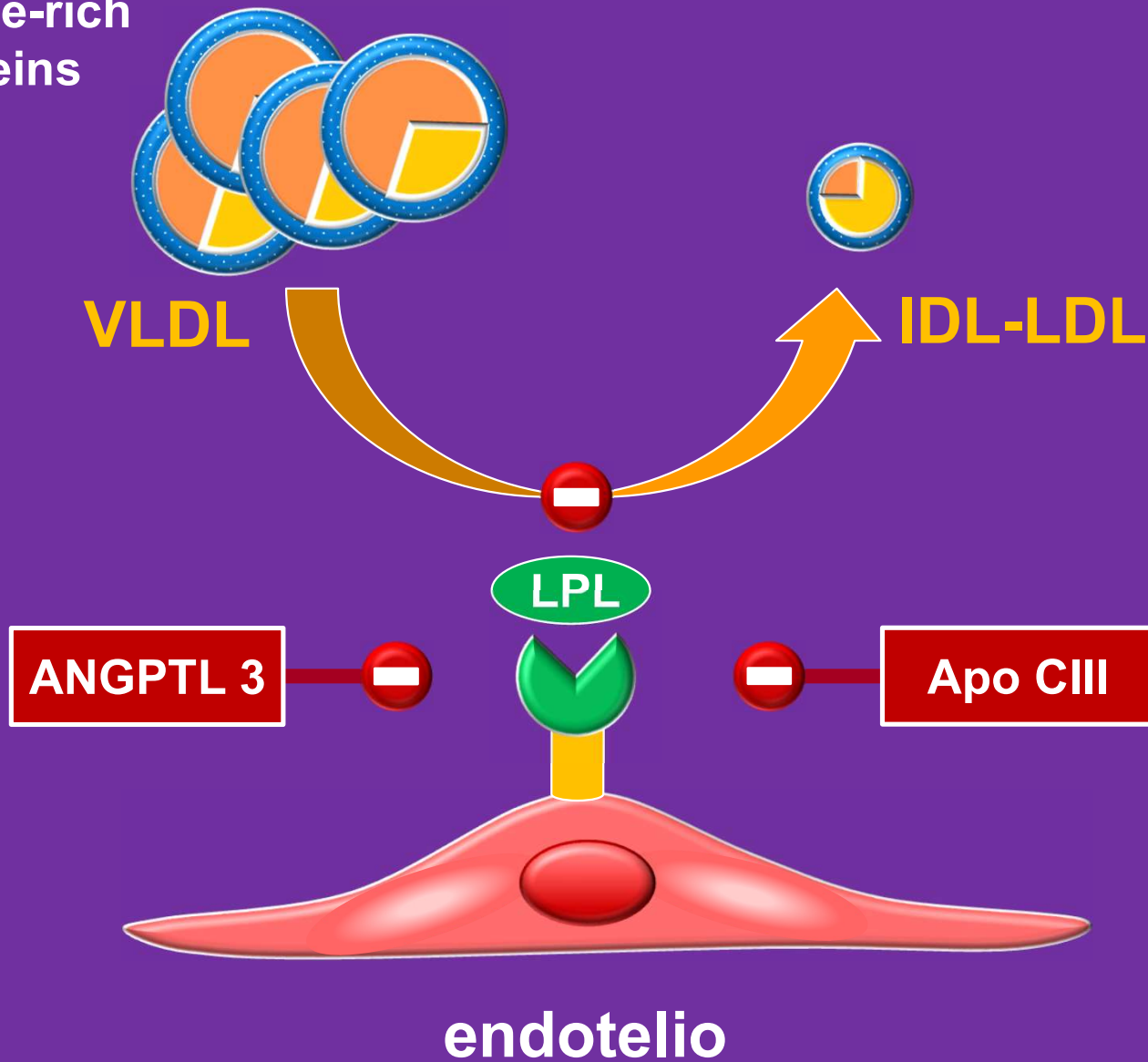
# TARGET GENETICI

# TARGET GENETICI

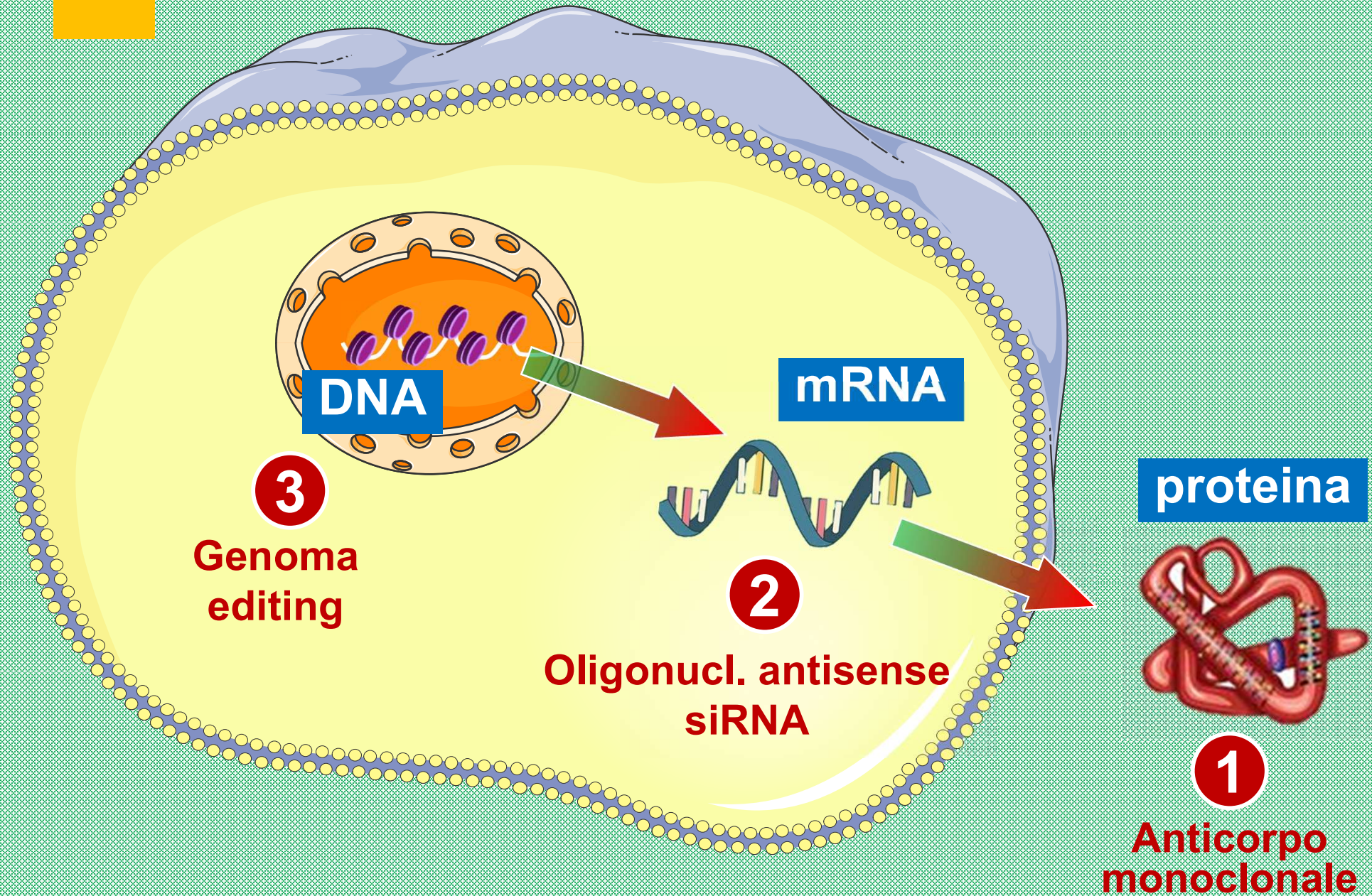


# Azione della Lipoproteinlipasi endoteliale (Kumari, Biomedicine 2021)

tryglyceride-rich  
lipoproteins



# Terapia genica: meccanismi generali





# Terapia genica delle dislipidemie

## **Inibitori monoclonali**

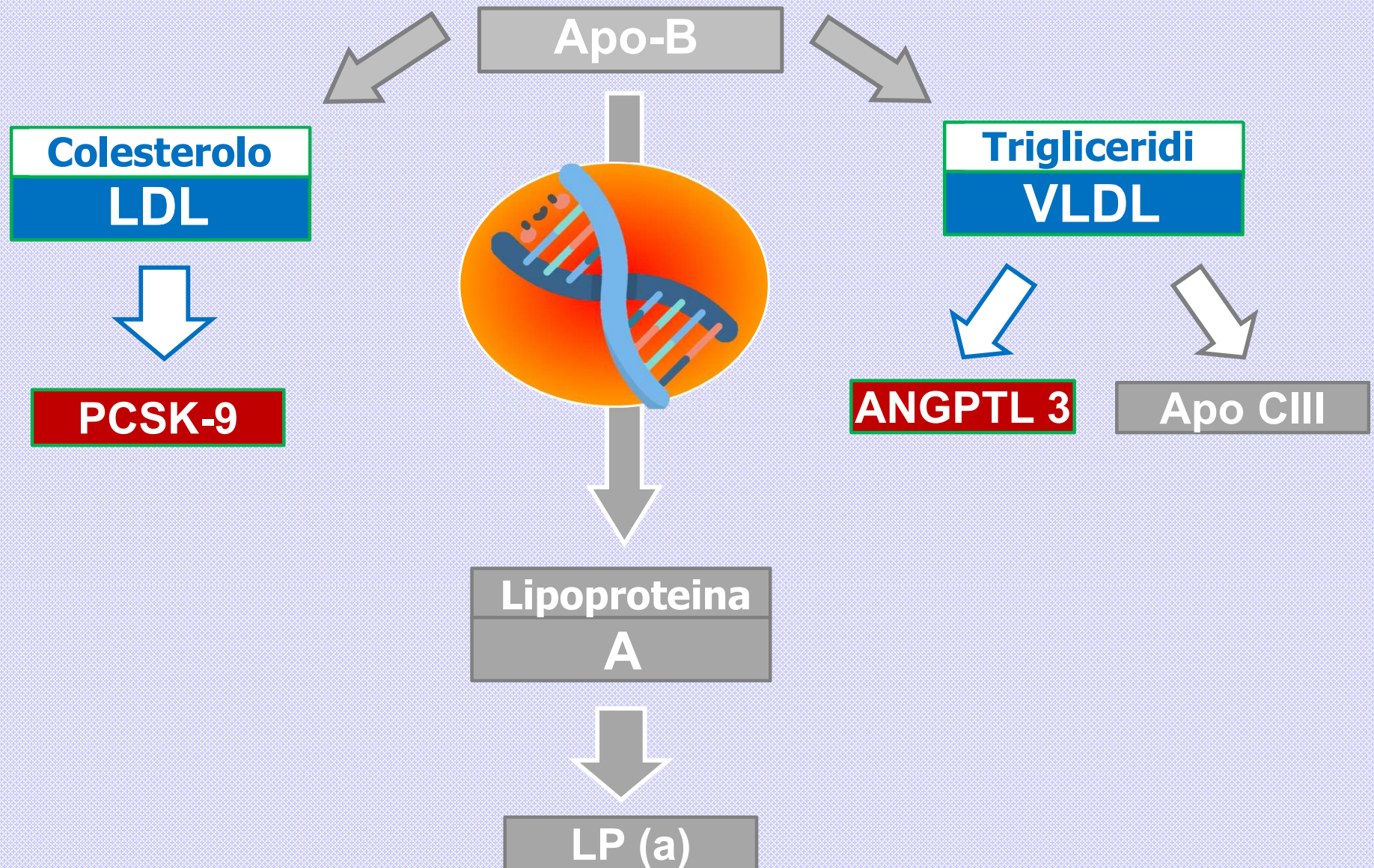
## **Inibizione del RNA messaggero**

- Antisense oligonucleotide (ASO)
- Silencing RNA (siRNA)

## **Editing del DNA**

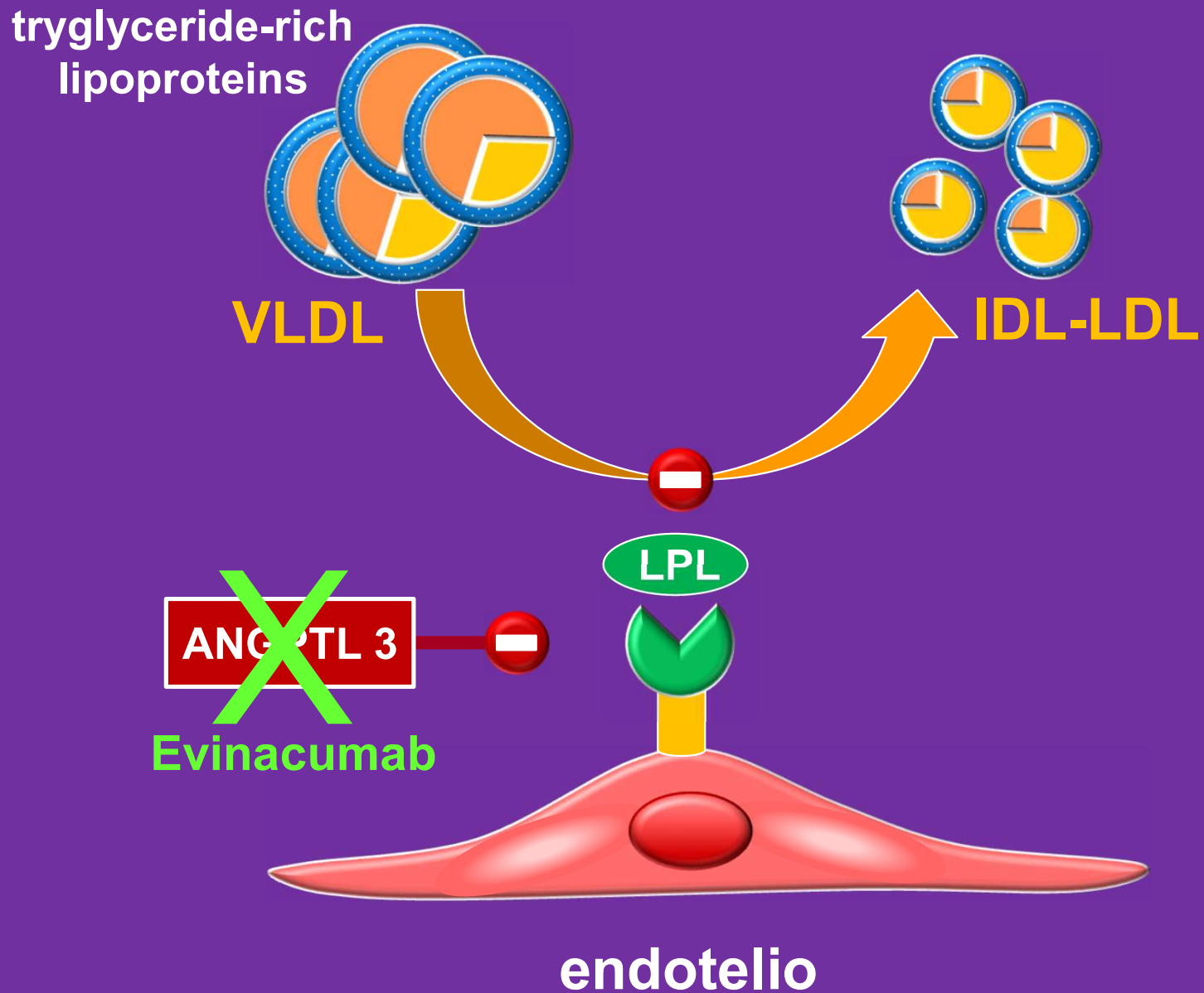
- CRISPR
- Base editing

# Anticorpi monoclonali



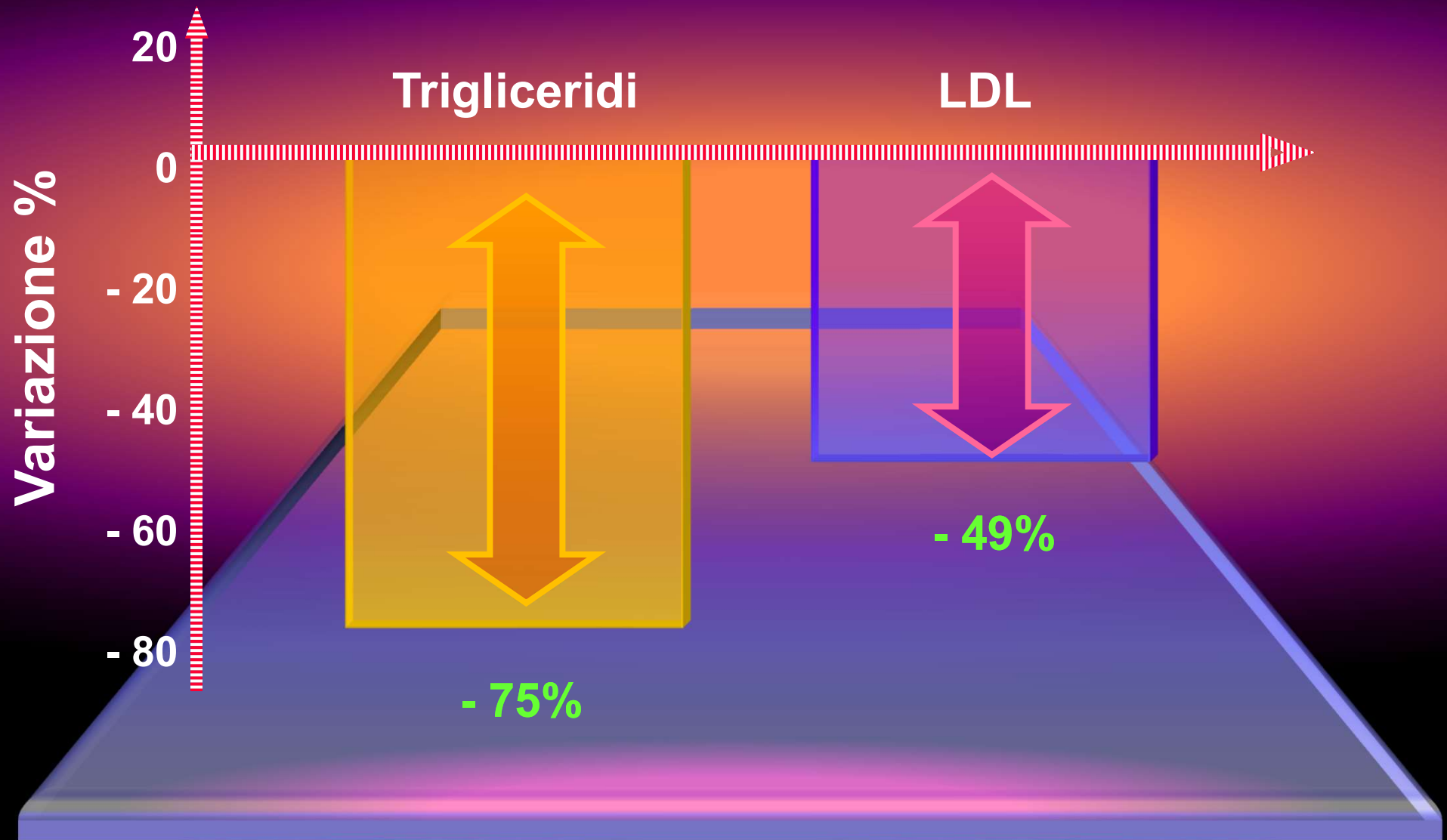
# Azione della Lipoproteinlipasi endoteliale

(Kumari, Biomedicine 2021)



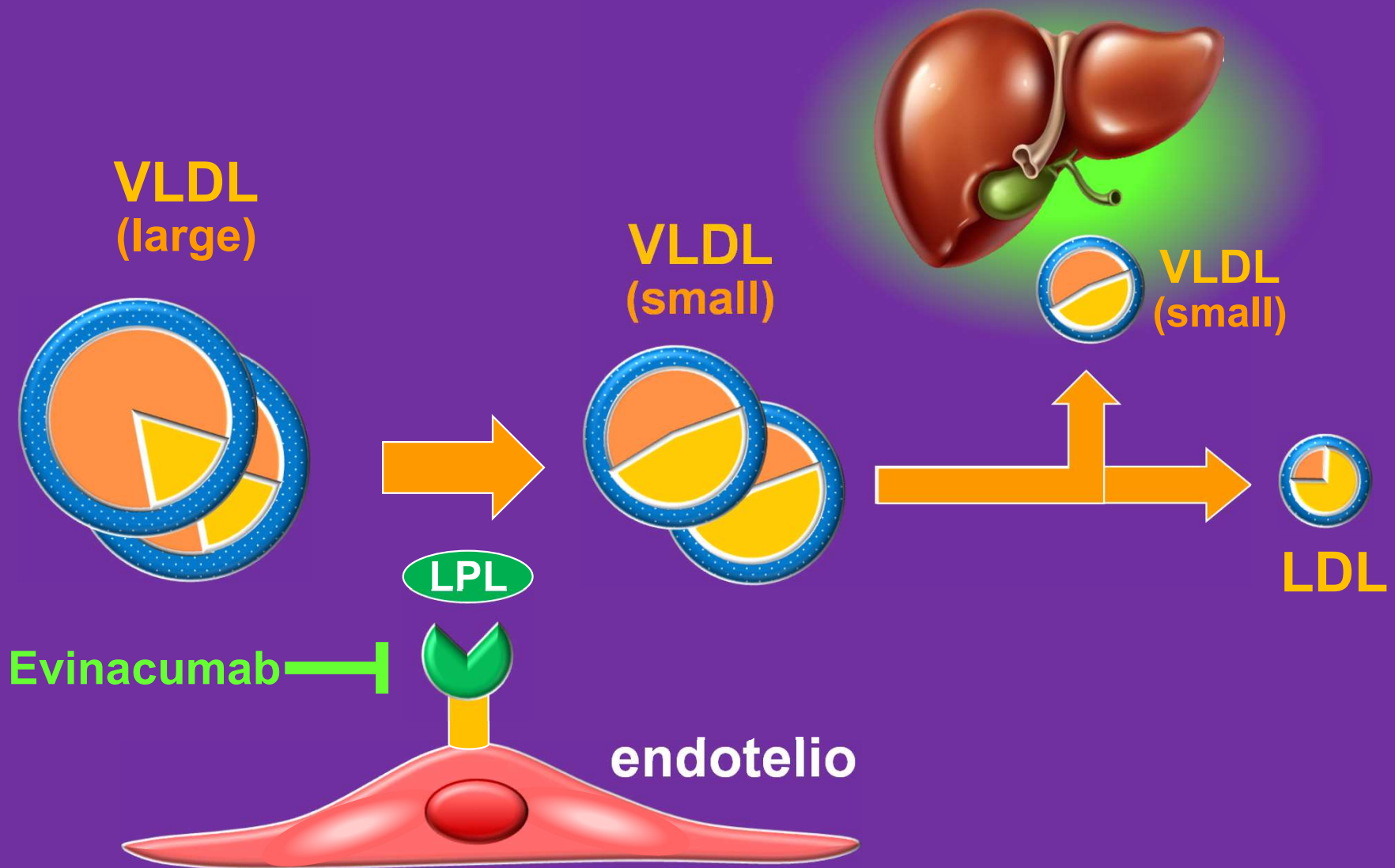
# Effetti lipidici di Evinacumab

(Ahmad, Circulation 2019)

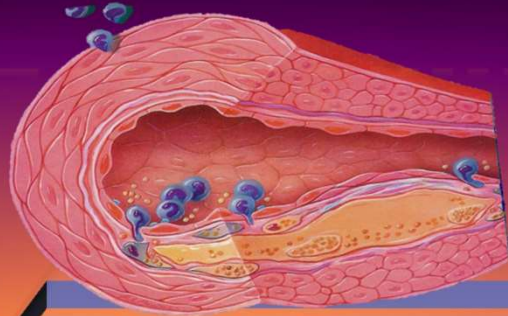


# Evinacumab: riduzione TGL e LDL

(Wang, J Lipid res 2015)

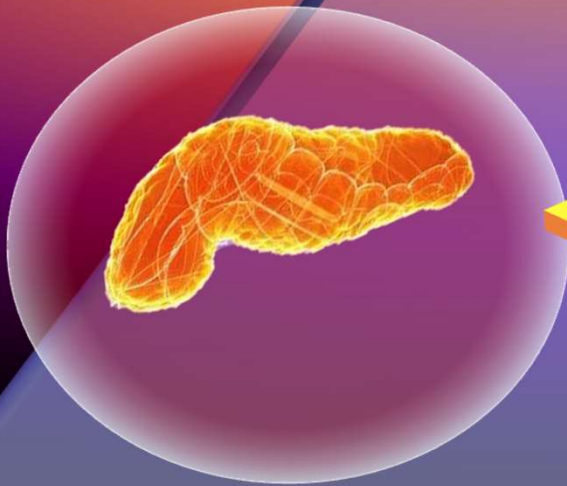


# Evinacumab

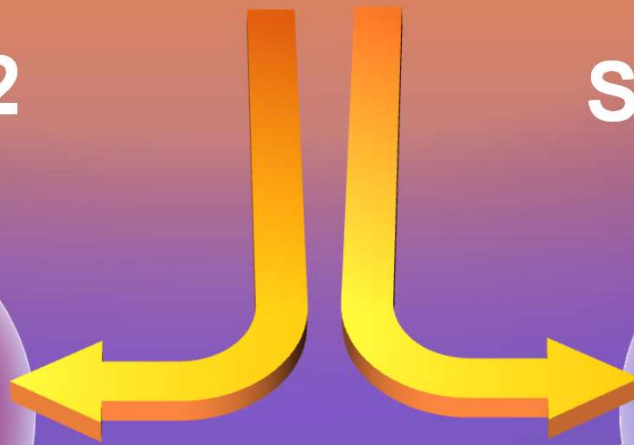
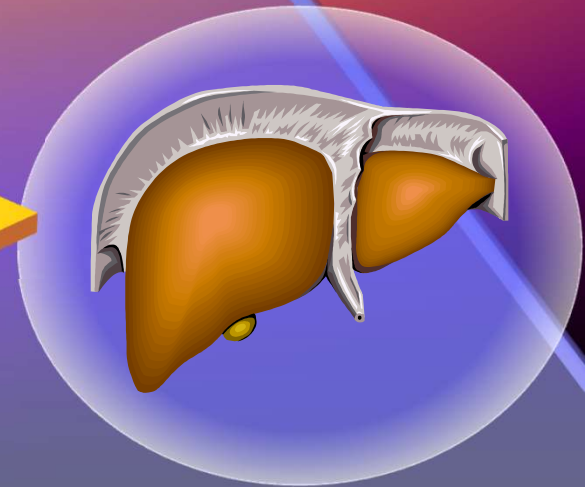


↓ Remnants  
VLDL-LDL

Diabete tipo 2



Steatosi Epatica



# Terapia genica delle dislipidemie

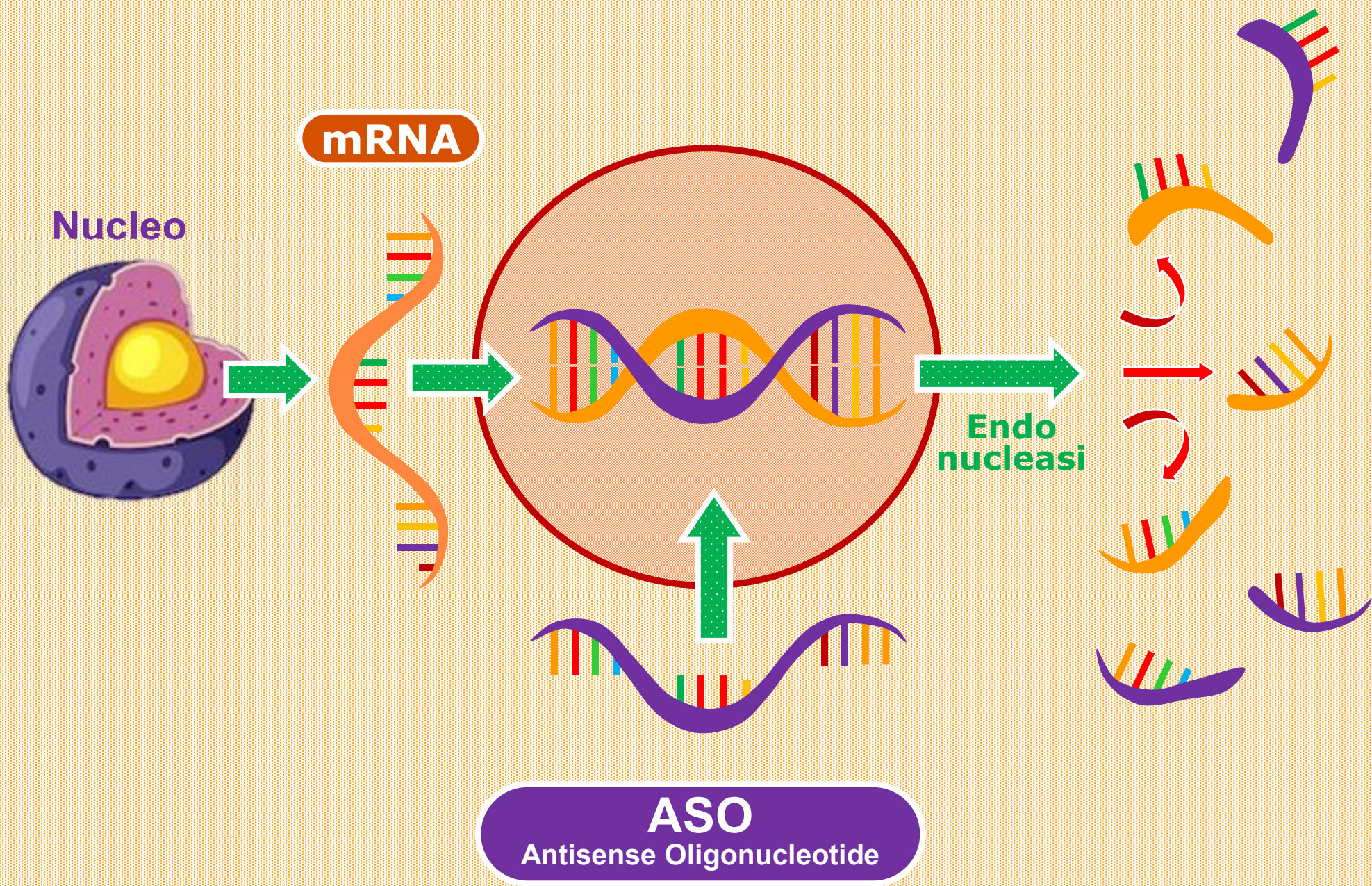
## ● Inibitori monoclonali

## ● Inibizione del RNA messaggero

- Antisense oligonucleotide (ASO)
- Small Interfering RNA (siRNA)

## ● Editing del DNA

- CRISPR
- Base editing



**mRNA**

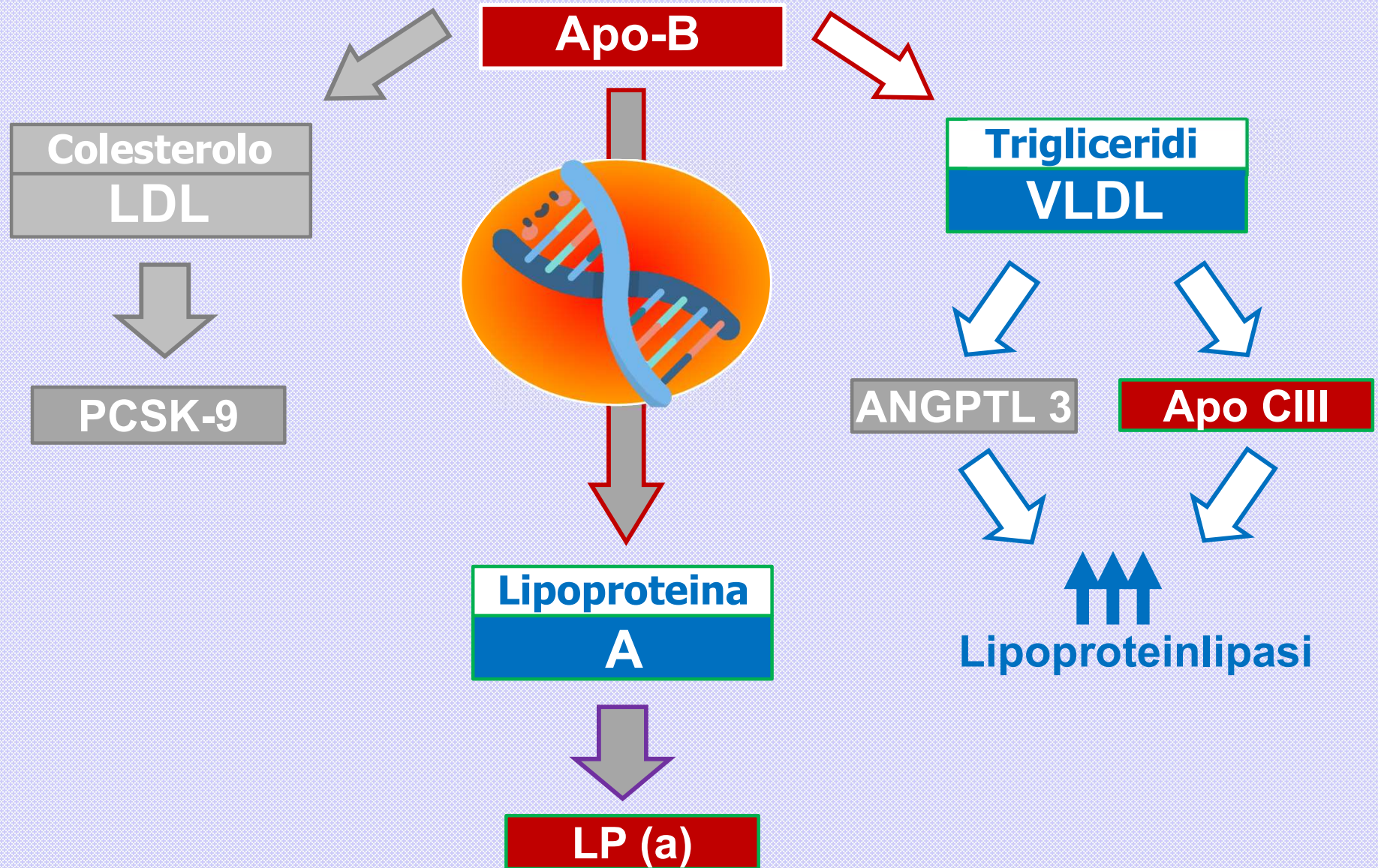
**Nucleo**

**Endo  
nucleasi**

**ASO**  
Antisense Oligonucleotide

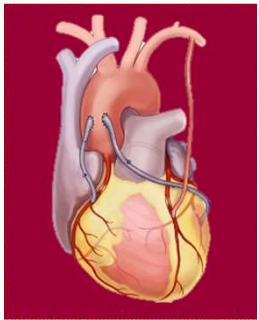


# ASO anti-sense oligonucleotide



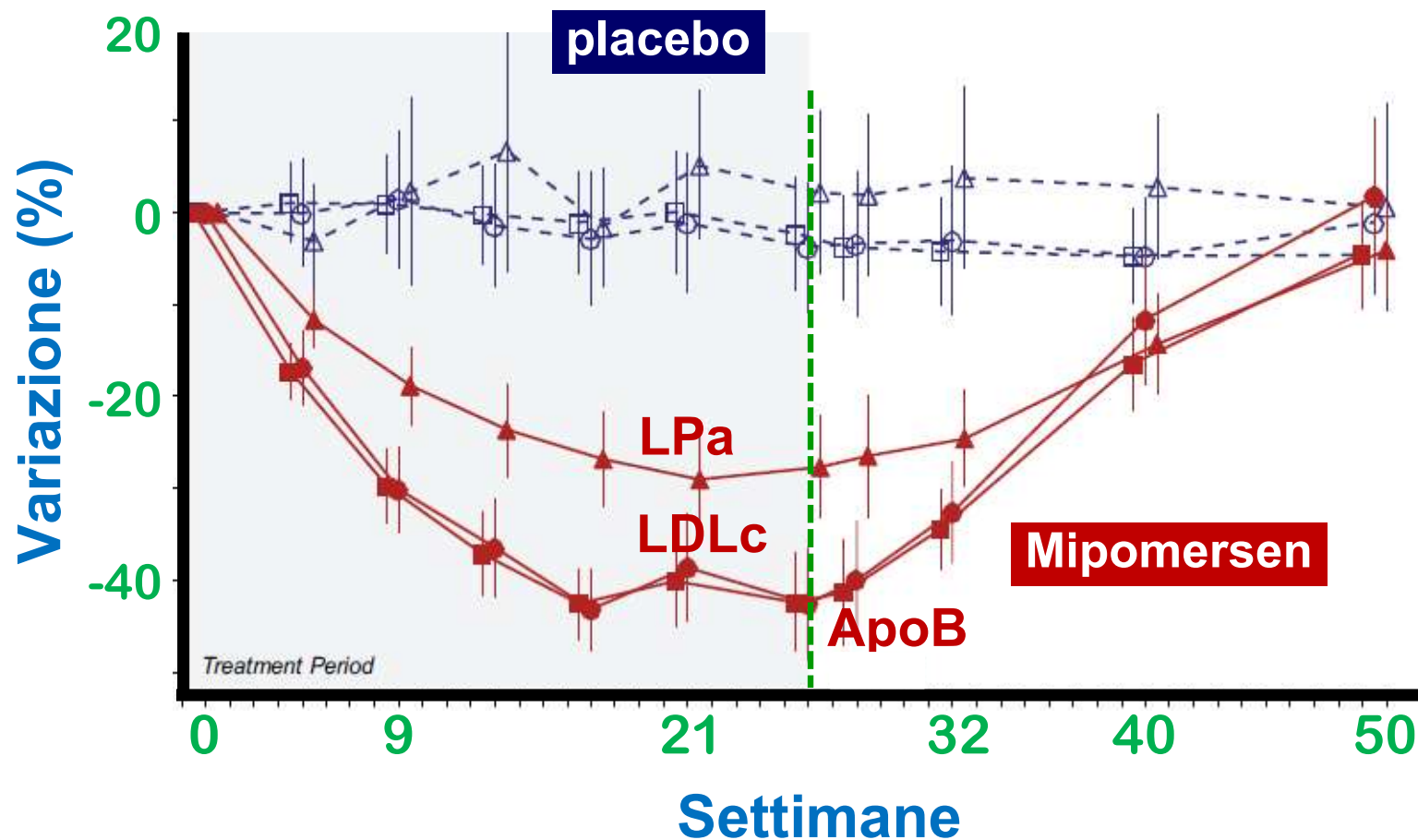
# ASO oligonucleotidi antisenso

- Apo B
- Apo C3
- LPa



# Mipomersen: antisense ASO anti-ApoB

(Thomas, JACC 2013)



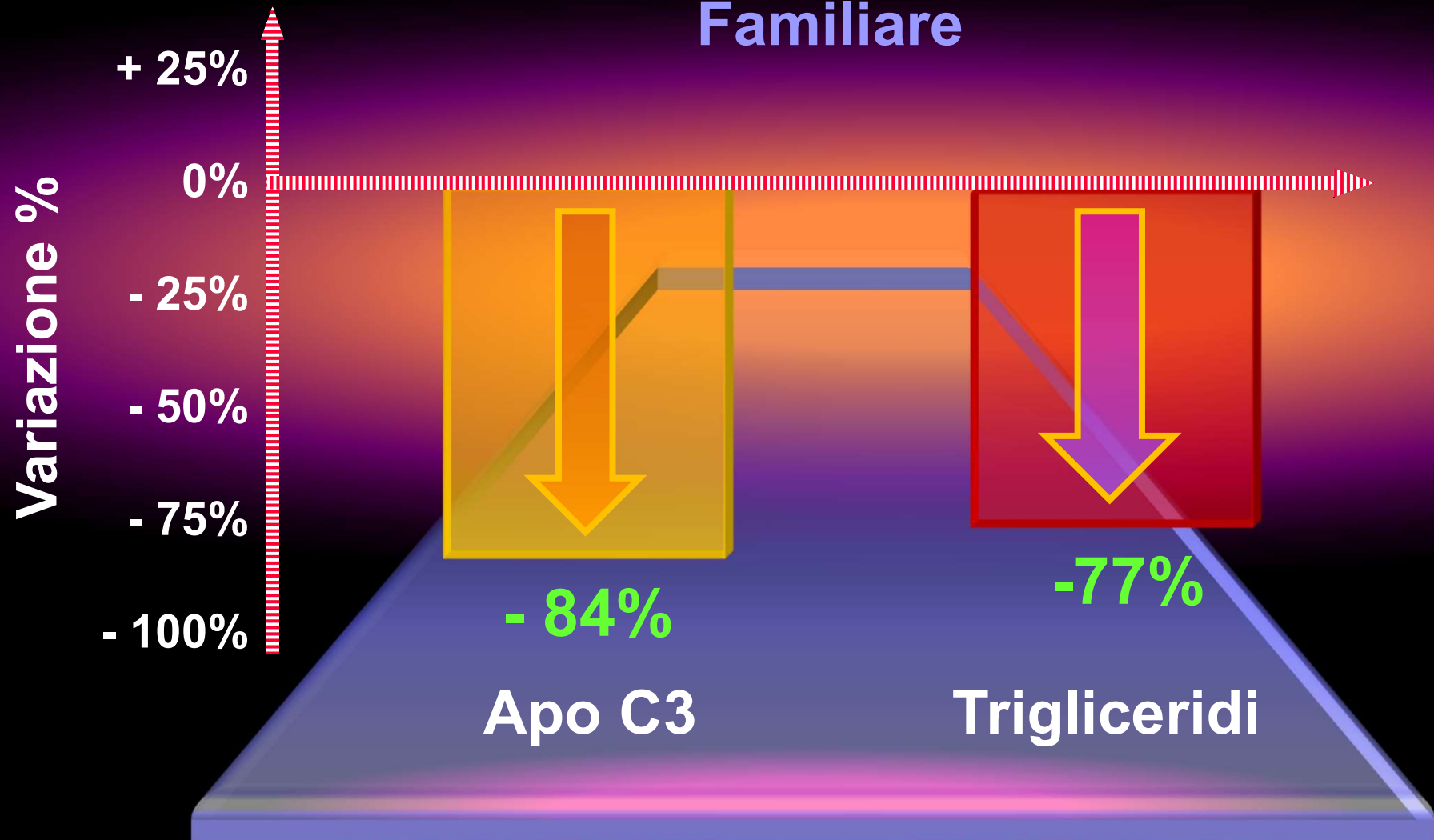
# ASO oligonucleotidi antisenso

- Apo B
- Apo C3
- LPa

# Volanesorsen: ASO anti Apo C3

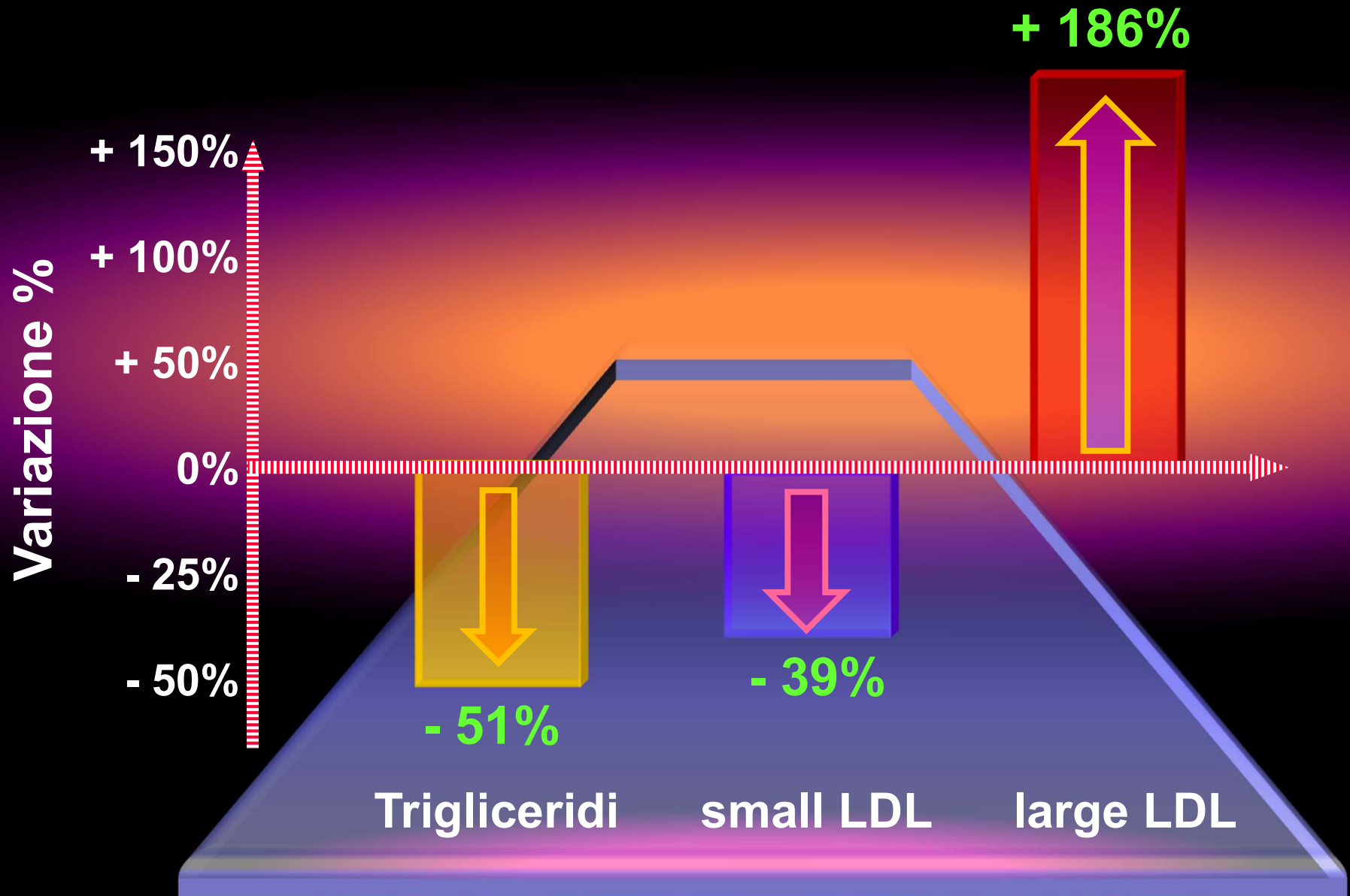
(trial APPROACH - Witztum, NEJM 2019)

## Chilomicronemia Familiare



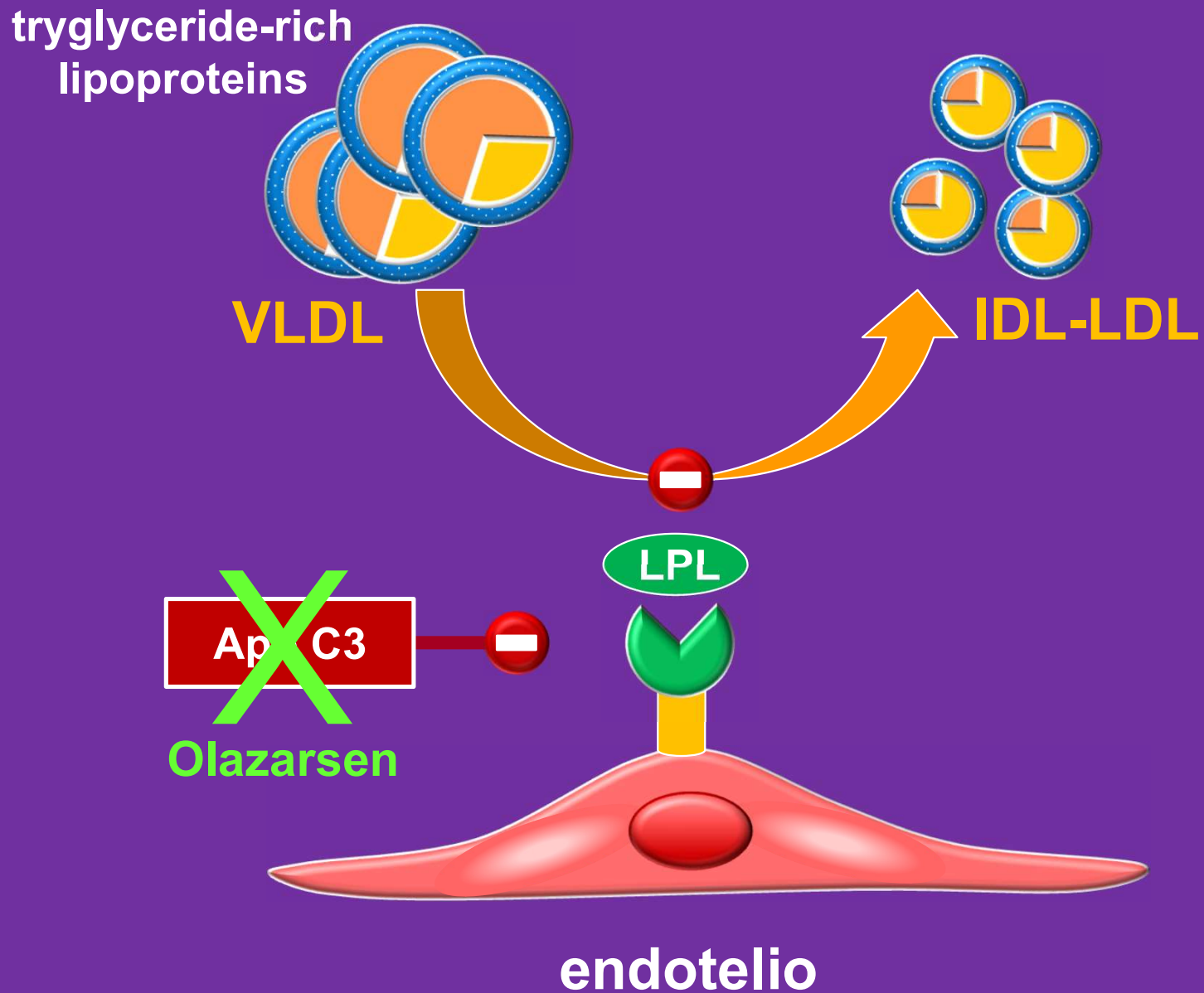
# Olazarsen: NAG - ASO anti Apo C3

(Karwatowska, J Clin Lipidol 2022)



# Azione della Lipoproteinlipasi endoteliale

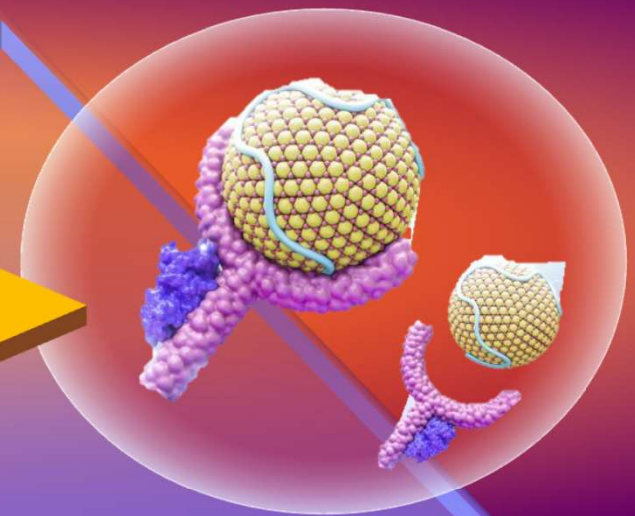
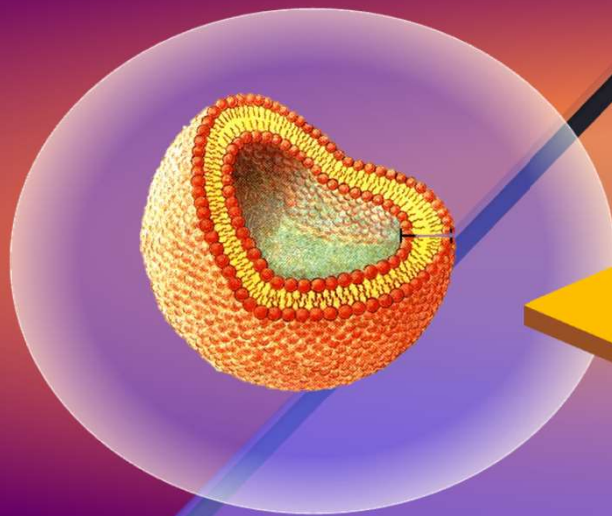
(Kumari, Biomedicine 2021)



# Terapia genetica delle ipertrigliceridemie

**Chilomicronemia  
familiare**

**Dislipidemia mista  
iperTgl - IperChol**



↓ Apo C3

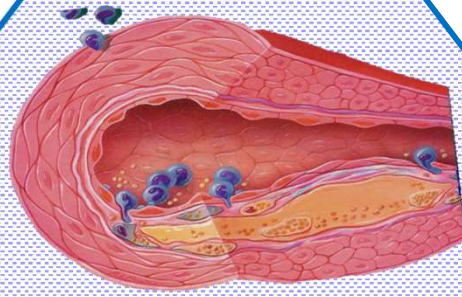
↓ ANGPTL-3



# ASO oligonucleotidi antisenso

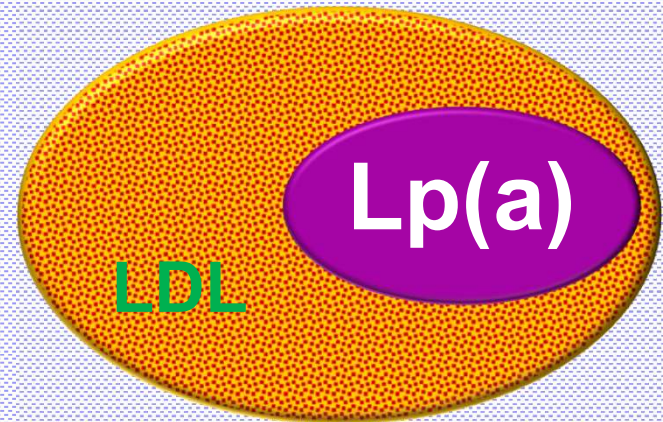
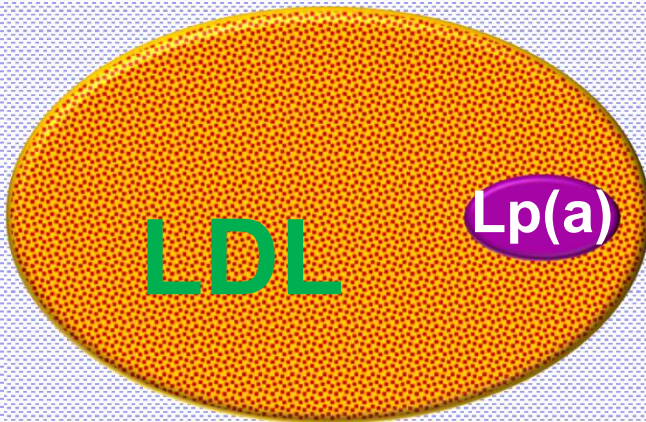
- **Apo B**
- **Apo C3**
- **LPa**

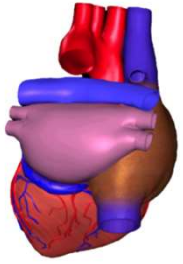
# LDL-Chol / ApoB



↑percolesterol

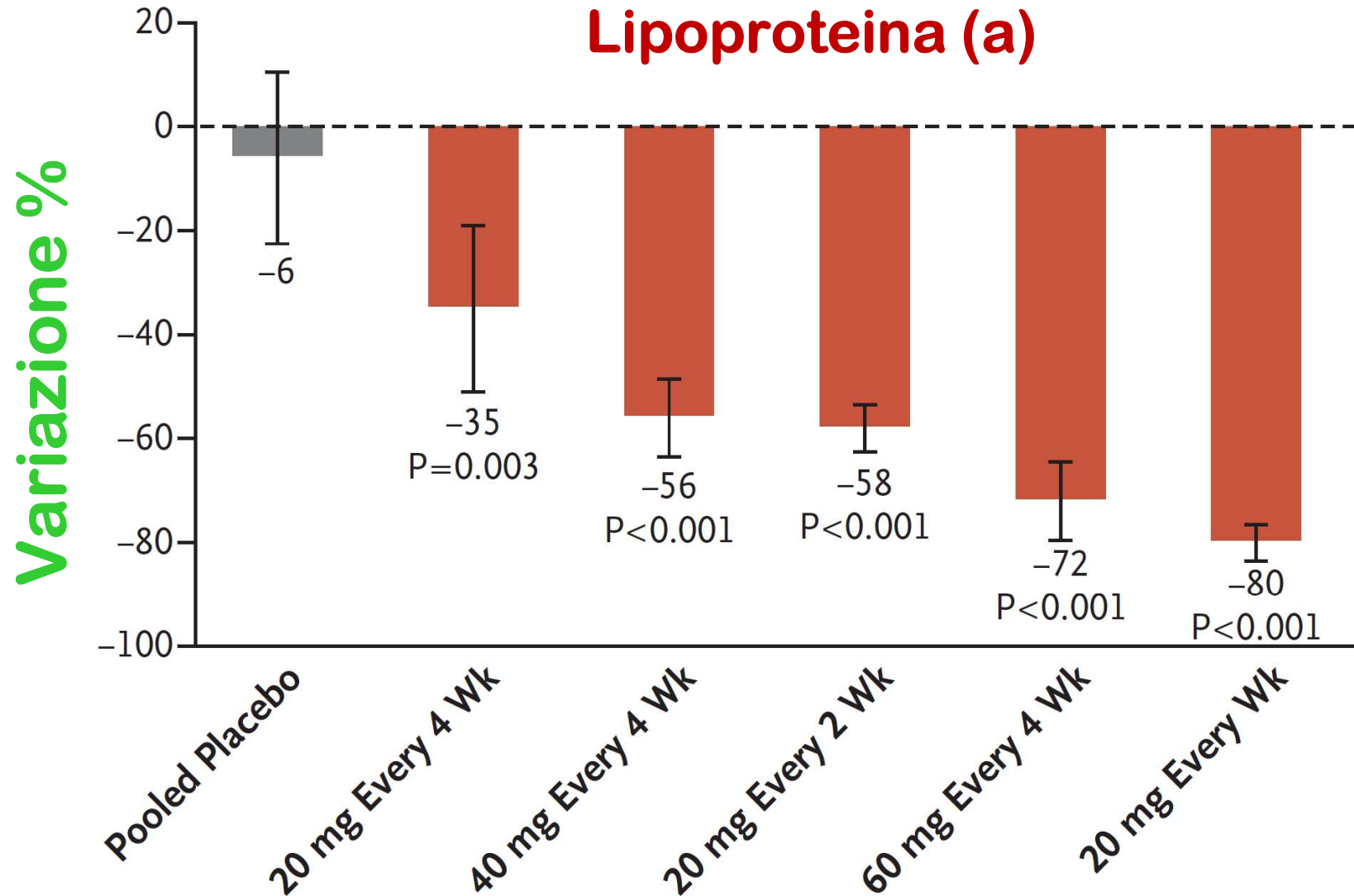
↑ Lp (a)





# Pelacarsen e riduzione della Lp (a)

(Tsimikas, NEJM 2020)



# Terapia genica delle dislipidemie

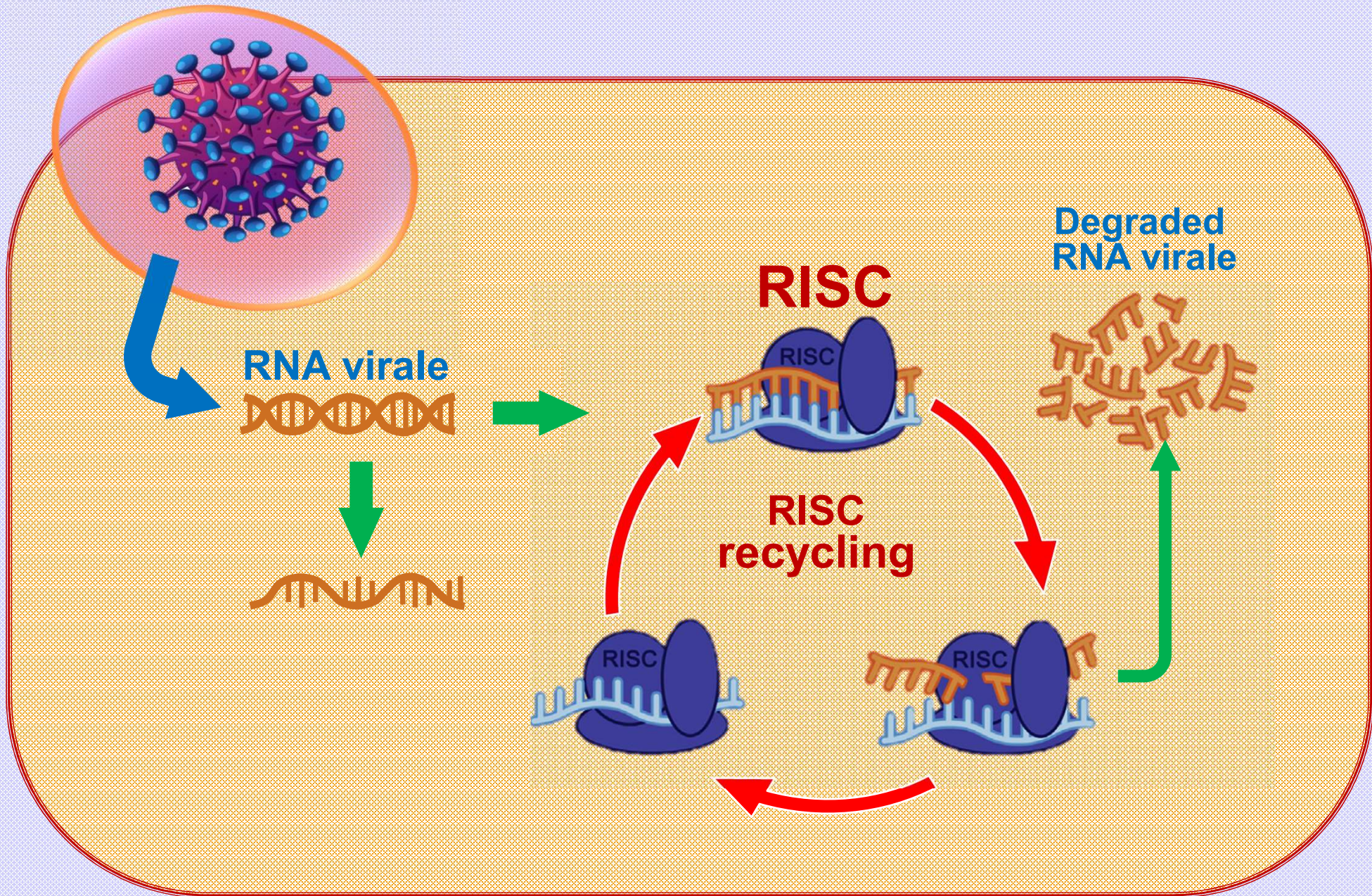
## Inibitori monoclonali

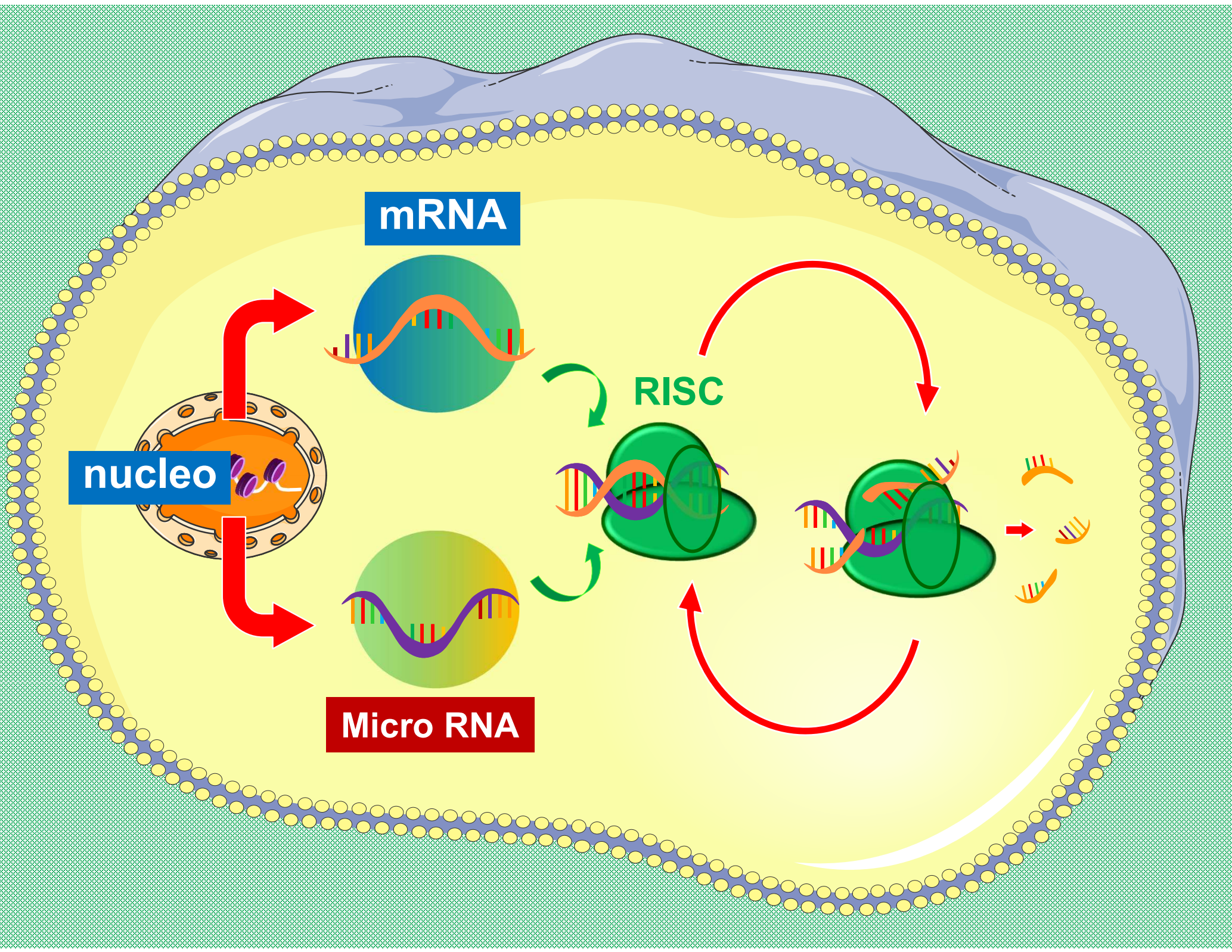
## Inibizione del RNA messaggero

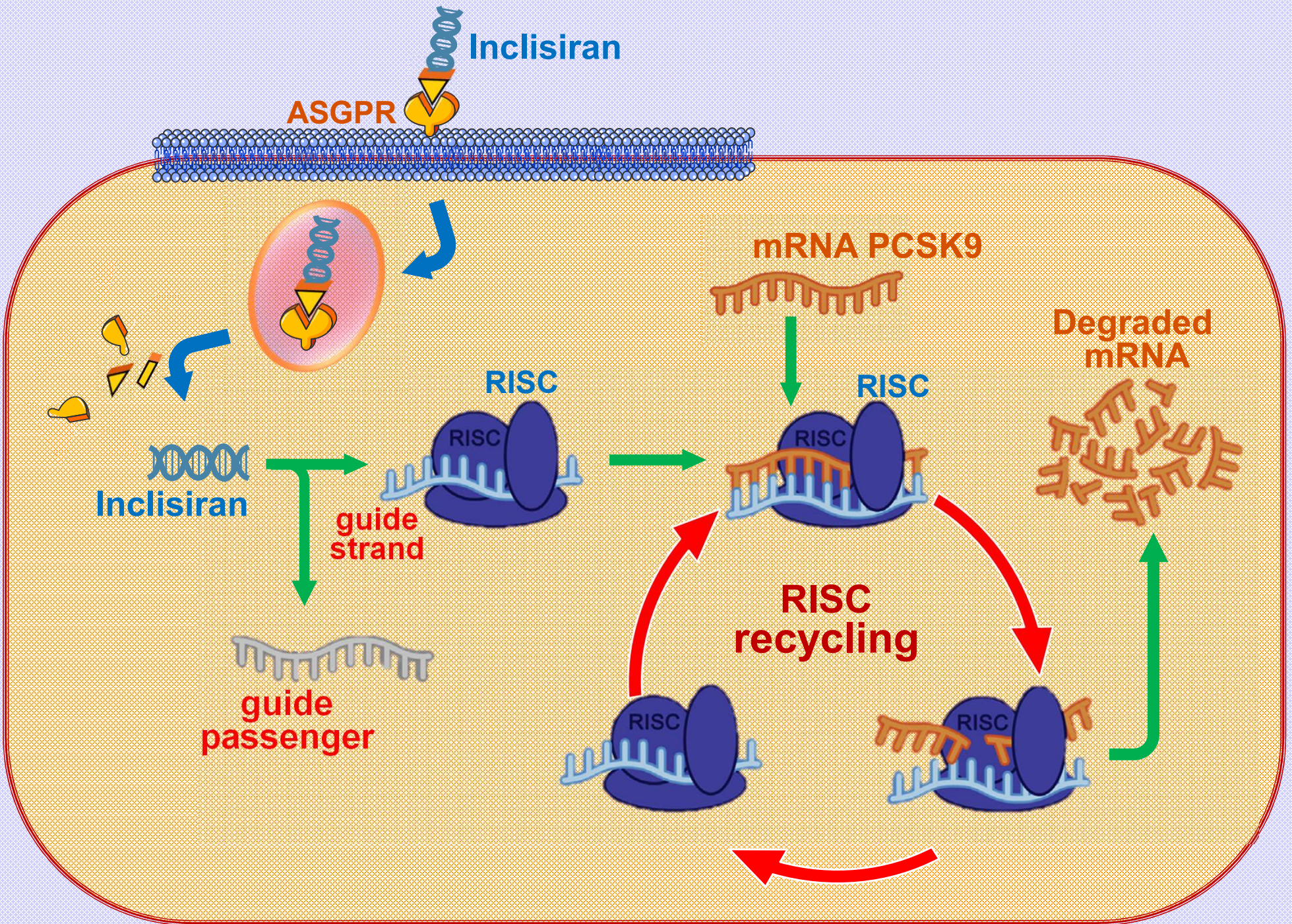
- Antisense oligonucleotide (ASO)
- Small Interfering RNA (siRNA)

## Editing del DNA

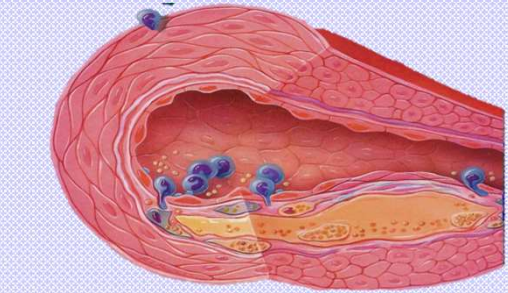
- CRISPR
- Base editing







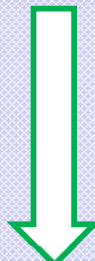
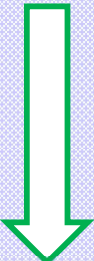
# Terapia con inibitori PCSK9



Inclisiran

Inclisiran

Inclisiran



anticorpi monoclonali

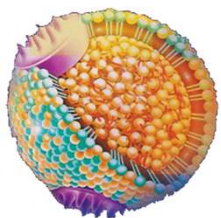
anticorpi monoclonali



mesi

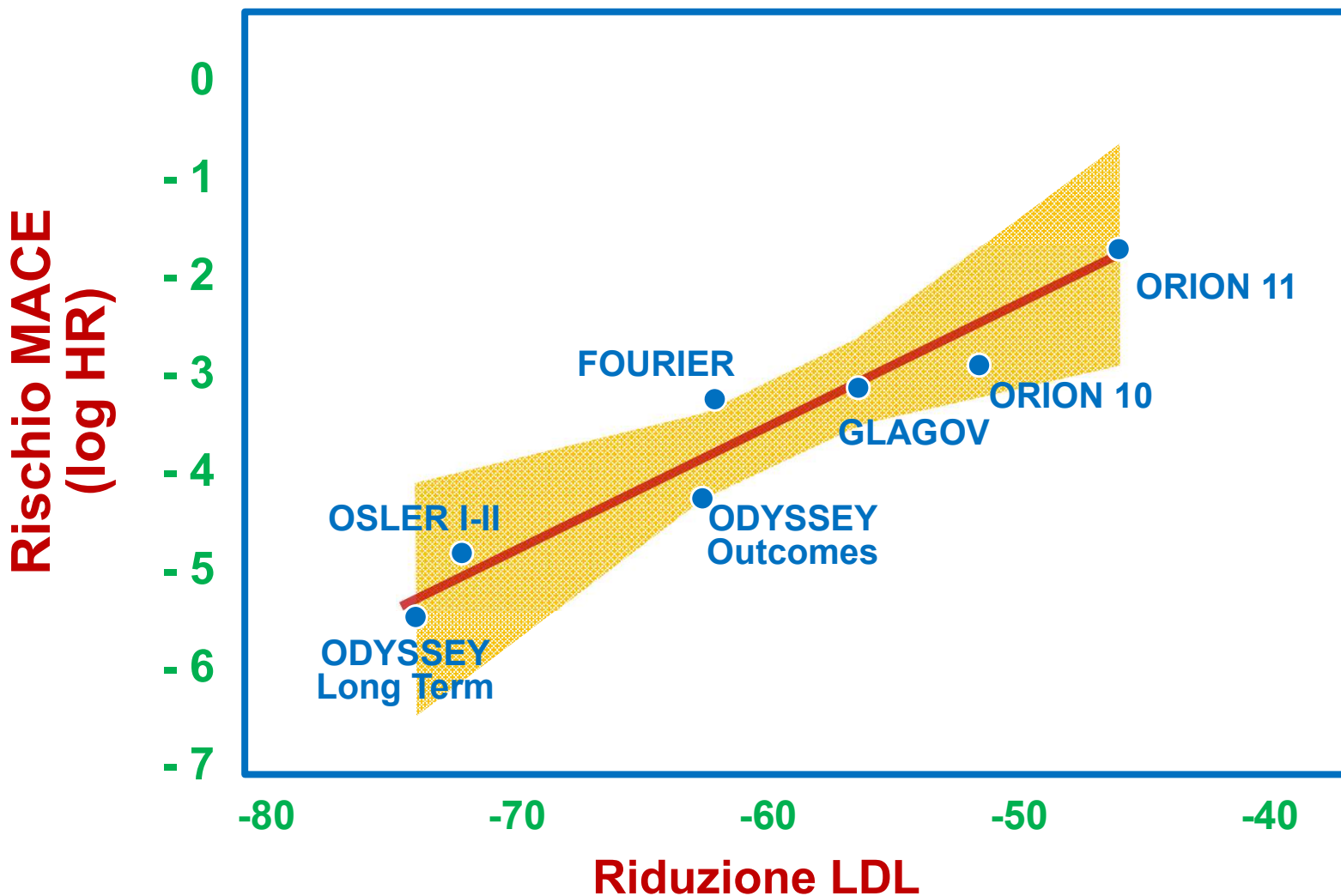




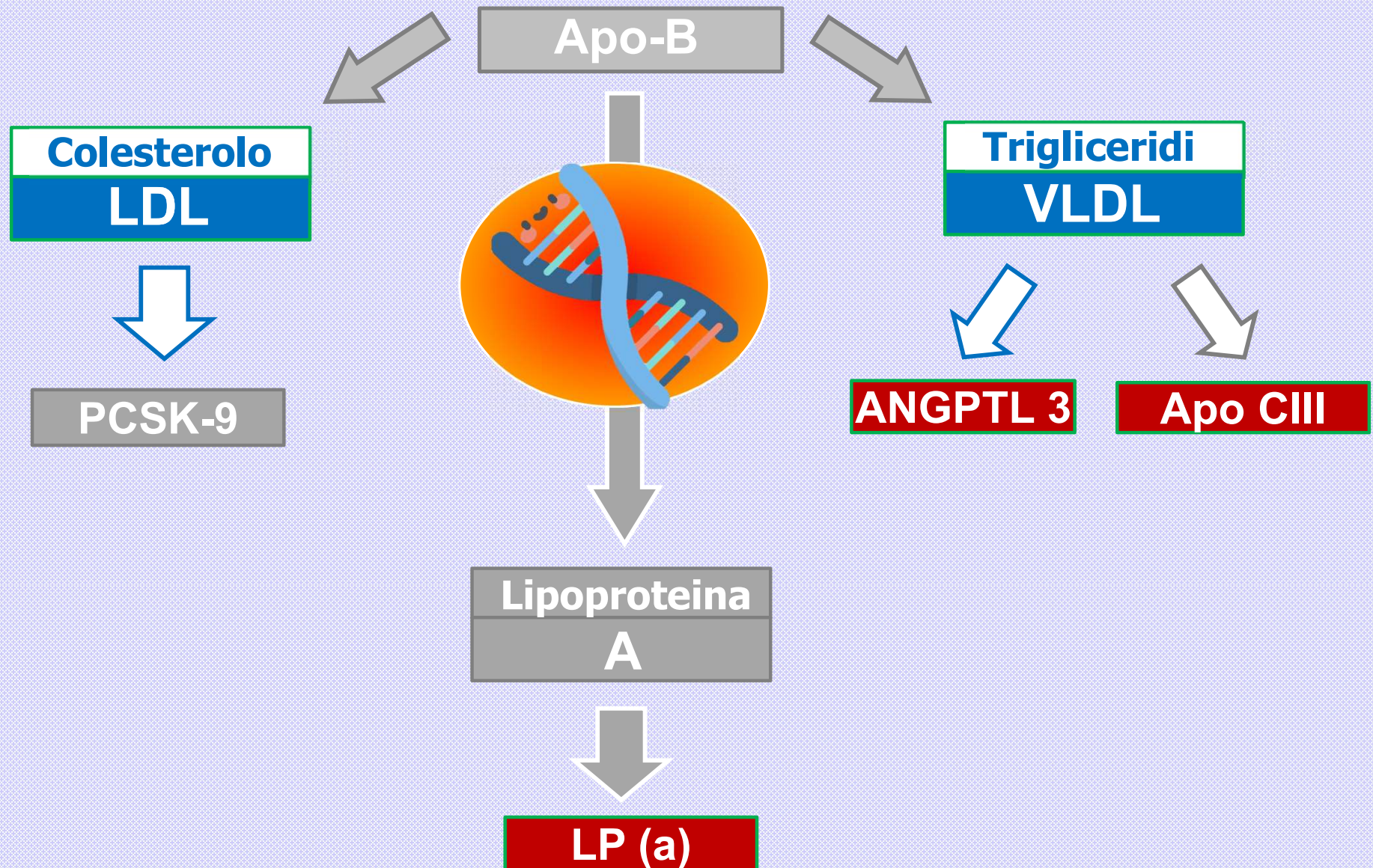


# Riduzione MACE LDL-correlata

(Cordero, Atherosclerosis 2020)



# Anticorpi monoclonali



# Terapia genica delle dislipidemie

## ● Inibitori monoclonali

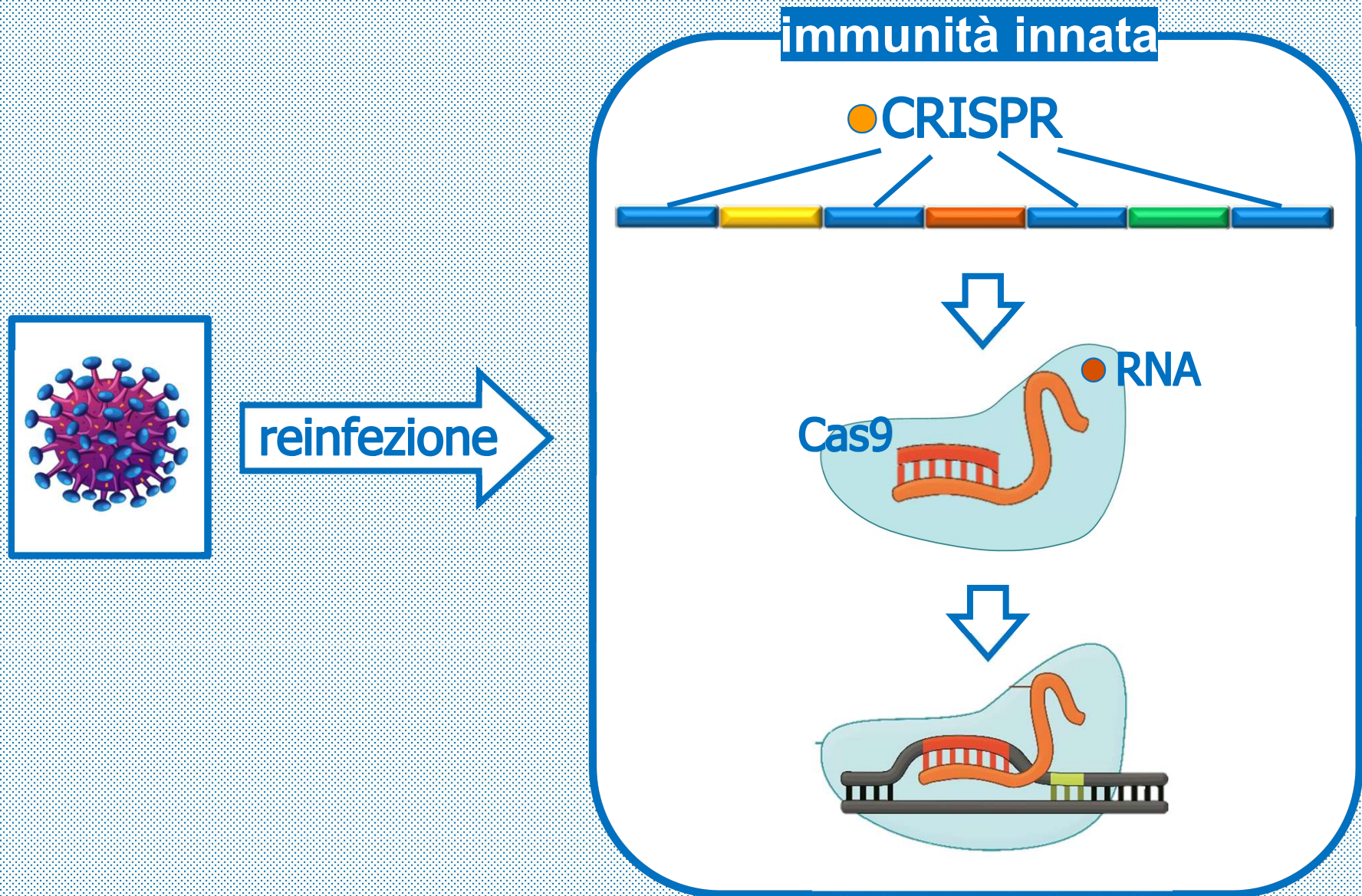
## ● Inibizione del RNA messaggero

- Antisense oligonucleotide (ASO)
- Small Interfering RNA (siRNA)

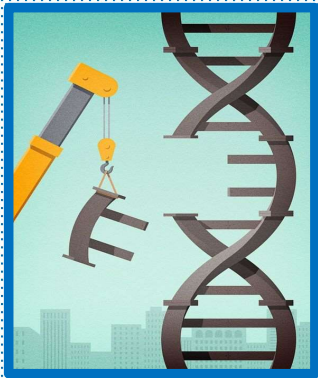
## ● Editing del DNA

- CRISPR-Cas 9
- Base editing

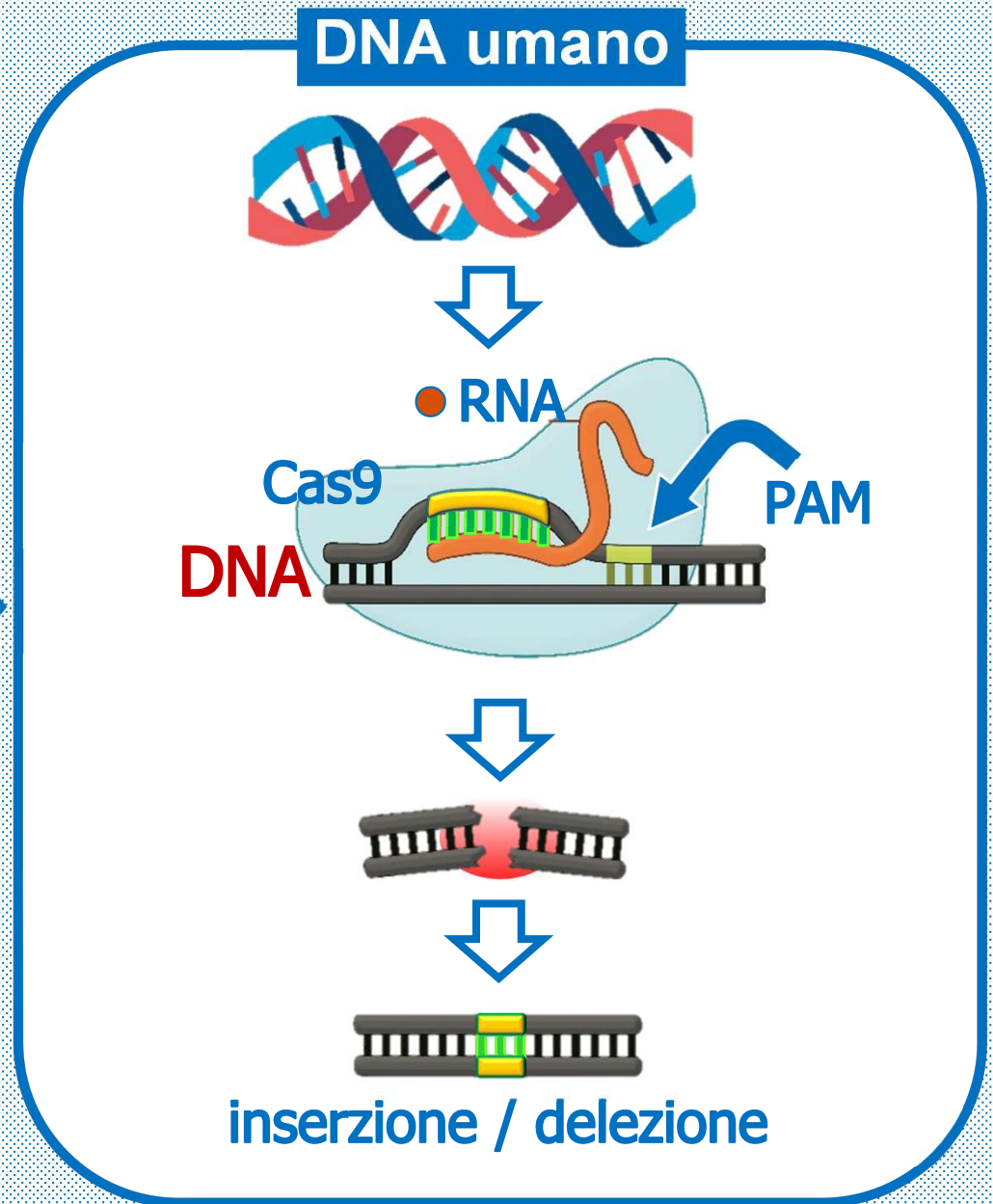
# NOBEL 2020: CRISPR-cas 9 nei batteri



# NOBEL 2020: CRISPR-cas 9

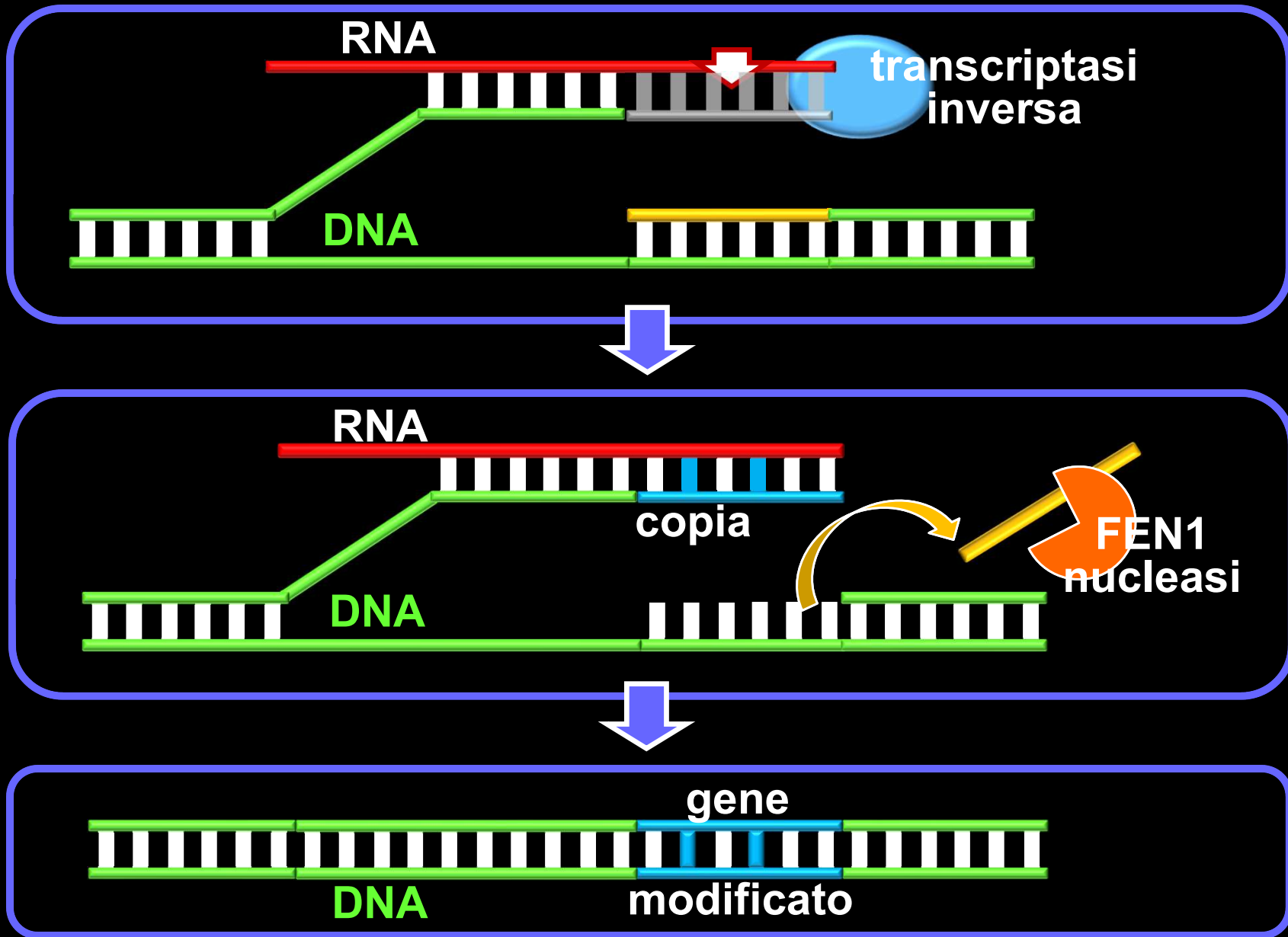


Gene Editing



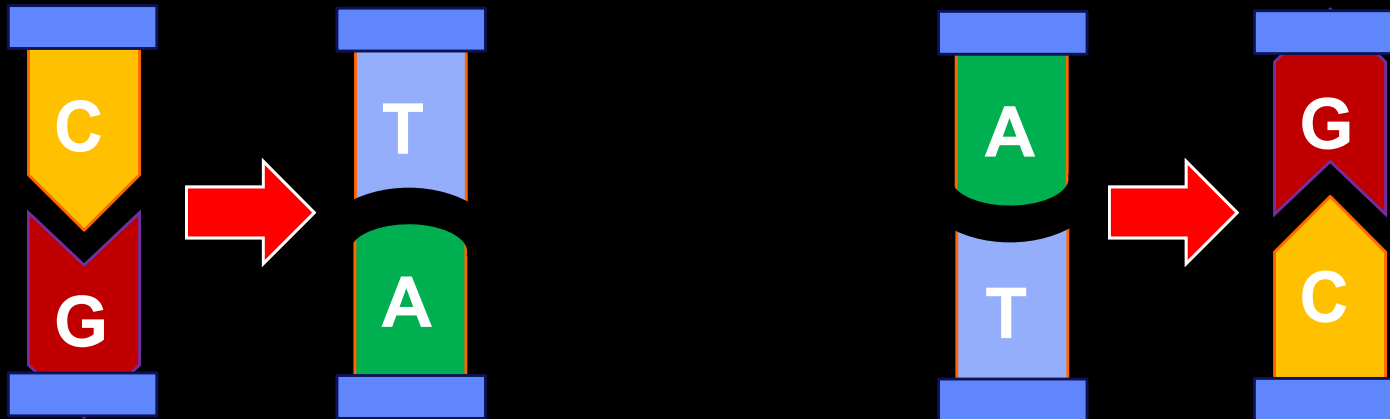
# Prime editing

(Scholefield, Gene Therapy 2021)



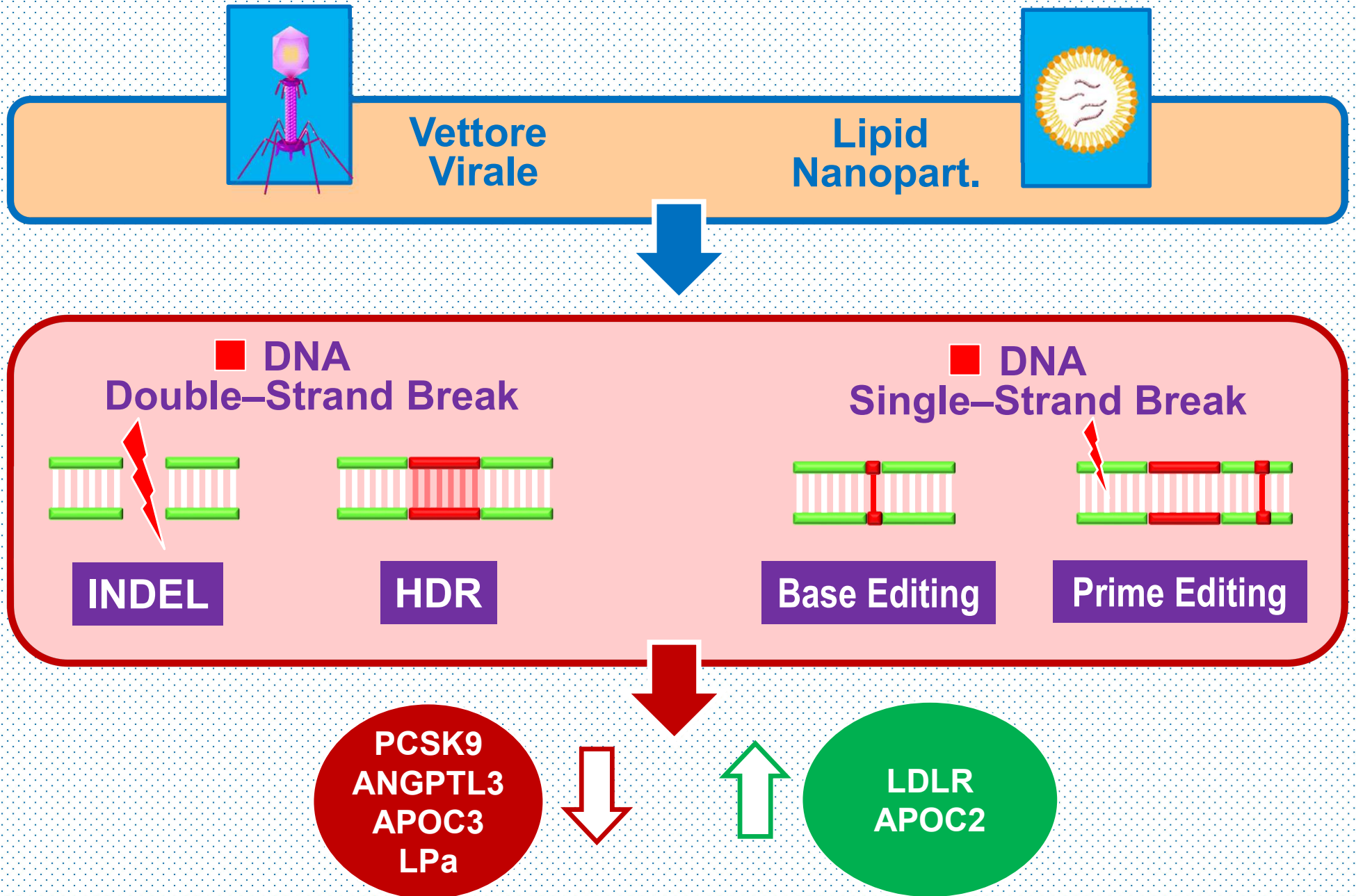


## Base Editing



# Editing genetico per le dislipidemie

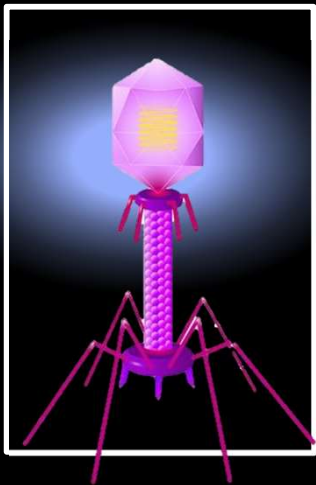
(Stankov, Atherosclerosis 2023)





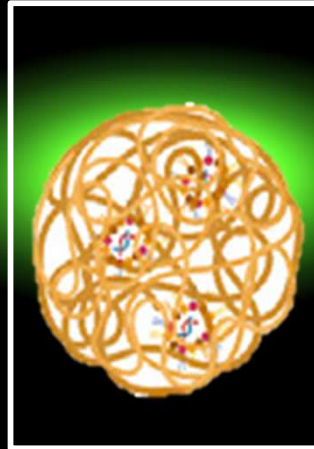


# Vettori

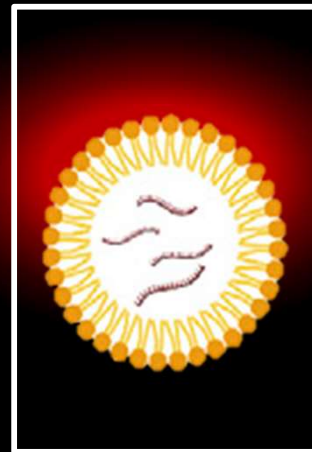


■ **A Adenovirus**

tossicità immunogenicità



■ **Polymer nanoparticle**



■ **Lipid nanoparticle**



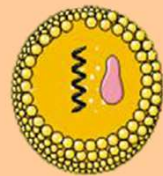
■ **Exosome**

Bio compatibilità

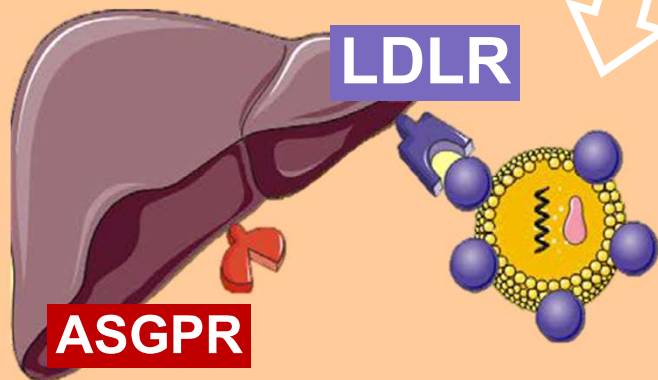
# Lipid Nano-Particle: delivery routes

(Hoekstra, ATVB 2023)

**Non-modified LNP**

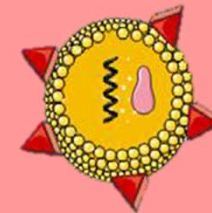


**LDLR**

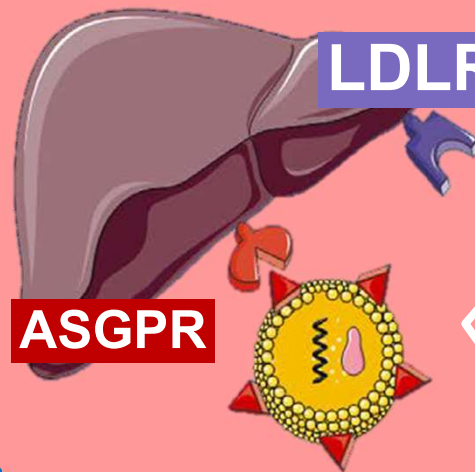


**ASGPR**

**Gal-Nac coupled LNP**



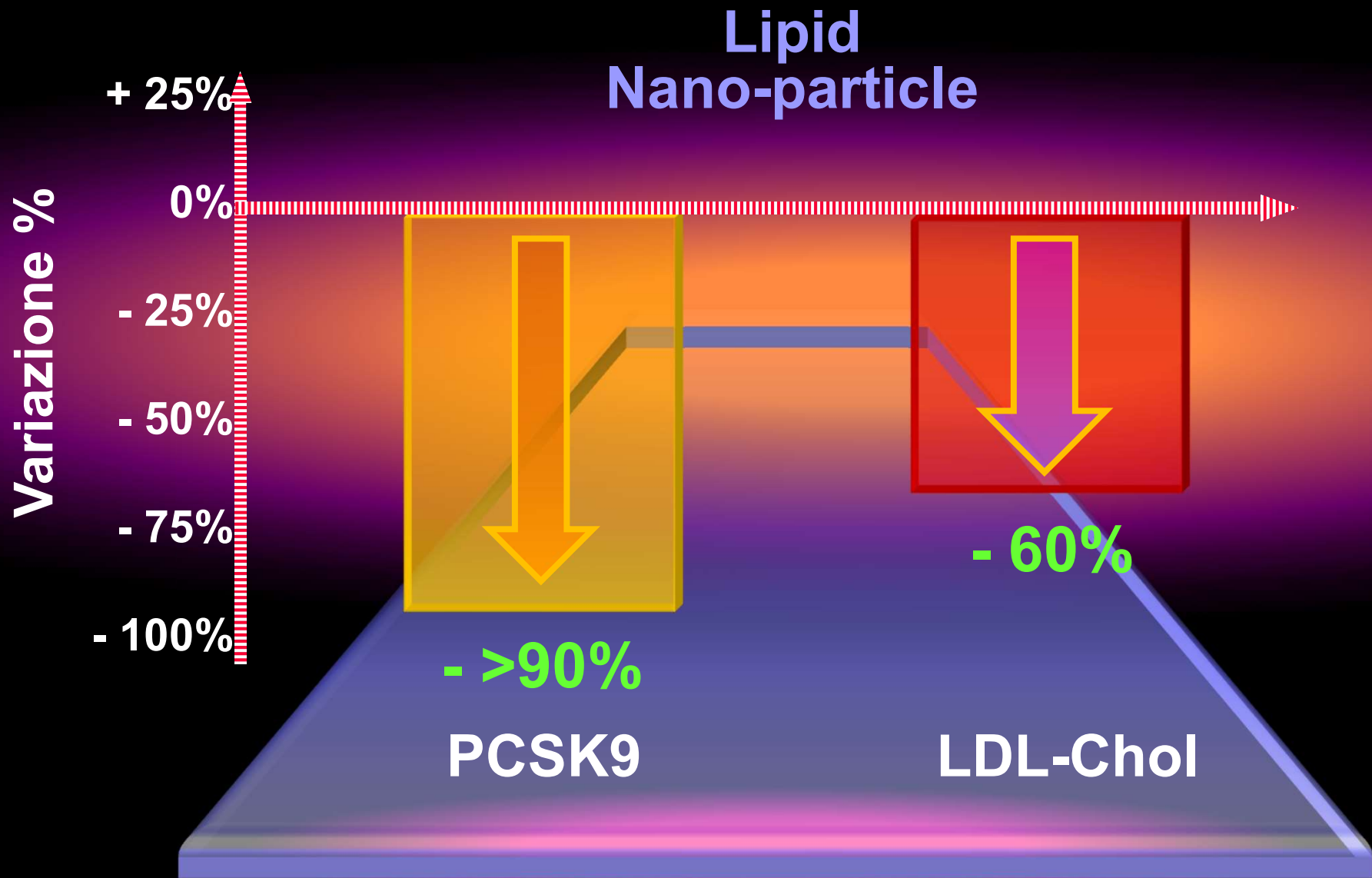
**LDLR**

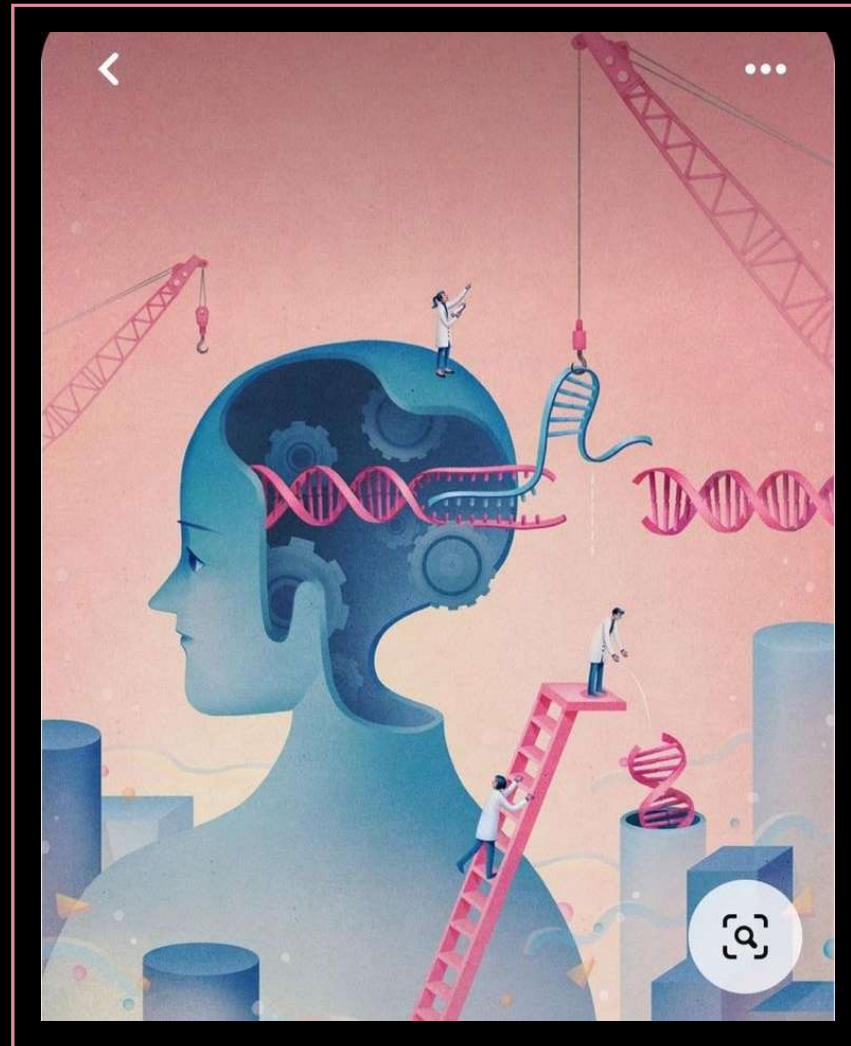


**ASGPR**

# Editing del gene PCSK9 nei macachi

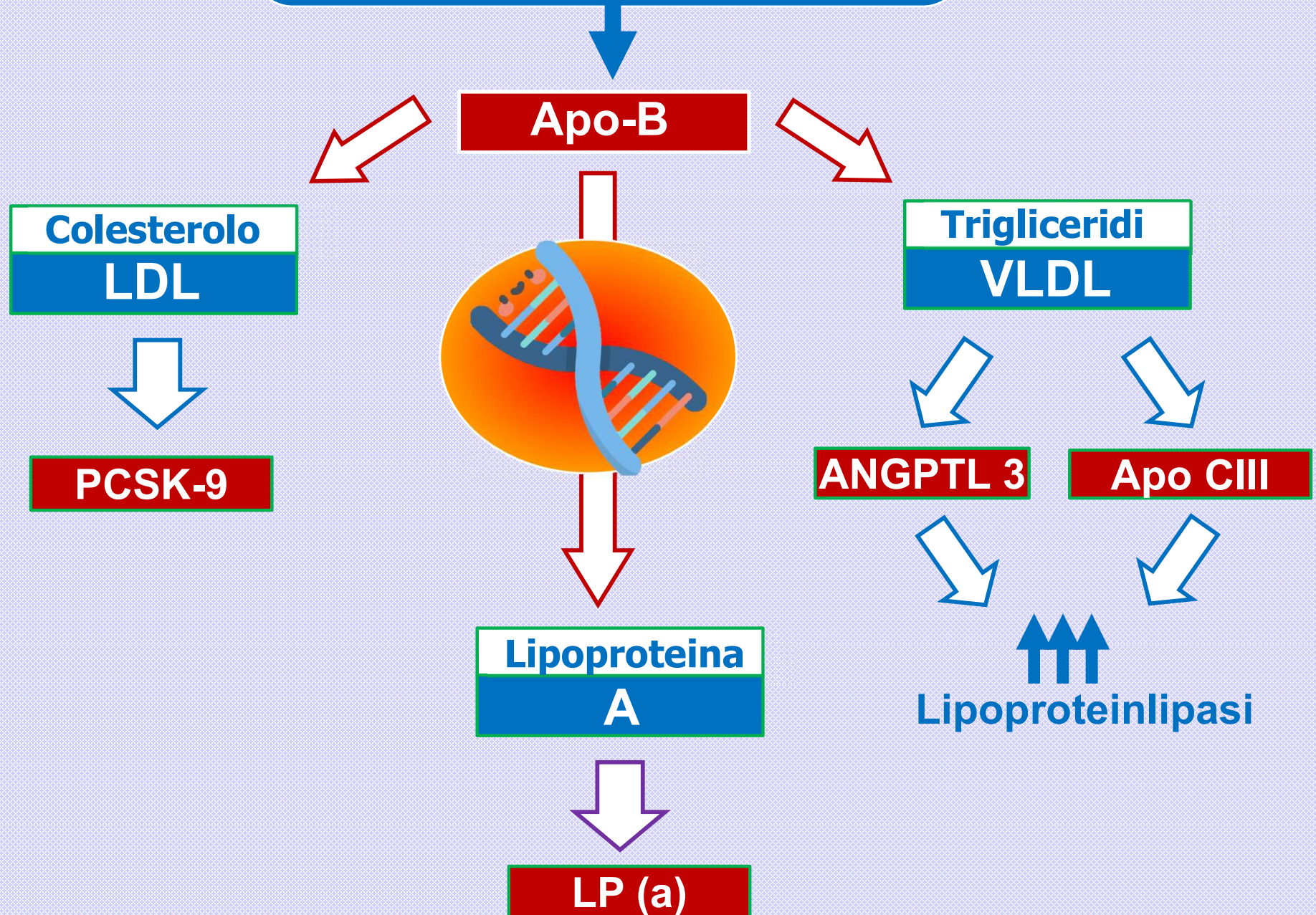
(Rothgangl, Nat Biotechnol 2021)



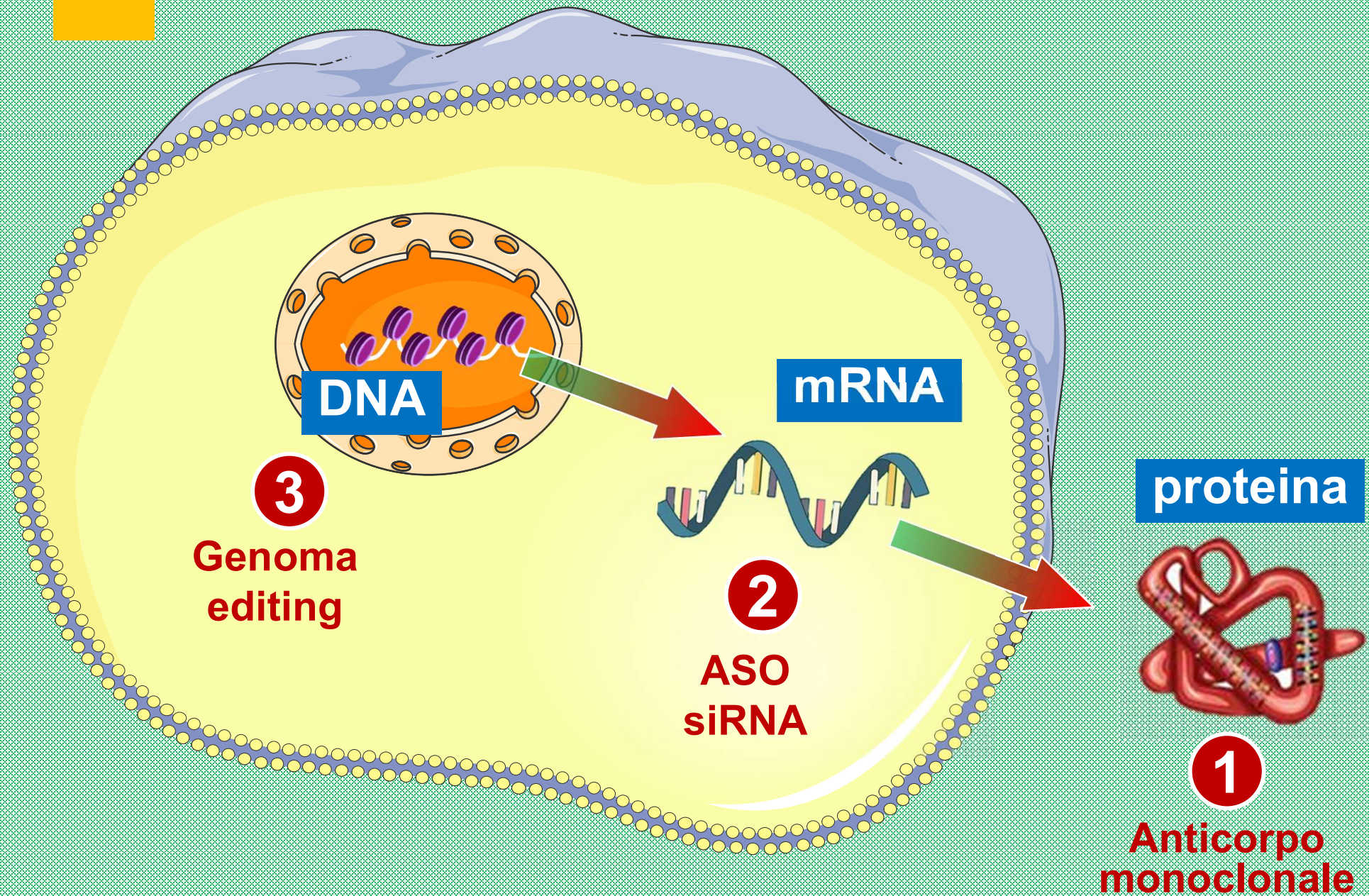


CONCLUSIONI

# TARGET GENETICI



# Terapia genica: meccanismi generali



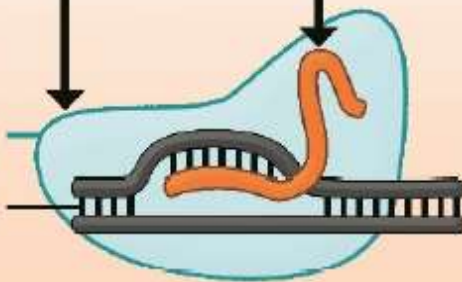
mRNA encoding  
base editor

guide RNA specific  
for *PCSK9*



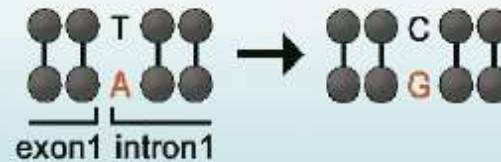
NUCLEUS

base editor  
*PCSK9* gene



splice site

base editing



*PCSK9* mRNA  
after editing



retention and read-through  
of intron 1



premature termination  
of *PCSK9* synthesis



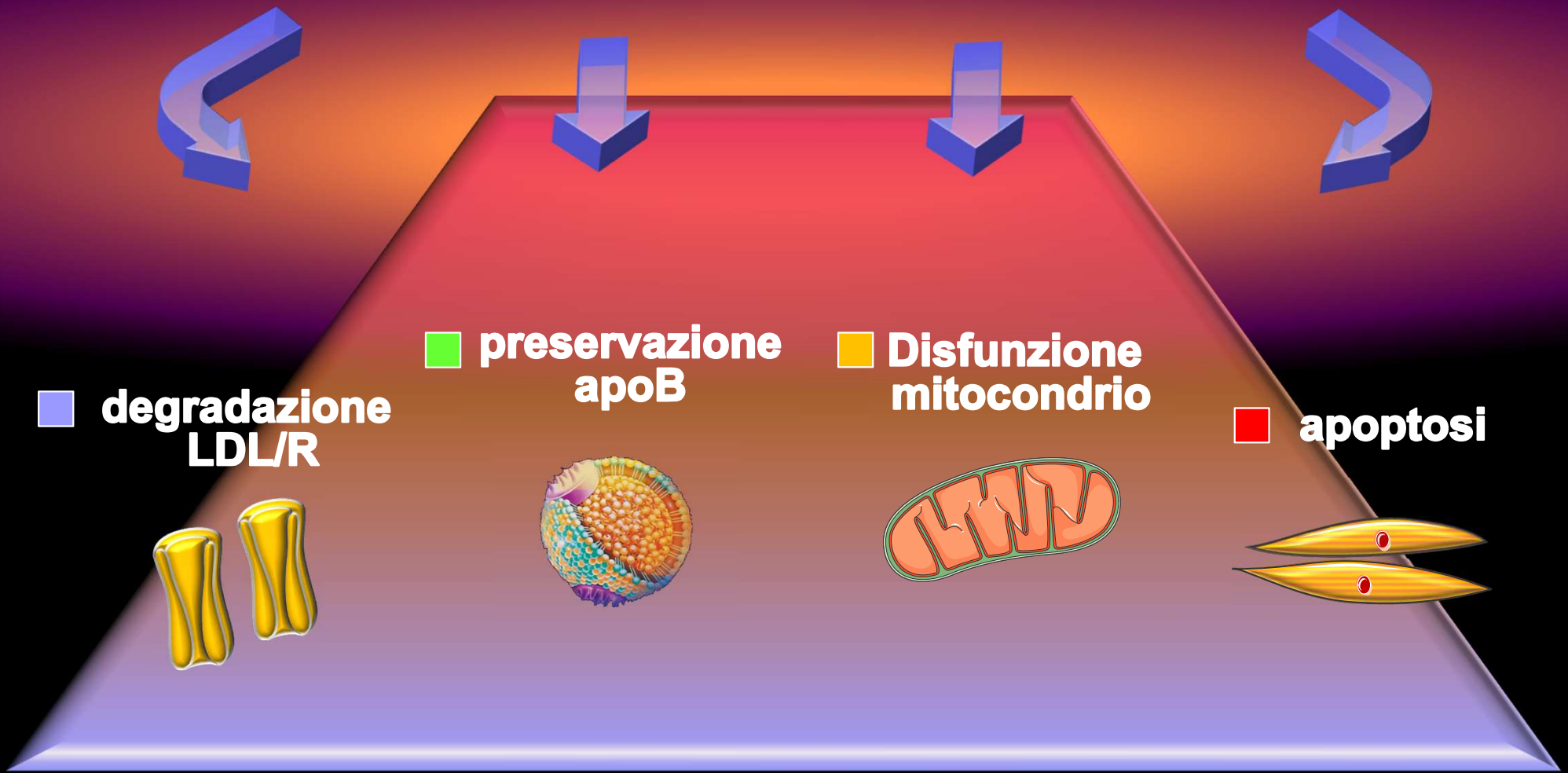
*PCSK9* ↓90%

HEPATOCTE

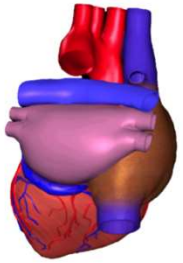
ooE

# Azioni intracellulari di PCSK/9

(Tang, Cardiovasc Diab 2020)



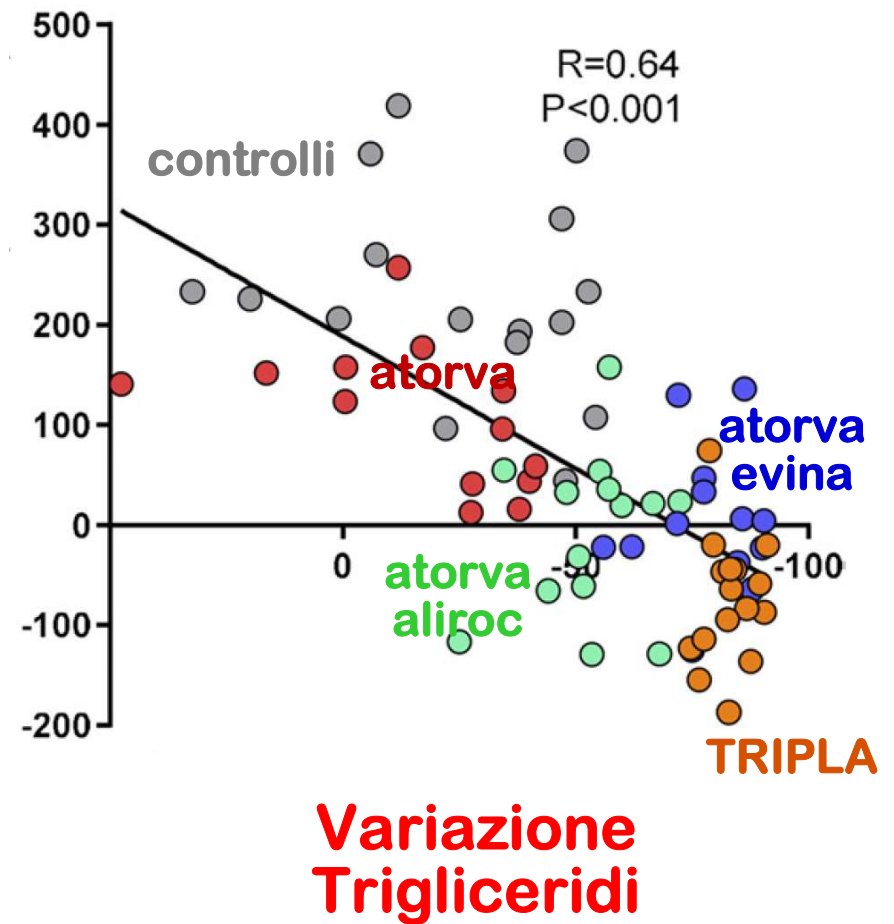
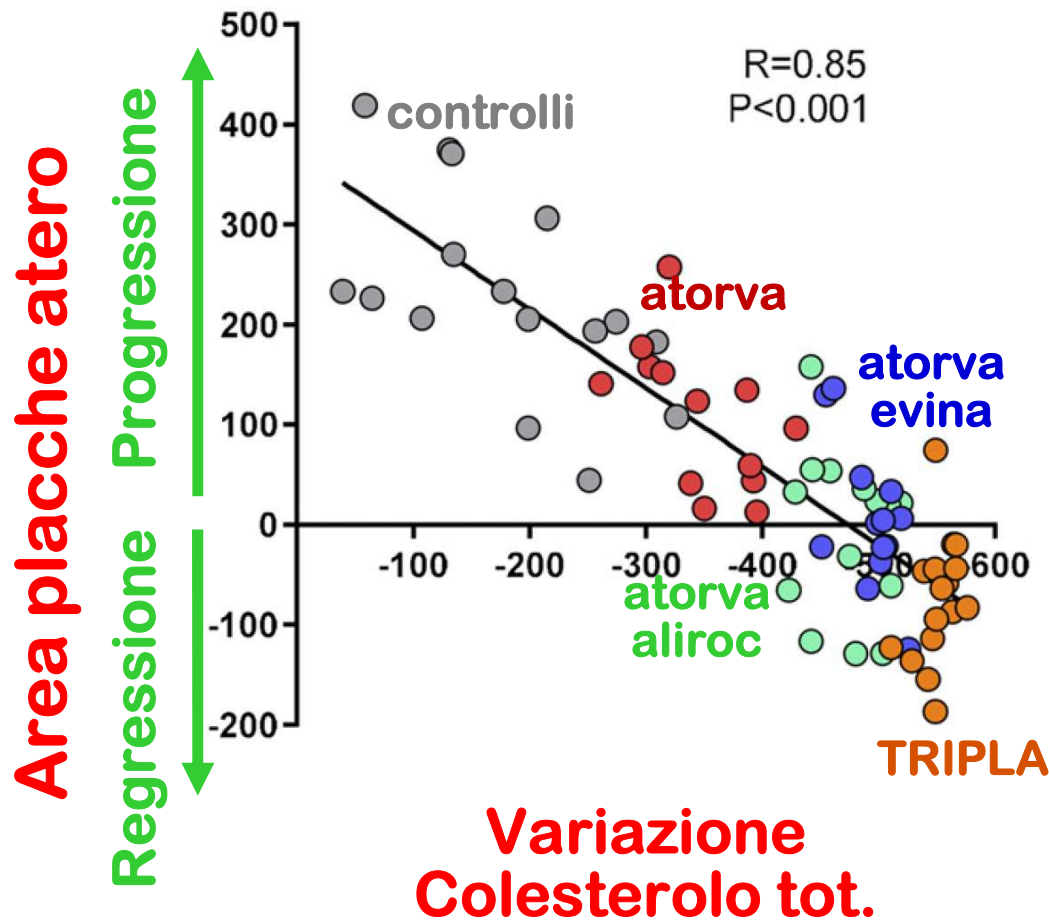




# Tripla terapia: eradicazione rischio residuo lipidico ?

(Pouwer, J Lipid Res 2020)

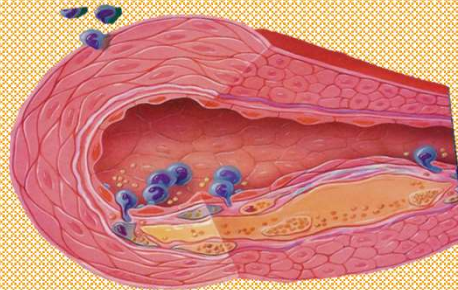
## Alirocumab + Evinacumab + Atorva



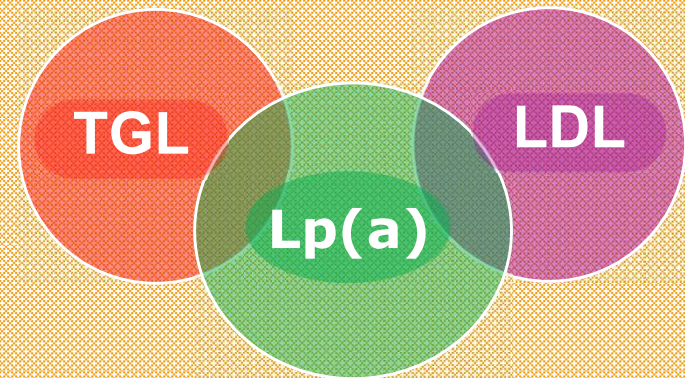
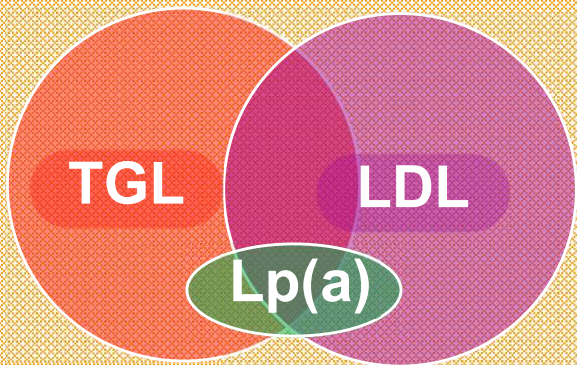
# Eradicazione rischio lipidico residuo

## Apolipoproteina B

dislipidemia



↑ Lp (a)



Statine - Bempe - Eze  
PCSK9i - Inclisiran  
Evinacumab

Pelacarsen  
(Olpasiran)