# NANOMEDICINA: UNA NUOVA ÈRA DEL FARMACO?

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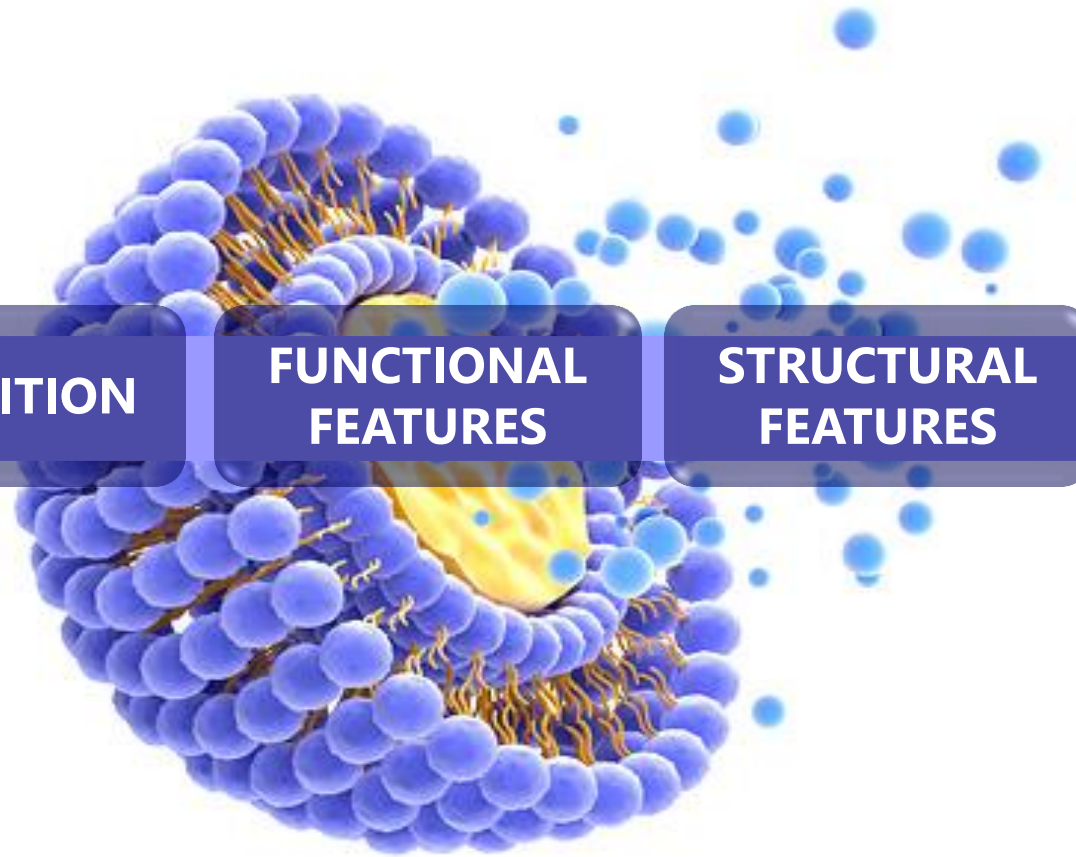
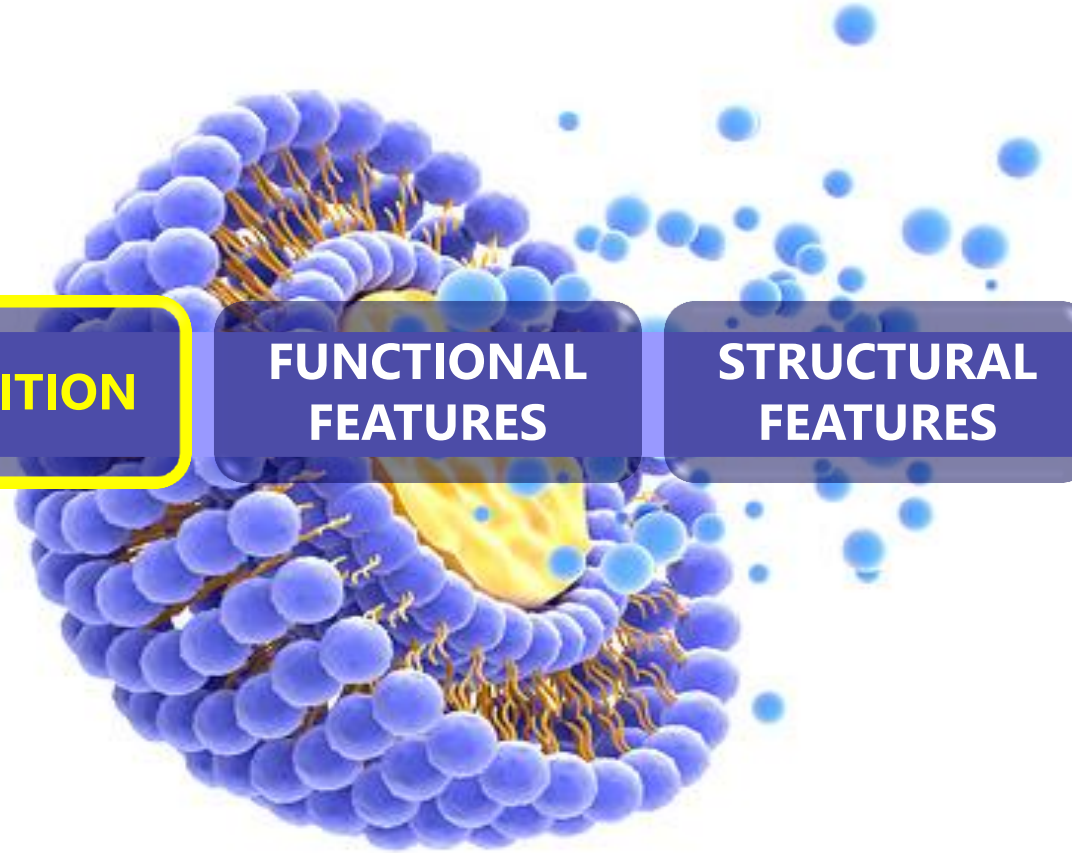


DEFINITION

FUNCTIONAL FEATURES

STRUCTURAL FEATURES

PRE-CLINICAL APPLICATION IN HD



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# WHAT'S NANOMEDICINE?

«Nanomedicine is a **branch of medicine** that applies the knowledge and tools of **nanotechnology** to the **prevention and treatment** of disease.»

*Nature*

[1] https://www.nature.com/subjects/nanomedicine

All the studies of "objects" sizing 1-100 nm.

NANOSCIENCE

Creation, manipulation and application of structures in the nanometer size range.[2]

NANOTECHNOLOGY

Application of Nanotechnology to Medicine

NANOMEDICINE

[2] Kawasaki and Player, **Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer.** *Nanomedicine* 2005. 1; 101-109

# FROM NANOMEDICINE TO NANOCARRIERS

Nanometer-sized particles have **optical**, **magnetic**, **chemical** and **structural properties** that distinguish them from bulk solids, with potential applications in medicine.

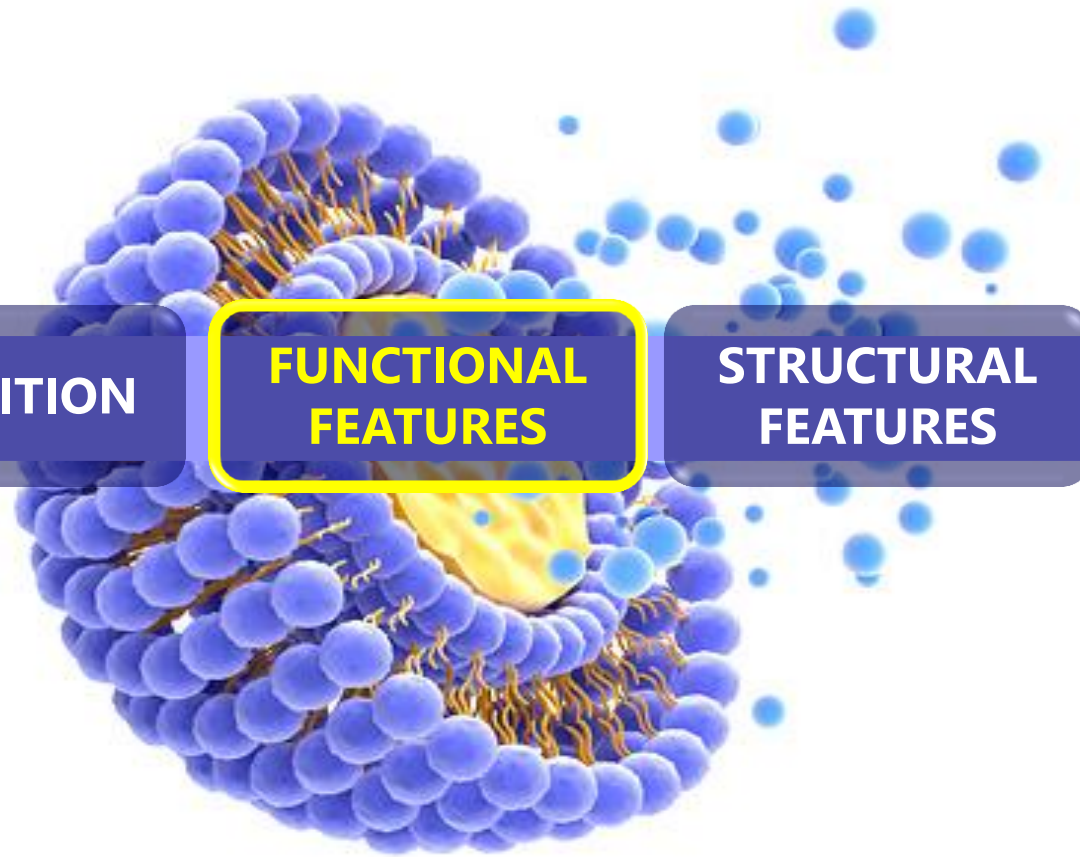
These Nanoparticles, called **Nanocarriers**, can be **engineered on surface** in order to **selectively transfer** a **cargo** (active ingredients, genetic material, contrast agents, etc.) to the **target cell**, thus creating innovative nanoscale **vehiculation systems**, called "**NanoMedicines**" (**NanoMed**).

[3] Bobo D et al, **Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date.** *Pharmaceutical Research* 2016. 33:2373-87

«We can imagine a future in which **nanocarriers**, **small** and **smart**, could flow free in the bloodstream, **get specifically target sites**, interact with them and **release the drugs**, to **cure tissues**, to **kill diseased cells** or to **fight with foreign invasors**.»

Robert S. Langer

Wolf Prize in Chemistry, Professor of Chemical and Biomedical Engineering at MIT



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# HOW DO NANOCARRIERS WORK?

## DRUG STABILIZATION AND PROTECTION

**INCREASED BIOAVAILABILITY**

## DRUG DELIVERY MODULATION

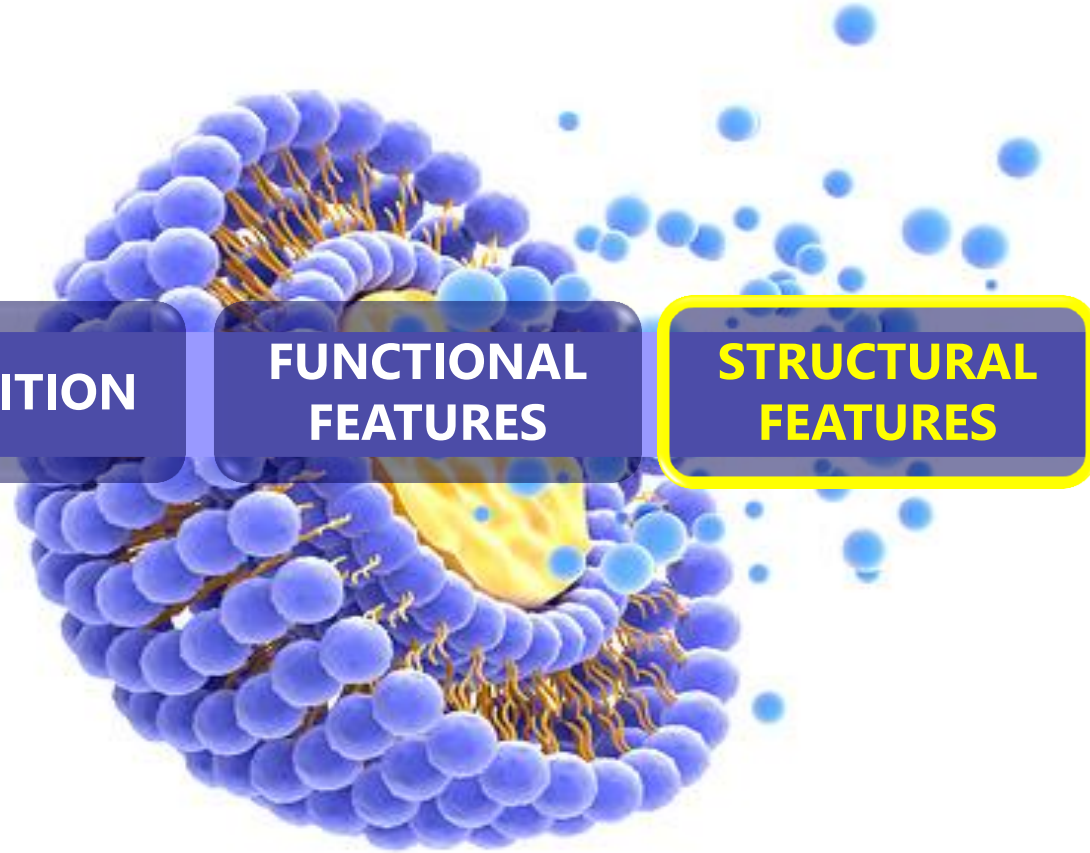
**INCREASED PHARMACOKINETICS**

## TARGETED RELEASE

- Passive («Enhanced Permeability and Retention»)
- Active (affinity between NanoMed-anchored ligands and target cell receptors)

**INCREASED THERAPEUTIC EFFECT**


[4] Agrahari V et al, **Challenges associated and approaches for successful translation of nanomedicines into commercial products**. *Nanomedicine (Lond.)* 2017. 12:819-23
[5] Etheridge ML et al, **The big picture on nanomedicine: the state of investigational and approved nanomedicine products**. *Nanomedicine* 2013. 9:1-14



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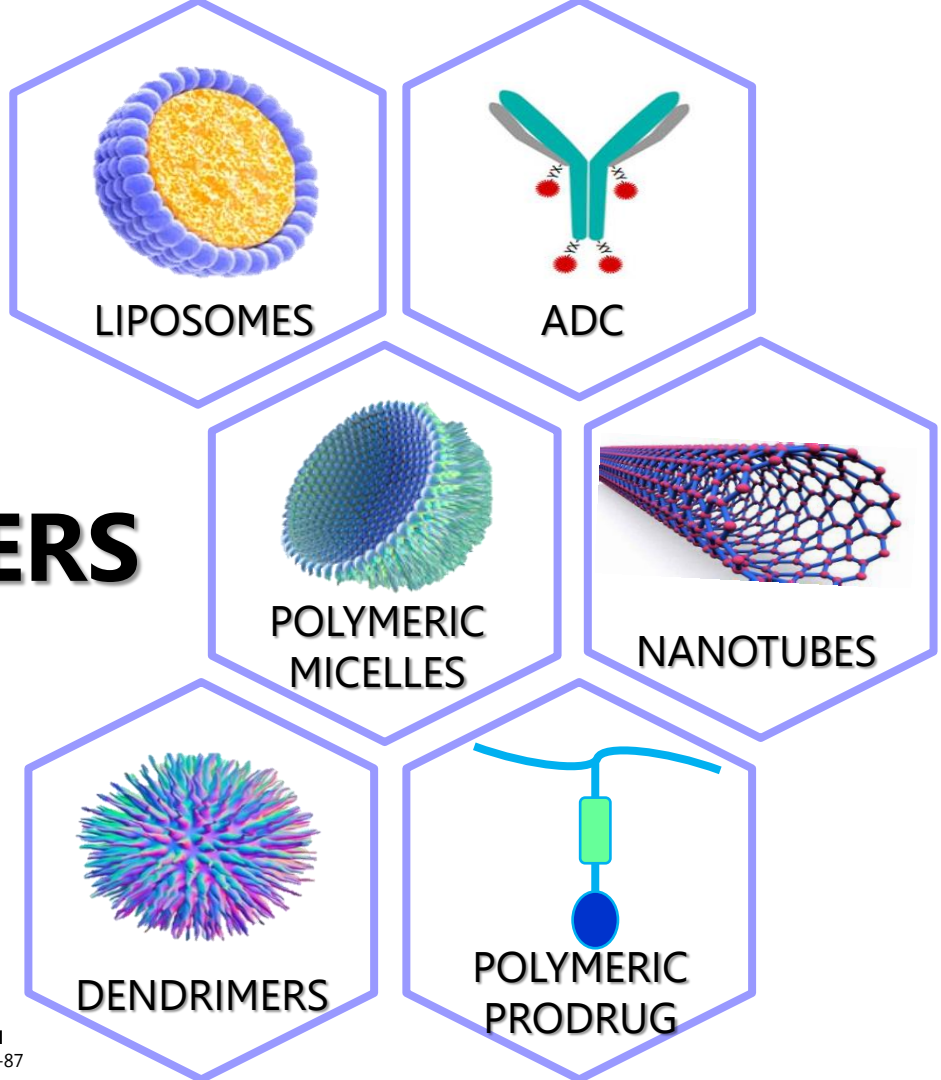
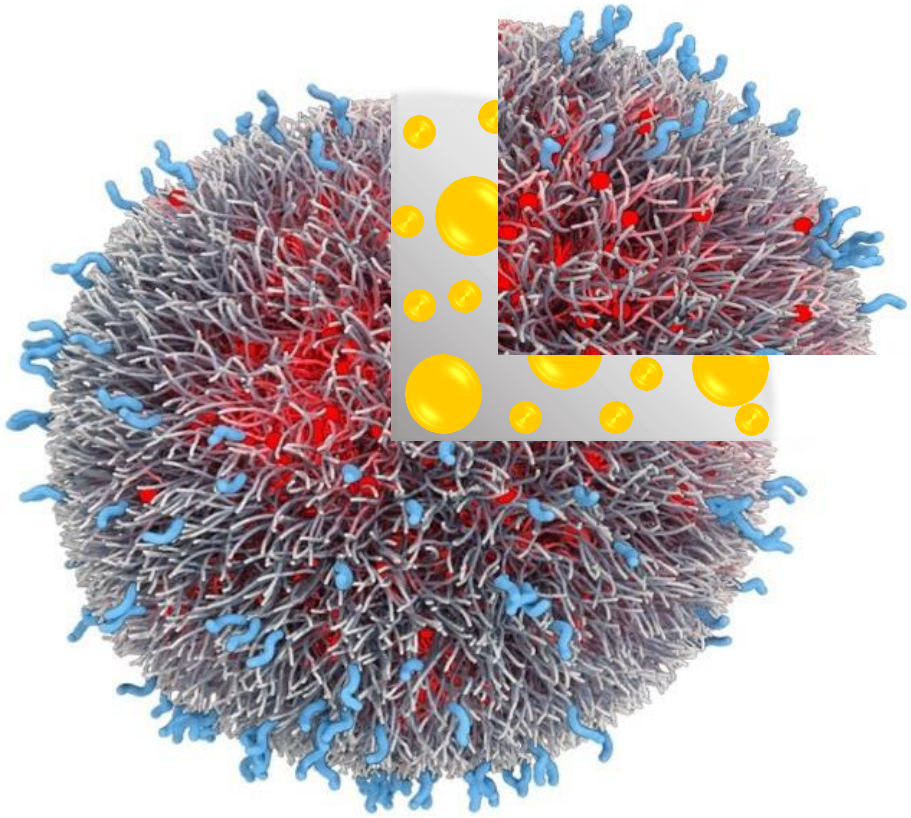
# NANOCARRIERS




[3] Bobo D et al, **Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date.** *Pharmaceutical Research* 2016. 33:2373-87

# POLYMERIC NANOPARTICLE (NP)



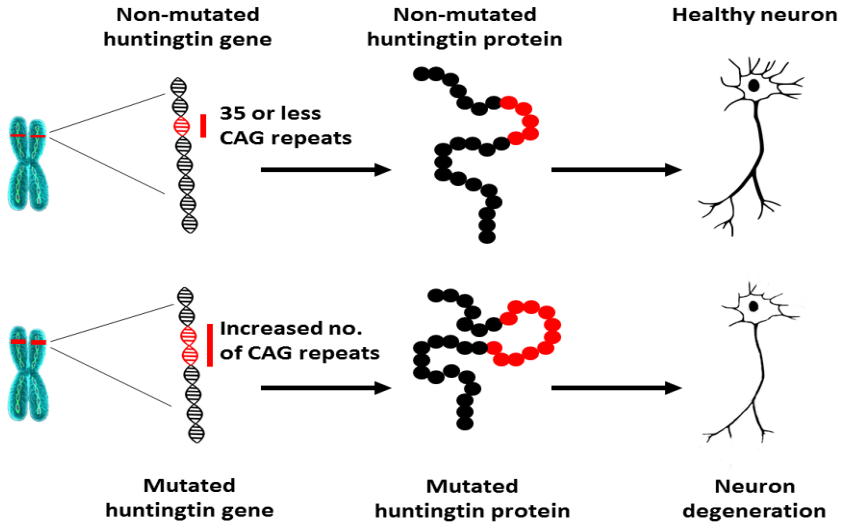
DRUG

LIGAND

POLYMER

# HUNTINGTON'S DISEASE (HD)

- Progressive **neurodegenerative** disorder
- **Autosomal dominant** disease
- Caused by a CAG expansion in the gene encoding the **huntingtin** (HTT) protein

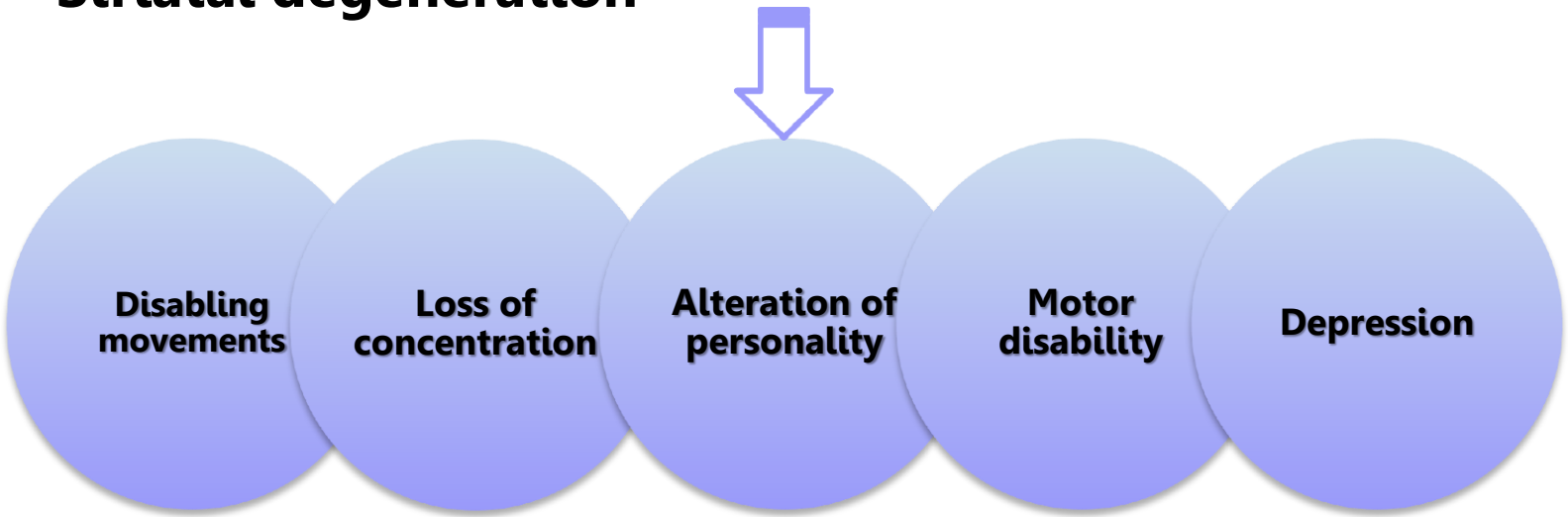



[6] The Huntington's Disease Collaborative Research Group, **A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes.** *Cell* 1993. 72:971–983
[7] Martin JB and Gusella JF, **Huntington's disease: pathogenesis and management**. *The New England Journal of Medicine* 1986. 375:1287-1276.

# HUNTINGTON'S DISEASE (HD)

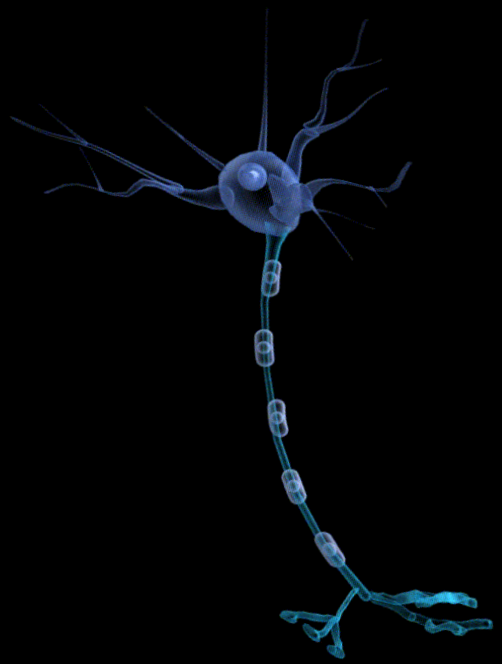
## ALTERATIONS

- **Atrophy** of the **basal ganglia**
- **Degeneration** of cells in the **frontal cortex**
- **Striatal degeneration**




[8] Vonsattel JP and DiFiglia M, **Huntington disease**. *Journal of Neuropathology & Experimental Neurology* 1998. 57:369–384;
[9] Ross CA et al, **Huntington disease: natural history, biomarkers and prospects for therapeutics.** *Nature Reviews Neurology* 2014. 10:204 –216

# WHAT HAPPENS IN HD BRAIN?



In mutated astrocytes:

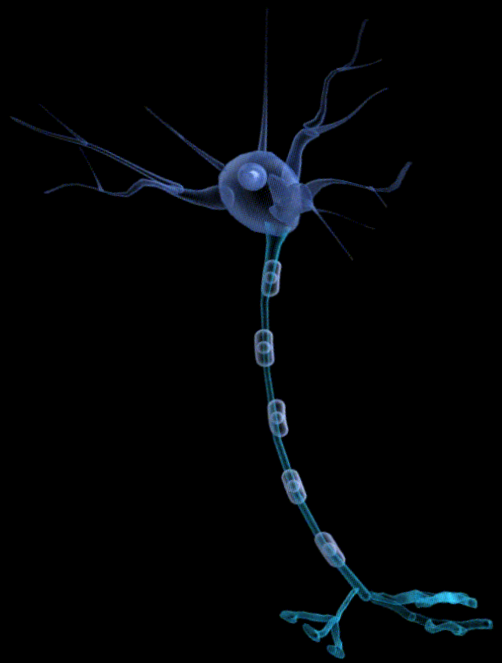
↓ CHOLESTEROL

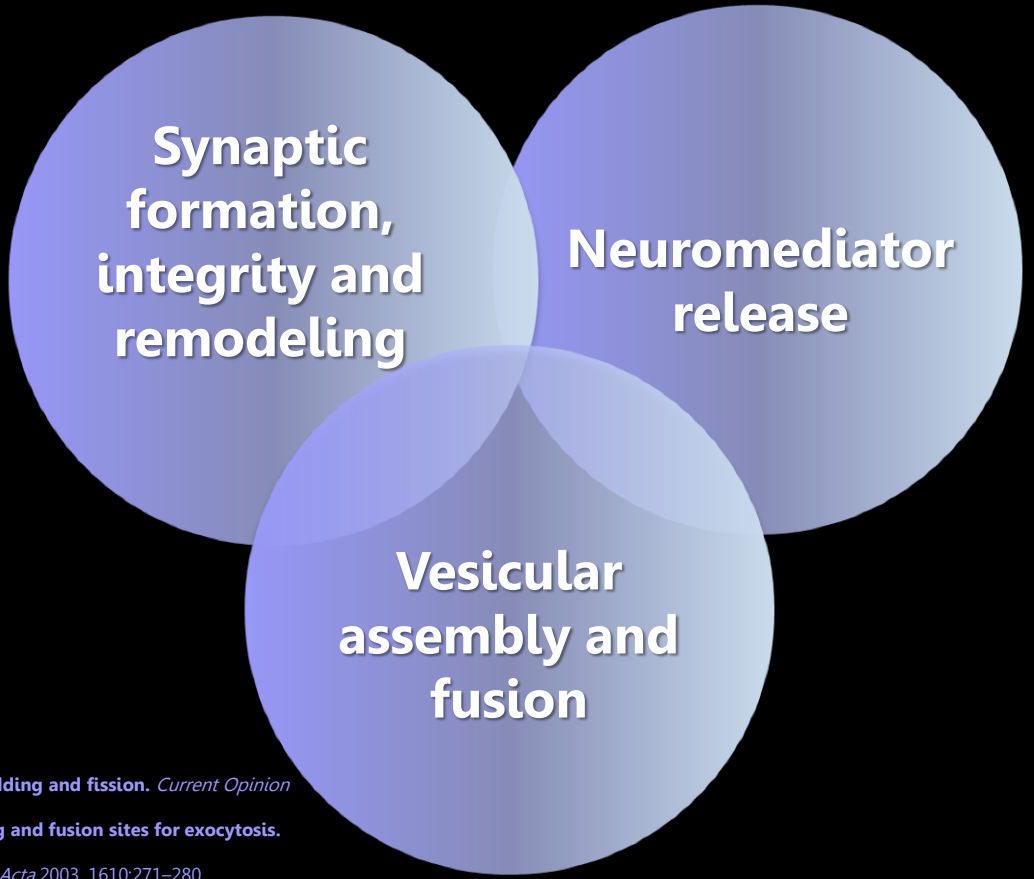
How can we note it?

**24-HYDROXY-CHOLESTEROL**

[10] Leoni V et al, **Plasma 24S-hydroxycholesterol correlation with markers of Huntington disease progression.** *Neurobiology of Disease* 2013. 55:37–43

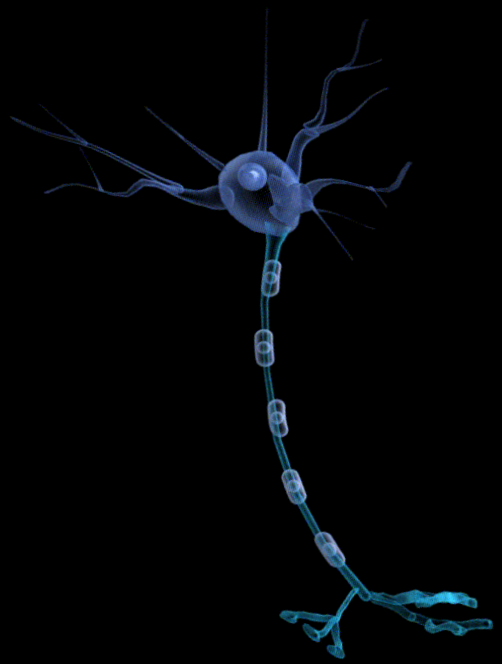
# CHOLESTEROL FUNCTIONS






[11] Huttner WB, Zimmerberg J, **Implications of lipid microdomains for membrane curvature, budding and fission.** *Current Opinion in Cell Biology* 2001. 13:478–484
[12] Lang T et al, **SNAREs are concentrated in cholesterol-dependent clusters that define docking and fusion sites for exocytosis.** *The EMBO Journal* 2001. 20:2202–2213
[13] Pfrieger FW, **Role of cholesterol in synapse formation and function.** *Biochimica et Biophysica Acta* 2003. 1610:271–280
[14] Thiele C et al, **Cholesterol binds to synaptophysin and is required for biogenesis of synaptic vesicles.** *Nature Cell Biology* 2000. 2:42-49
[15] Mauch DH et al, **CNS synaptogenesis promoted by glia-derived cholesterol**. *Science* 2001. 294:1354–1357

# ↓ CHOLESTEROL



- CEREBRAL MALFORMATION
- ALTERATE COGNITIVE FUNCTIONS
- MARKED ALTERATION OF SYNAPTIC TRANSMISSION
- ALTERATE COMMUNICATION BETWEEN STRIATUM AND CORTEX, AS WELL AS BETWEEN NEURONS WITHIN THE STRIATUM

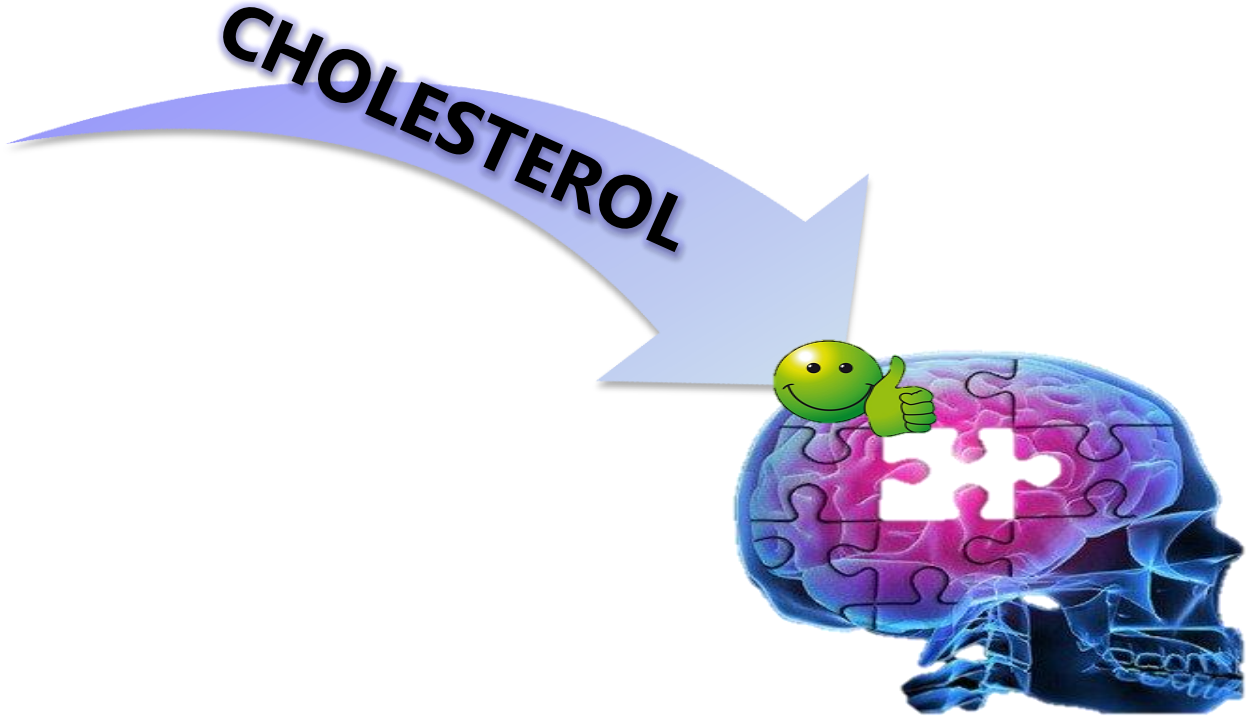
[16] Valenza M, Cattaneo E , **Cholesterol dysfunction in neurodegenerative diseases: is Huntington's disease in the list?** *Progress in Neurobiology* 2006. 80:165–176
[8] Vonsattel JP, DiFiglia M, **Huntington disease**. *Journal of Neuropathology & Experimental Neurology* 1998. 57:369–384

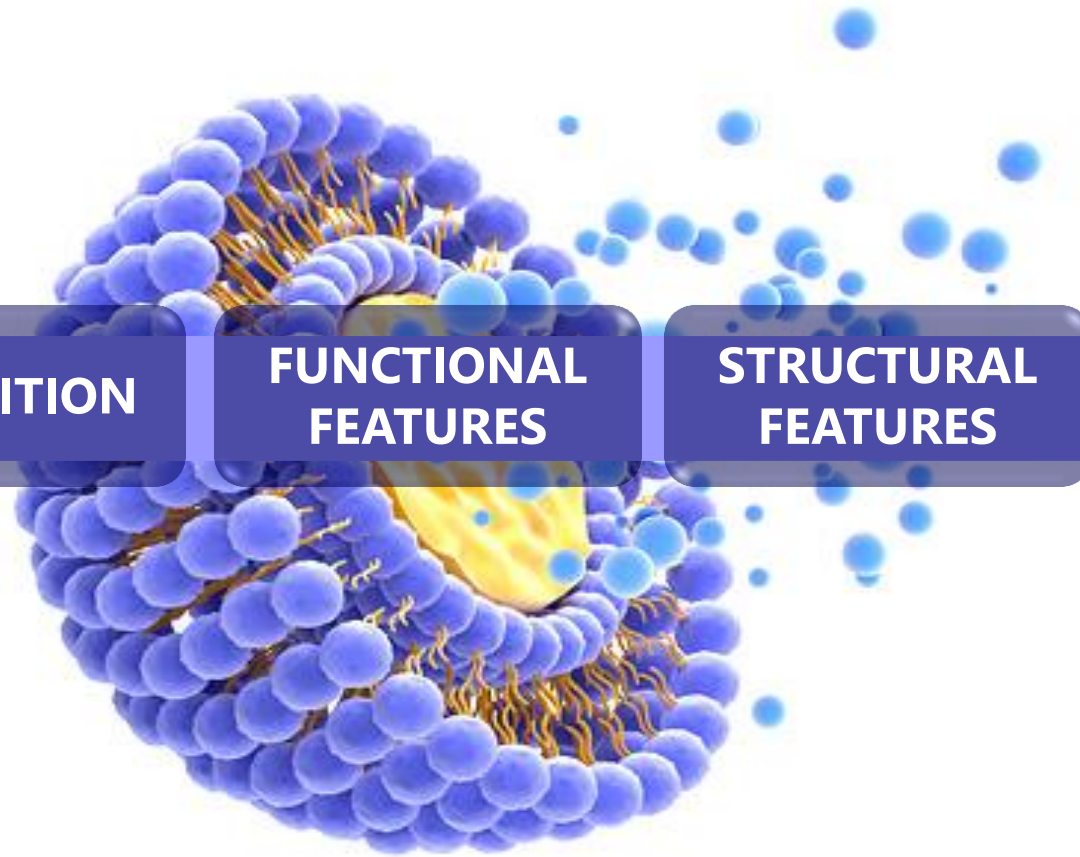
# A SIGNIFICANT LIMITATION

**CHOLESTEROL**

[17] Dietschy JM, Turley SD, **Thematic review series: brain Lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal.** *The Journal of Lipid Research* 2004. 45:1375–1397.

# HOW CAN WE OVERCOME THIS LIMITATION?





DEFINITION

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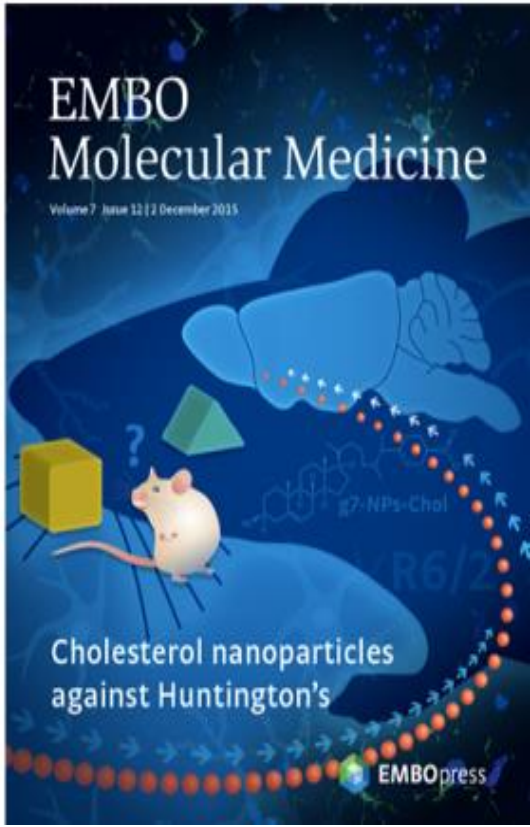
# THE PAPER

Published online: November 20, 2015

*Research Article*

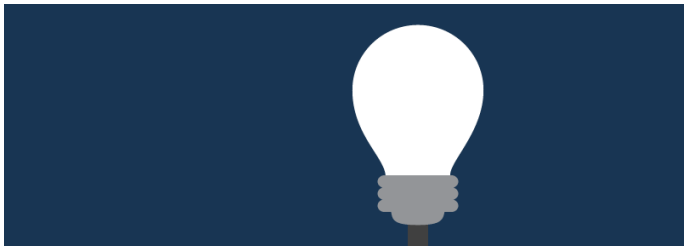
## Cholesterol-loaded nanoparticles ameliorate synaptic and cognitive function in Huntington's disease mice

Marta Valenza[1,†], Jane Y Chen[2,†], Eleonora Di Paolo[1,‡], Barbara Ruozi[3,‡], Daniela Belletti[3], Costanza Ferrari Bardile[1], Valerio Leoni[4,5], Claudio Caccia[4], Elisa Brilli[1], Stefano Di Donato[4,§], Marina M Boido[6], Alessandro Vercelli[6], Maria A Vandelli[3], Flavio Forni[3], Carlos Cepeda[2], Michael S Levine[2], Giovanni Tosi[3] & Elena Cattaneo[1,*]



# WHAT MUST NPs BE ABLE TO DO?

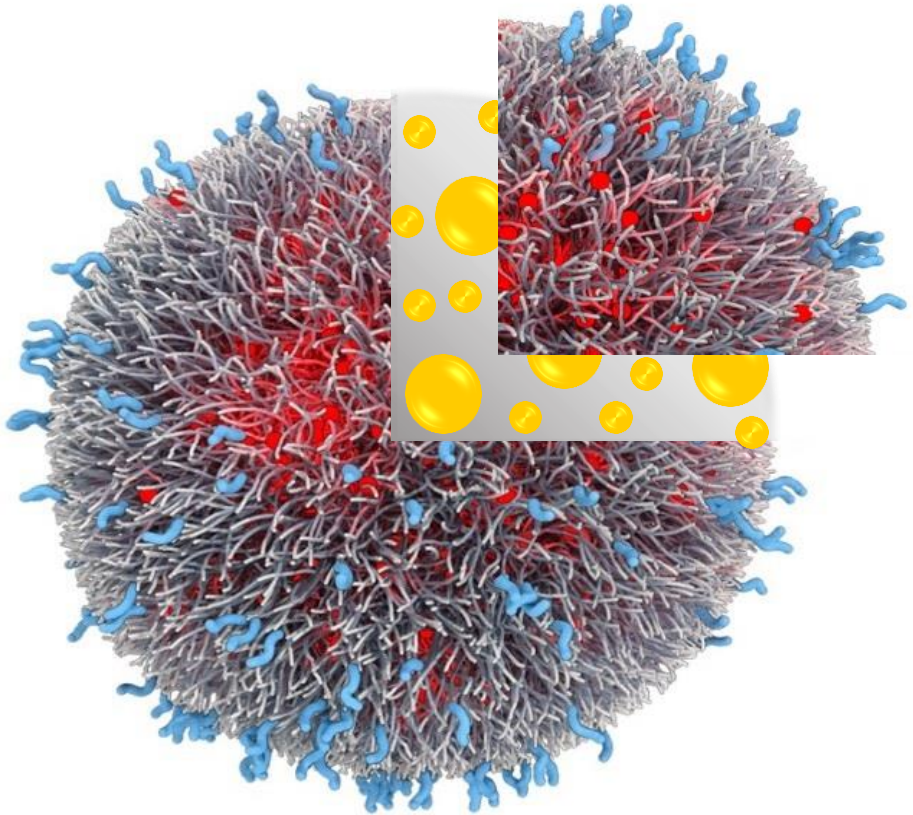
- **Cross** the **BBB**
- Load **high amounts** of Cholesterol (Chol)



- **Stably** circulate after administration without toxicity
- **Modulate** the release of Chol in the brain (efficacy with **few administration phases**)

[18] Belletti D et al, **Exploiting the versatility of Cholesterol in Nanoparticles formulation**. *International Journal of Pharmaceutics* 2016. 511:331-340

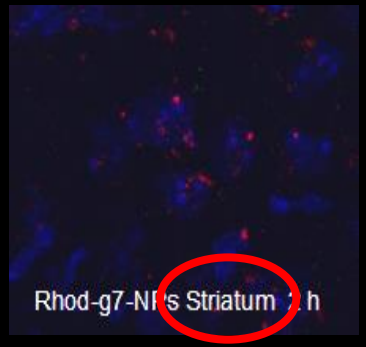
# THE G7-NP-CHOL



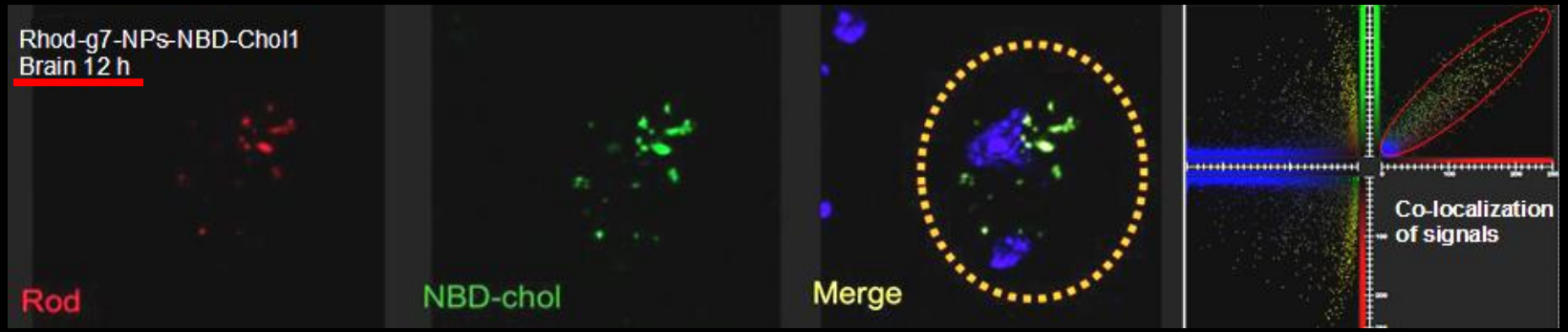
CHOLESTEROL

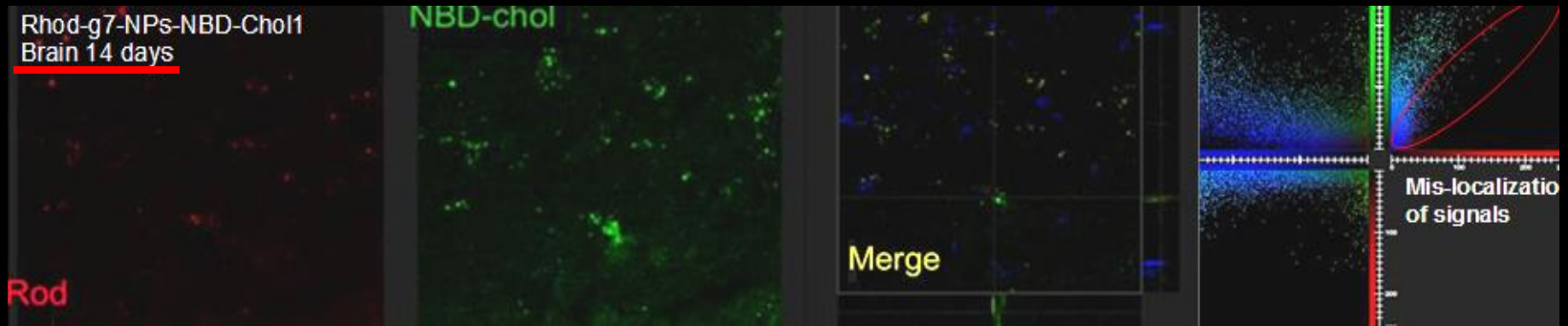
g7

PLGA


Striatum

Cortex 2 h


Rhod-g7-NPs-NBD-Chol1
Brain 12 h
Rod
NBD-chol
Merge
Co-localization
of signals

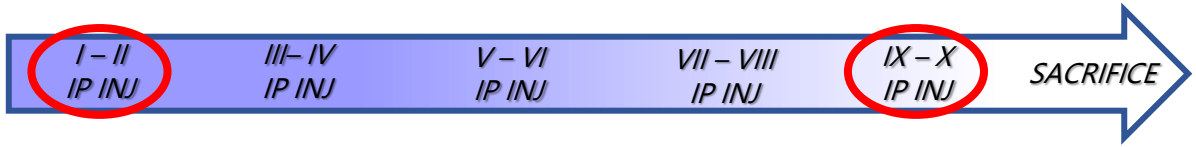

Rhod-g7-NPs-NBD-Chol1
Brain 14 days
NBD-chol
Rod
Merge
Mis-localizatio
of signals

# PATTERN OF ADMINISTRATION

HD SYMPTOMS IN **R6/2 MICE**

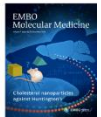
**AGE** OF MICE (WS)

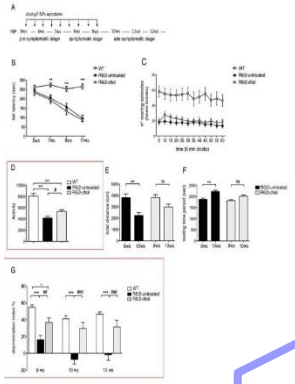
**~15 µG OF CHOLESTEROL** IN THE HD MICE BRAIN




Research Article

Cholesterol-loaded nanoparticles ameliorate synaptic and cognitive function in Huntington's disease mice



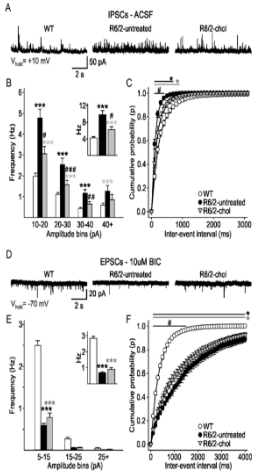


GABAergic transmission

Locomotor activity, resting time and mean velocity

**RESCUE OF SYNAPTIC COMMUNICATION**

Object recognition and recovery of memory deficit




Recovered levels of several synaptic proteins

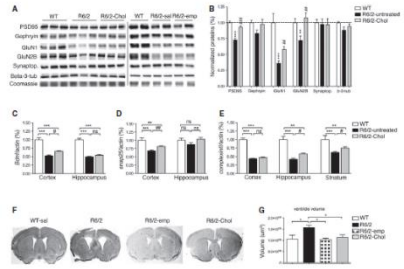
Improved expression of genes involved in neuro-transmission in the pathological areas

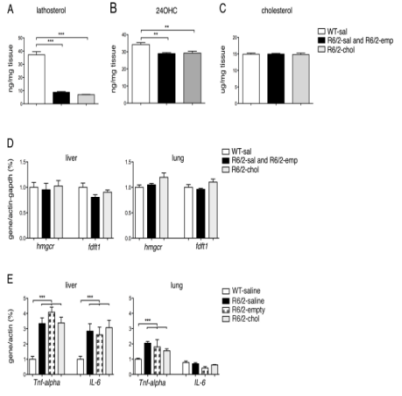
**IMPROVEMENT OF GENERAL ACTIVITY AND LEVELS OF SYNAPTIC PROTEINS**

Alteration of metabolite or precursors of cholesterol

Slight effects on mRNA levels of inflammatory genes in liver and lungs of the treated mice

Effect on mRNA levels of cholestero-genic genes in liver and lungs of the treated mice





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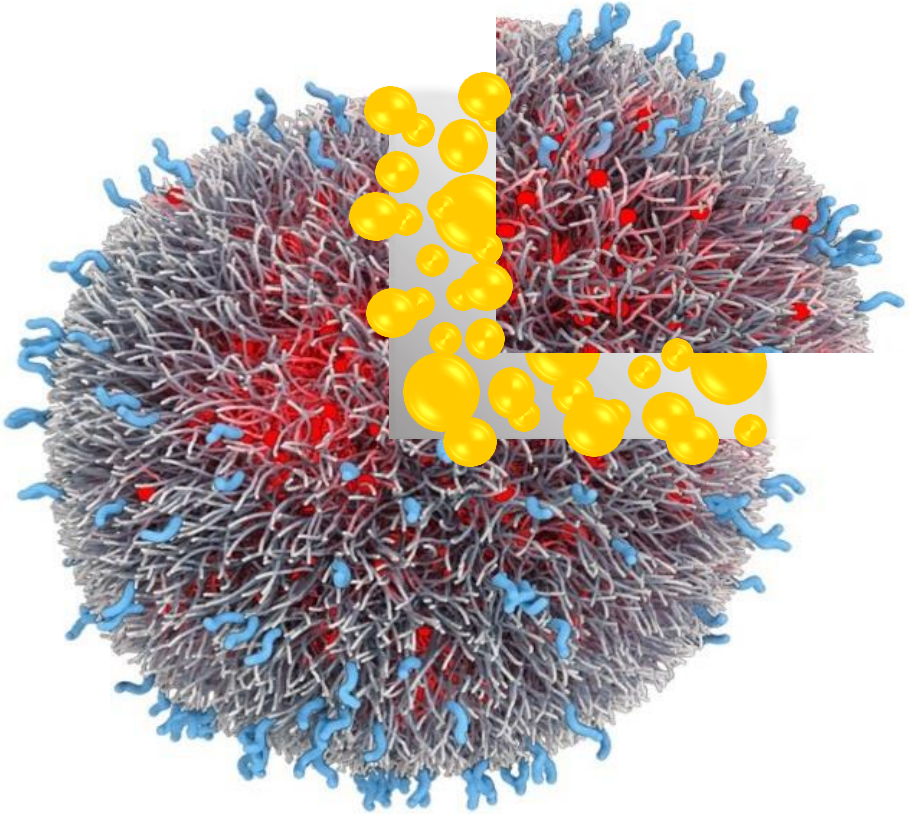
# THE NEXT LEVEL



More Cholesterol

Few Administrations

Research Article

Cholesterol-loaded nanoparticles ameliorate synaptic and cognitive function in Huntington's disease mice

EMBO Molecular Medicine

# TAKE HOME MESSAGES

- **Nanomedicine** uses nanotechnology in order to prevent and treat diseases
- Nanocarriers can selectively transfer a cargo to the target cell, creating **nanoscale vehiculation systems**
- Using Nanocarriers, **bioavailability**, **pharmacokinetics** and **therapeutic efficacy** are increased
- Several studies demonstrate the ability of Nanocarriers to **cross BBB**, giving a chance to treat neurodegenerative diseases

**INVASIVE TREATMENT**

**vs**

**NON-INVASIVE TREATMENT**

# HOW COULD WE IMAGINE A NANOCARRIER?

# THANK YOU FOR YOUR ATTENTION

**SPECIAL THANKS TO**
**Prof.ssa** Daniela **GIULIANI**
**Prof.ssa** Barbara **RUOZI**
**Prof.** Giovanni **TOSI**
**Prof.** Davide **MAZZI**

~~The End~~ Start

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