

The nose knows: optimizing nanoparticle properties is the shortest route from the bench to the brain

Prof. Eliana M. Lima

Full Professor

*Pharmaceutical Nanotechnology
School of Pharmacy – UFG*

Controlled Release Society



Brazilian Local Chapter



PHILADELPHIA, PA
JULY 13-18, 2025



**NEXT-GENERATION
DELIVERY INNOVATIONS**

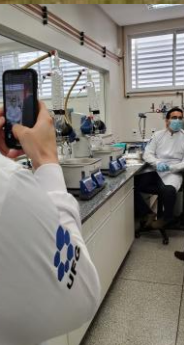


Controlled Release Society



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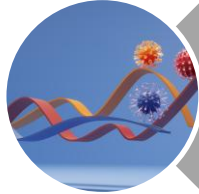
**The goal of drug
delivery**



**Getting it
right:**



The right drug

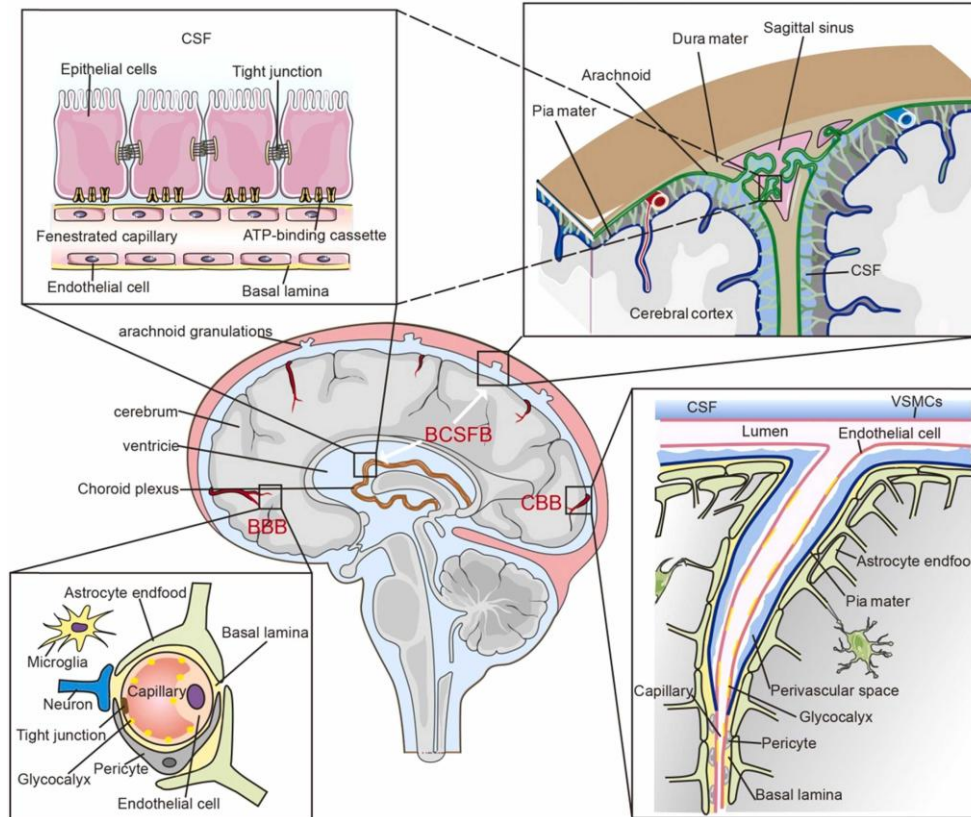


The right dose



The right target

BIOLOGICAL BARRIERS FOR BRAIN DRUG DELIVERY



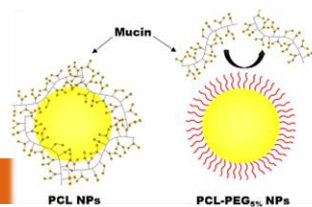
Blood-brain barrier
(**BBB**)

Blood-cerebrospinal
fluid barrier (**BCSFB**)

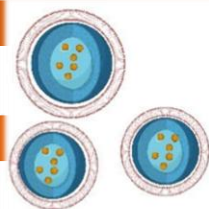
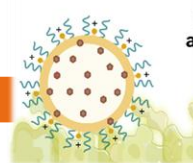
Cerebrospinal fluid-
brain barrier (**CBB**)

From the bench

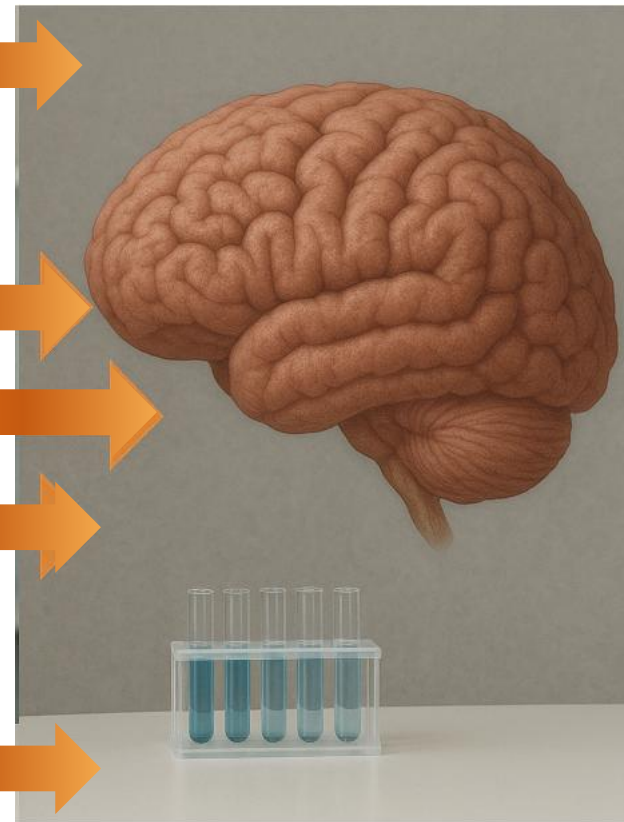
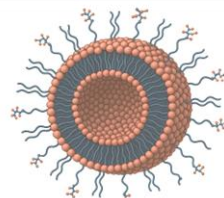
To the brain



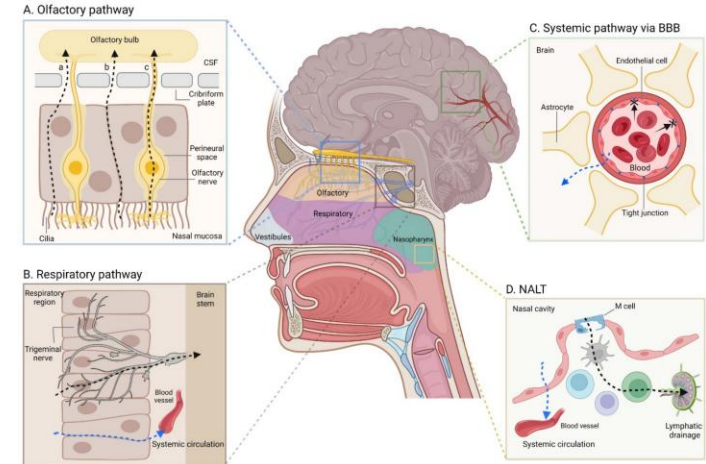
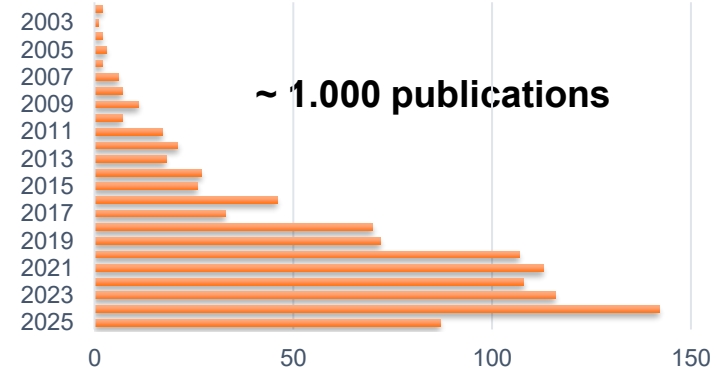
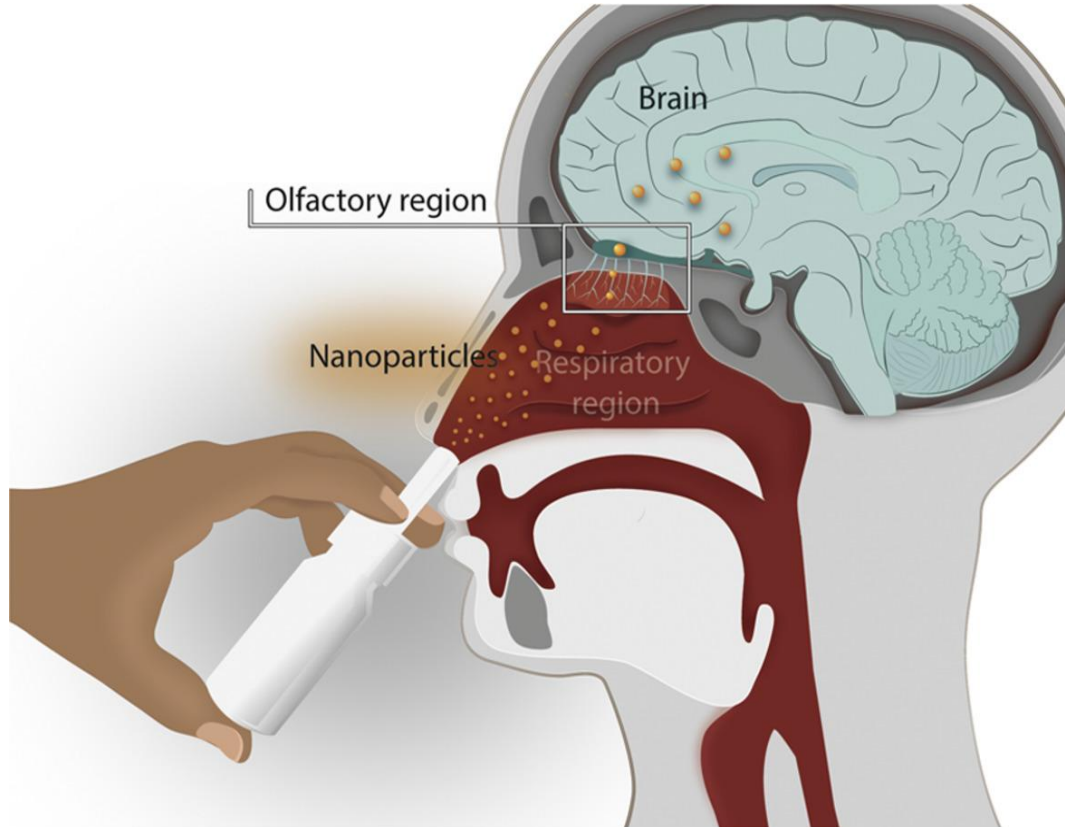
DOTAP
Pluronic® F127
POH

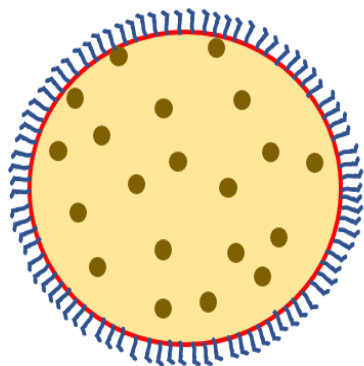


BIOMIMETIC DELIVERY
SYSTEM (NP-MB)



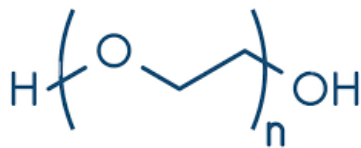
NOSE-TO-BRAIN DELIVERY



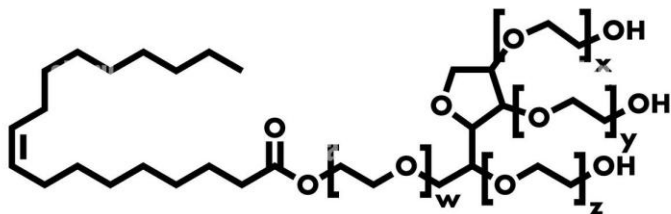


Melatonin-loaded
polycaprolactone NPs

polysorbate 80
surface



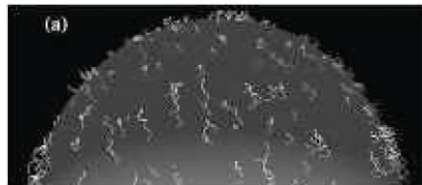
polyethylene glycol



polysorbate-80

The role of PEG

Mushroom



Brush



**Strategy to
promote long
circulation**

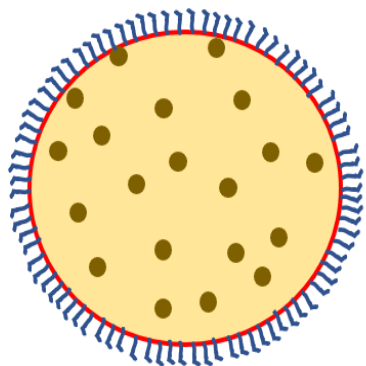
**Complement
system
activation**

**Protein
Corona**

**Mucus
penetration**

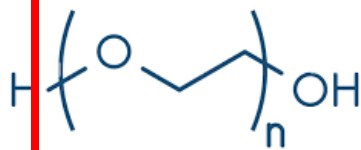
DE OLIVEIRA VIANA, I.M. et al. Acta Pharmaceutica Sinica B, v. 3, p. S22113835210007,
VIANA, I.M.O. et al. Nanoscale, v. 8, p. 1-20, 2020.
GRENIER, P. et al. JOURNAL OF CONTROLLED RELEASE, v. 287, p. 121-131, 2018.
BERTRAND, N. et al. Nature Communications, v. 8, p. 777, 2017.



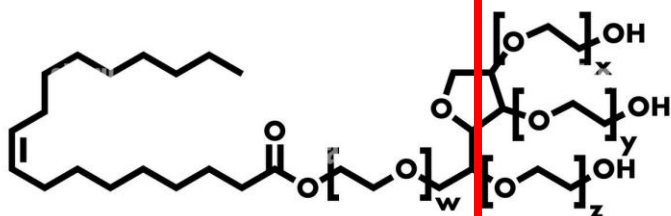


Melatonin-loaded
polycaprolactone NPs

polysorbate 80
surface



polyethylene glycol



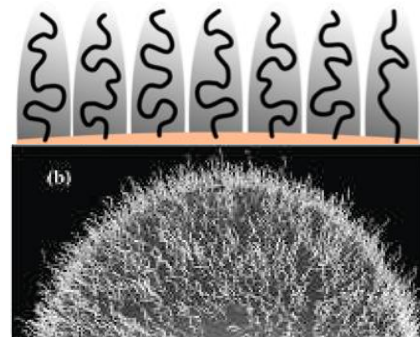
polysorbate-80

The role of PEG

Mushroom



Brush



Strategy to
promote long
circulation

Complement
system
activation

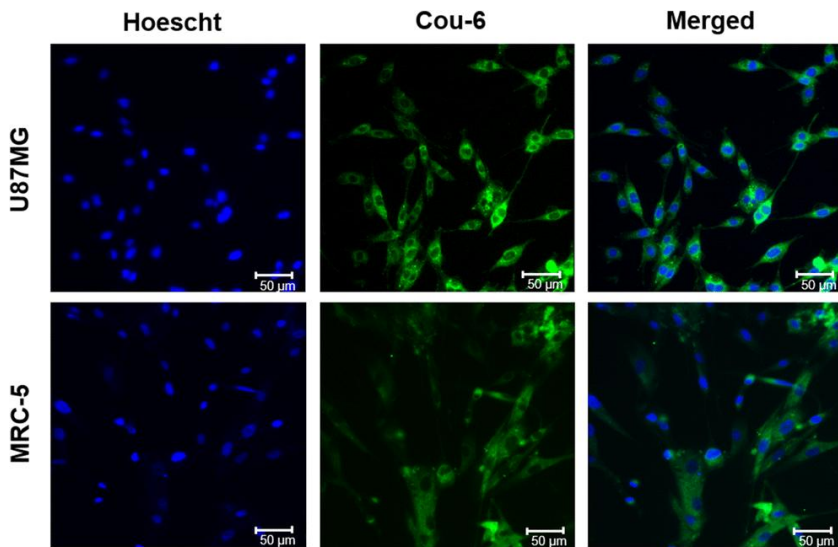
Protein
Corona

Mucus
penetration

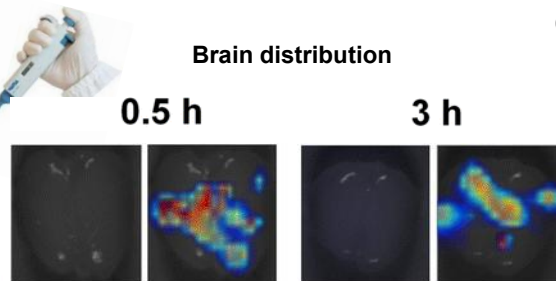
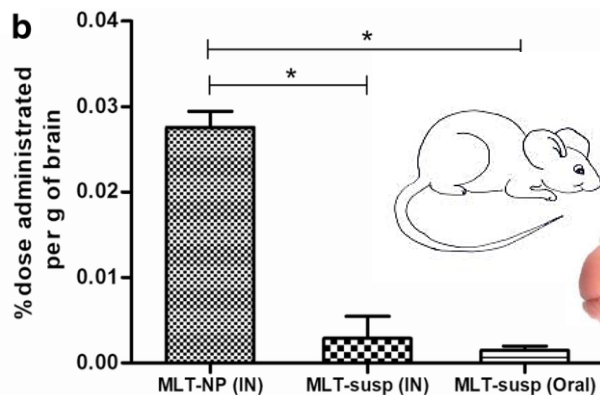
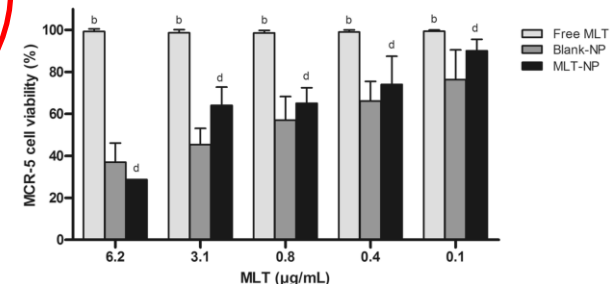
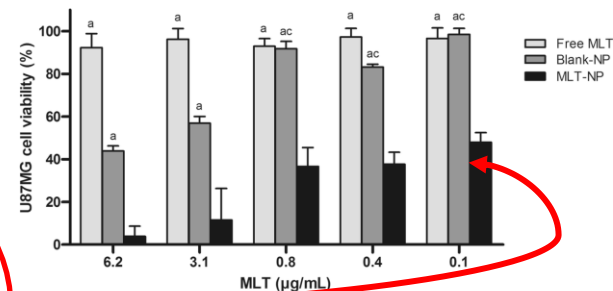
DE OLIVEIRA VIANA, I.M. et al. Acta Pharmaceutica Sinica B, v. 3, p. S22113835210007,
VIANA, I.M.O. et al. Nanoscale, v. 8, p. 1-20, 2020.
GRENIER, P. et al. JOURNAL OF CONTROLLED RELEASE, v. 287, p. 121-131, 2018.
BERTRAND, N. et al. Nature Communications, v. 8, p. 777, 2017.

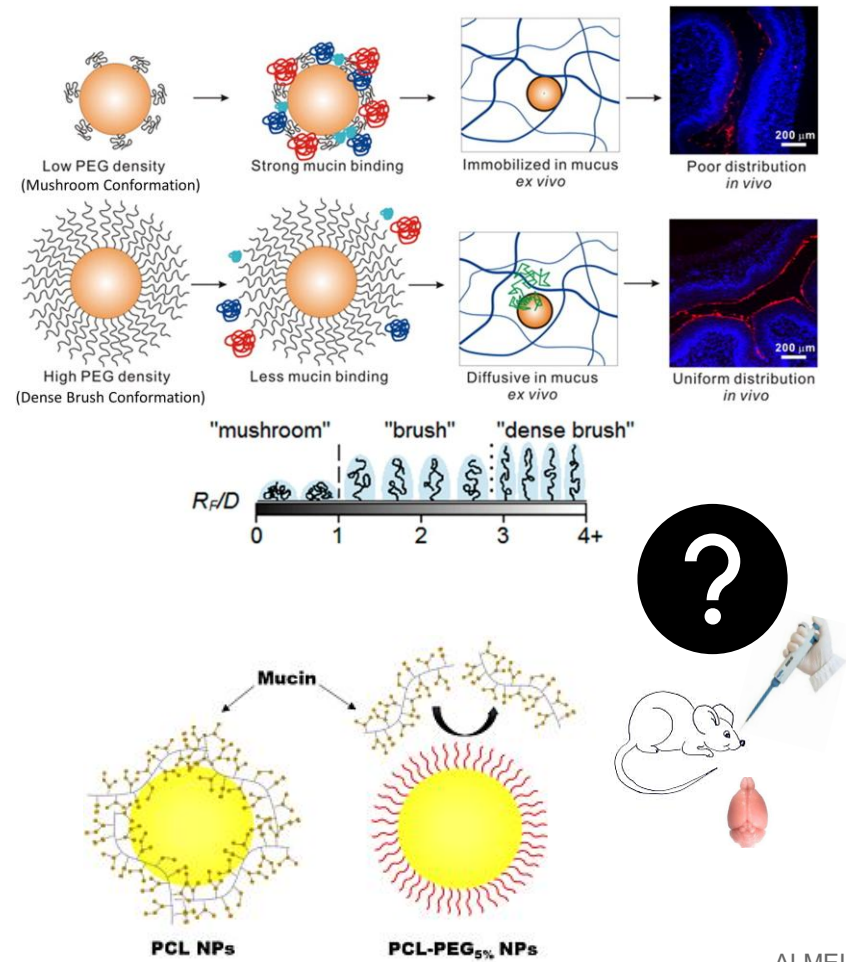


N2B delivery of melatonin-loaded PCL NPs

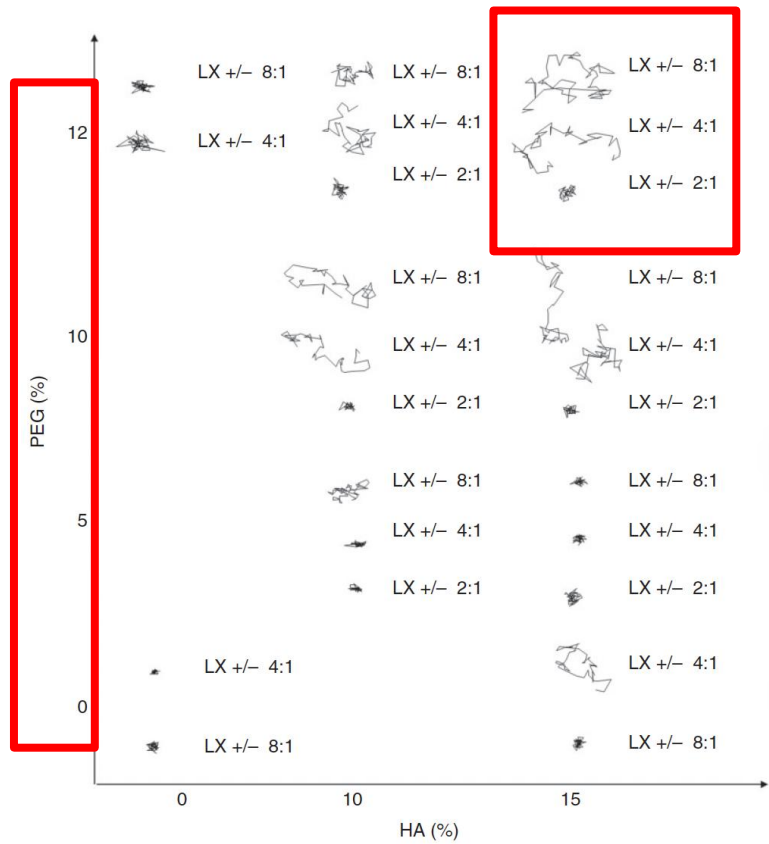


Selectivity towards glioma cells

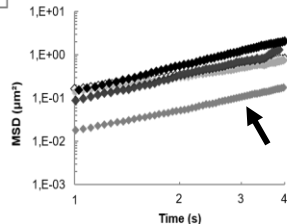




NP Mobility in pulmonary mucus



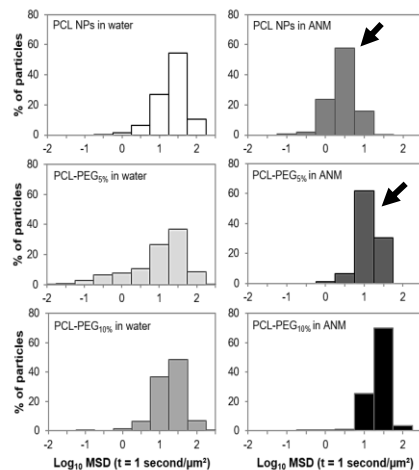
A



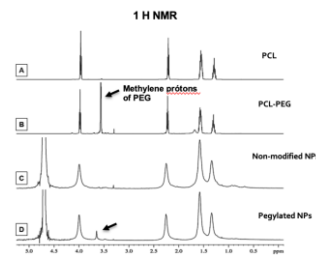
Particles mean MSD
at time = 1 s (μm^2)

- 9.9 ◇ PCL NPs in water
- 5.2 ♢ PCL-PEG5% NPs in water
- 10.2 ♢ PCL-PEG10% NPs in water
- 1.7 ♢ PCL NPs in ANM
- 7.7 ♢ PCL-PEG5% NPs in ANM
- 13.3 ♢ PCL-PEG10% NPs in ANM

B

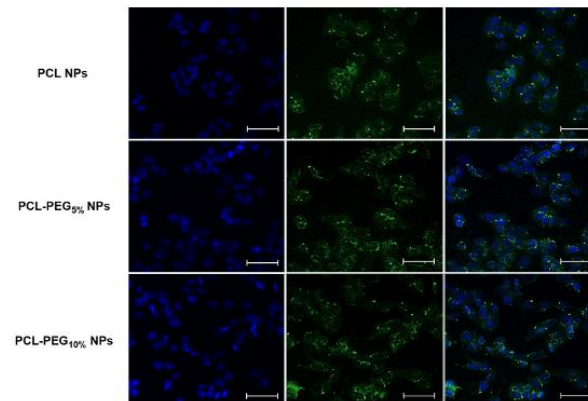


Mucus diffusivity by NTA

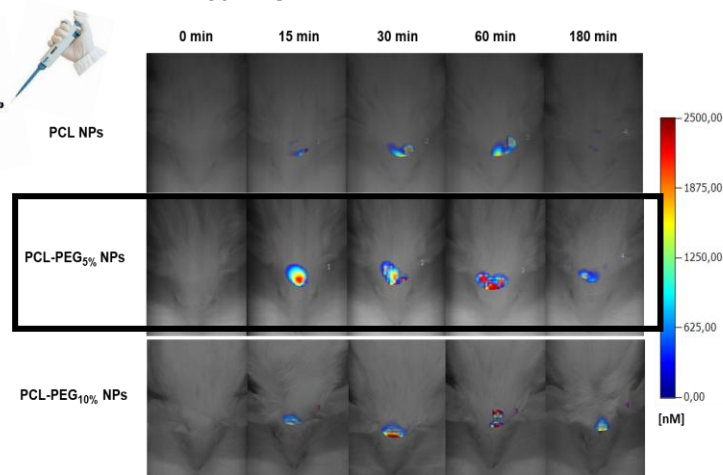


Formulation	Mean diameter (nm)	PdI	ζ-potential (mV)	EE% of BEX	Total PEG content (wt%)	Surface PEG content (wt%)	PEG density (I)
PCL-NPs	103.5 ± 8	0.109 ± 0.02	-39.9 ± 4	67.2 ± 3	n.a.	n.a.	n.a.
PCL-PEG _{1%} NPs	117.6 ± 4	0.118 ± 0.03	-26.2 ± 6*	n.a.	0.29 ± 0.03	0.12 ± 0.02	0.3 ± 0.1
PCL-PEG _{3%} NPs	118.5 ± 5	0.158 ± 0.02	-20.2 ± 5*	n.a.	0.74 ± 0.02	0.31 ± 0.02	0.8 ± 0.1
PCL-PEG _{5%} NPs	120.2 ± 5	0.149 ± 0.03	-19.7 ± 3*	66.8 ± 3	1.10 ± 0.03	0.62 ± 0.03	1.9 ± 0.2
PCL-PEG _{10%} NPs	117.1 ± 6	0.194 ± 0.03	-9.3 ± 4*	n.a.	1.96 ± 0.05	1.72 ± 0.03	4.6 ± 0.5

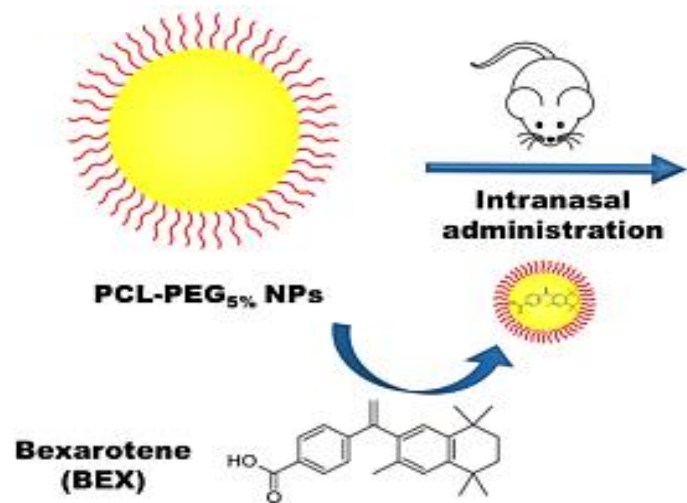
Cellular uptake by RMPI 2650 epithelial nasal cells



IR-780 NPS



Quantification of BEX in brain tissue



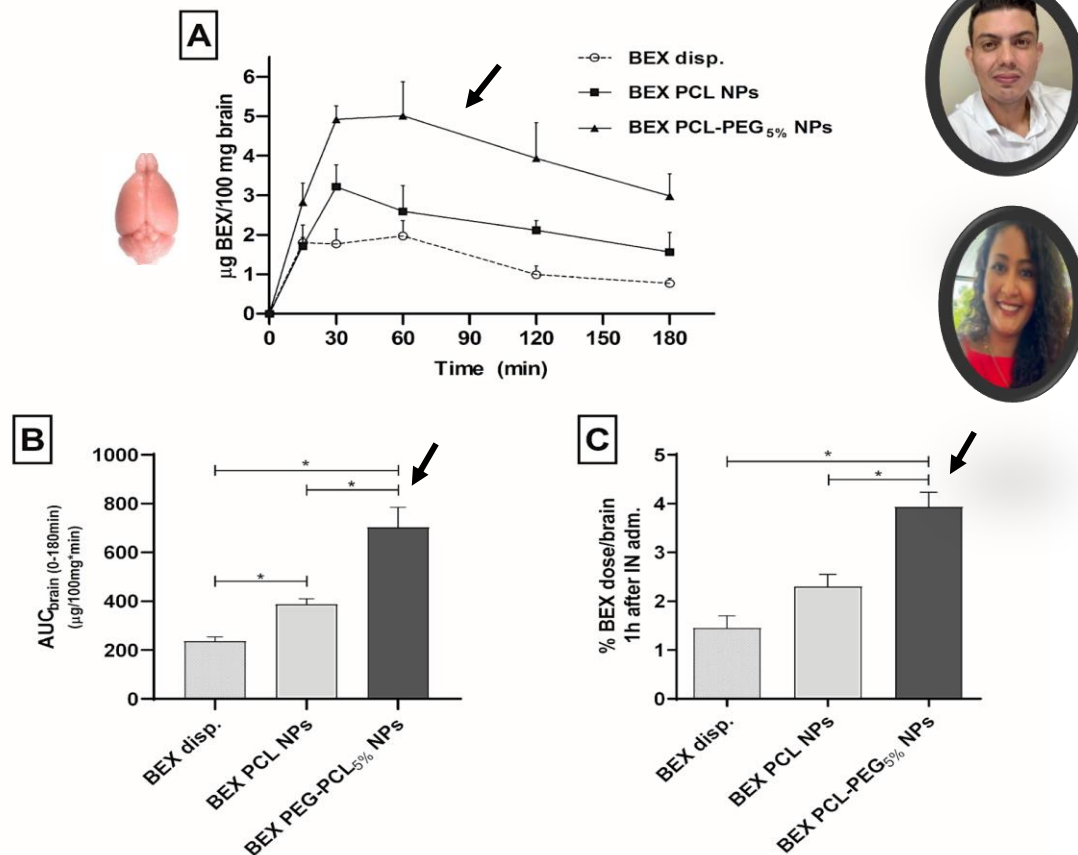
Drug Delivery and Translational Research
<https://doi.org/10.1007/s13346-020-00816-2>

ORIGINAL ARTICLE



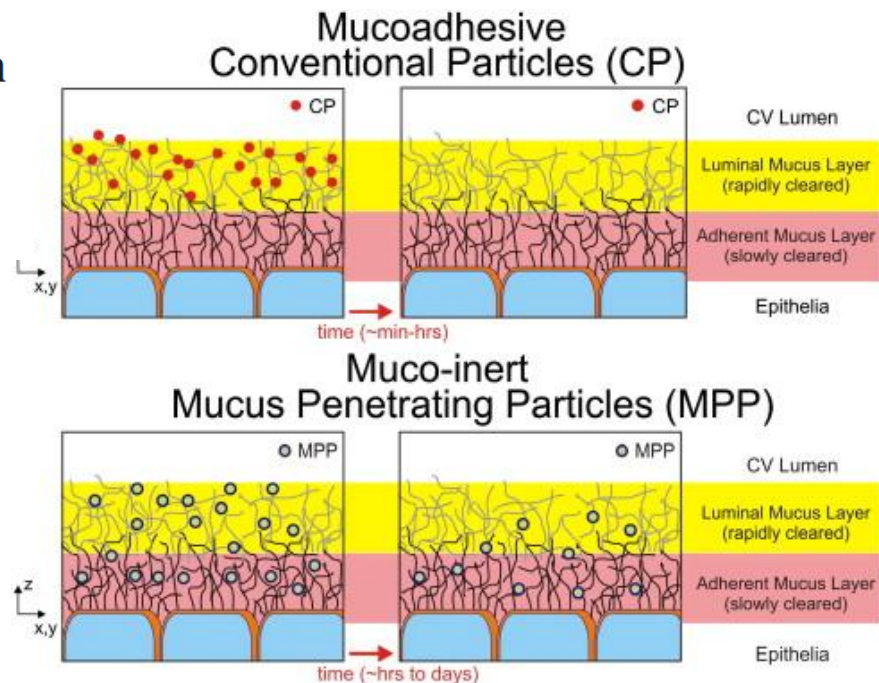
Nose-to-brain drug delivery mediated by polymeric nanoparticles: influence of PEG surface coating

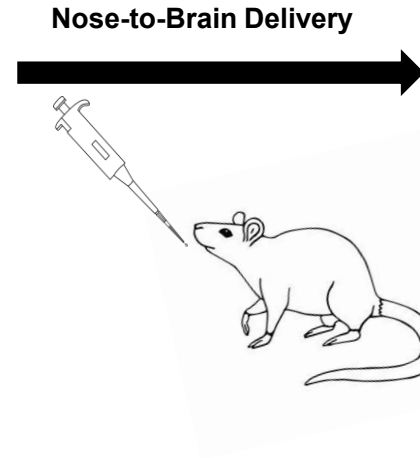
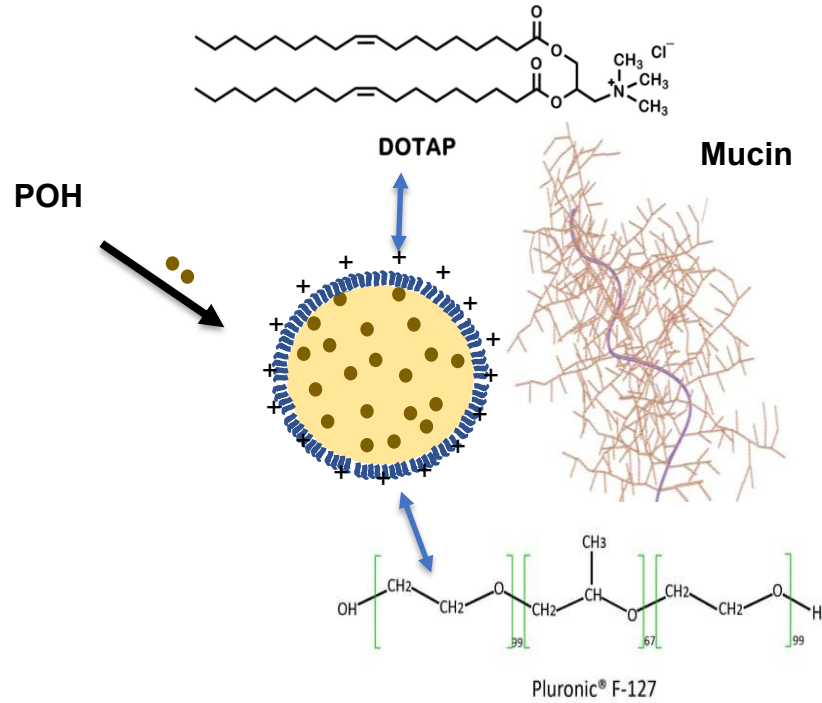
Edilson Ribeiro de Oliveira Junior¹ · Lilian Cristina Rosa Santos¹ · Mariana Arraes Salomão¹ · Thais Leite Nascimento¹ · Gerlon de Almeida Ribeiro Oliveira² · Luciano Moraes Liao² · Eliana Martins Lima¹



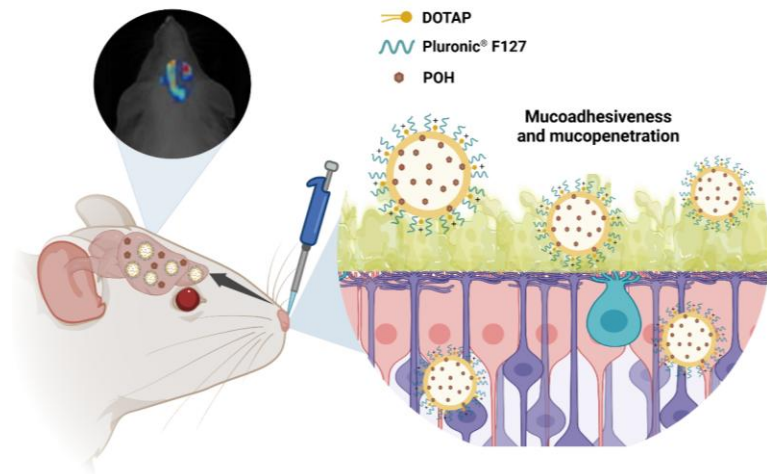
Mucus adhesion vs. mucus penetration? Screening nanomaterials for nasal inhalation by MD simulation

Xiaoshu Gao^a, Yin Xiong^a, Hening Chen^a, Xuheng Gao^a, Jiaxin Dai^a, Yutong Zhang^a,
Wanhang Zou^a, Yang Gao^b, Zhenyan Jiang^a  , Bing Han^a  

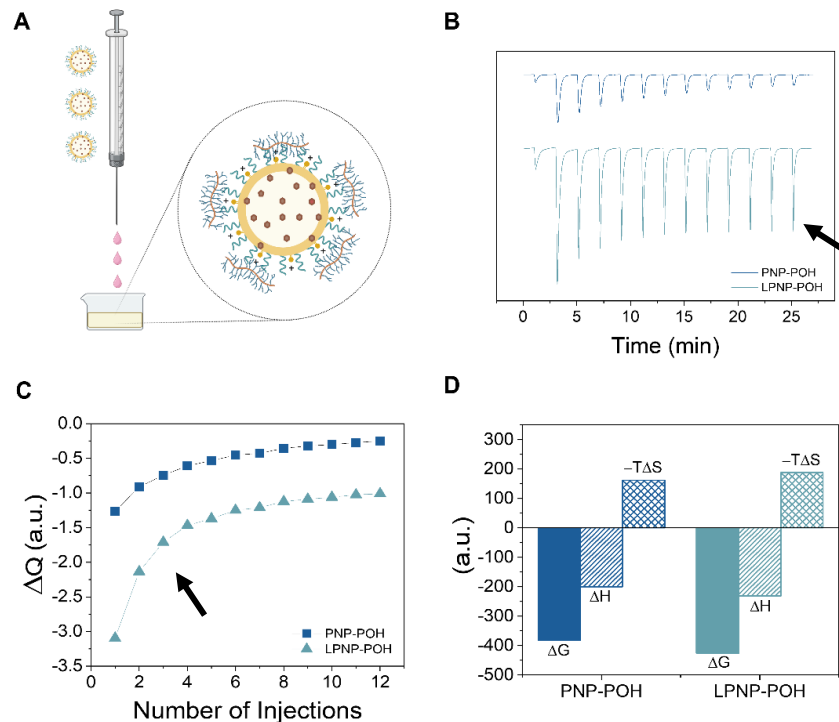




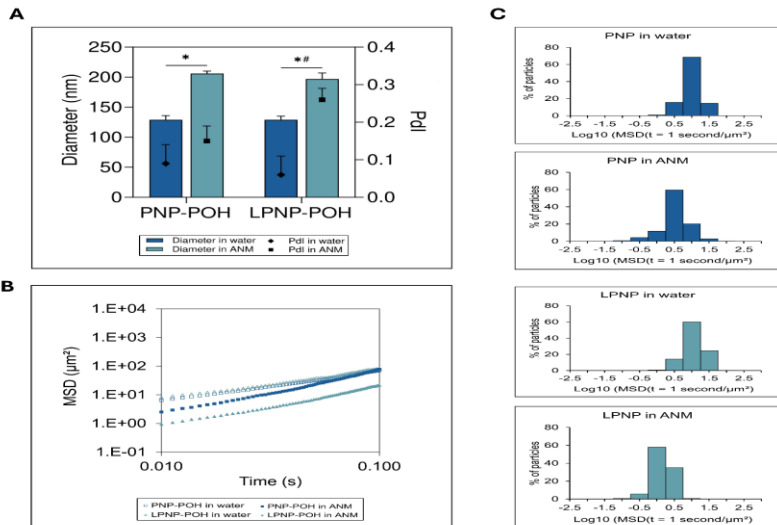
Optimized Mucus Adhesion and Penetration of Lipid-Polymer improve N2B Delivery of Perillyl Alcohol for Glioblastoma Therapy



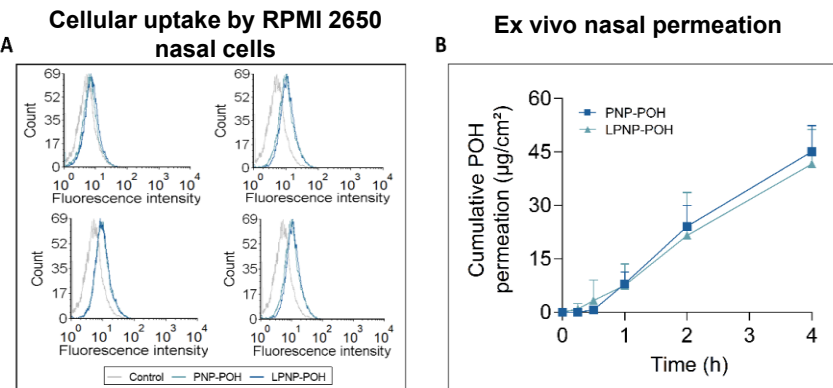
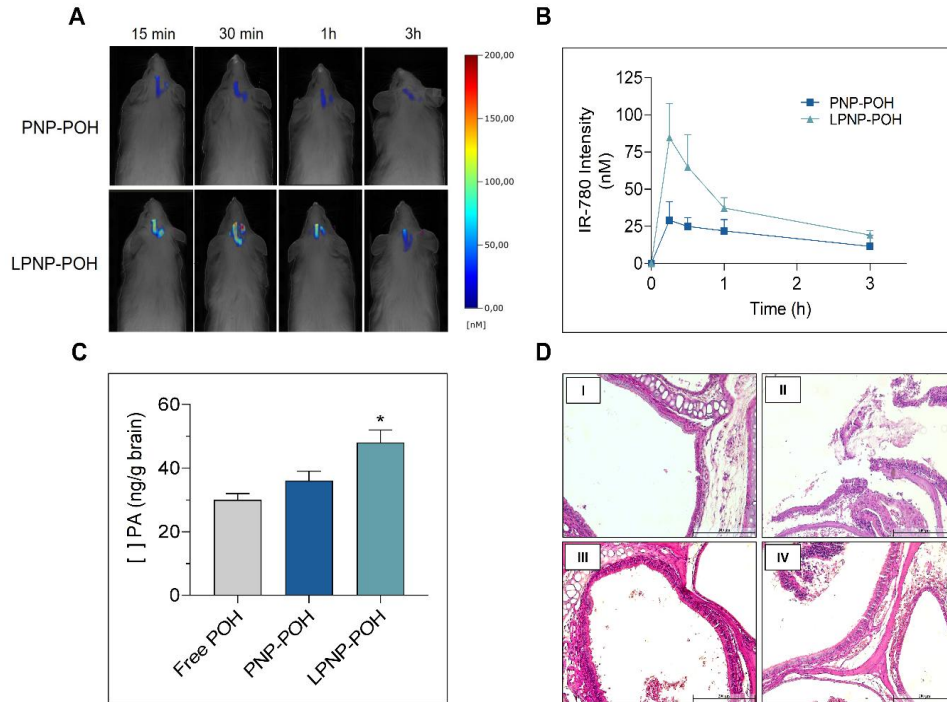
ITC experiments for PNP-POH and LPNP-POH nanoparticles titration in a (2% w/v) mucin:water solution



Nanoparticles diffusivity in ANM

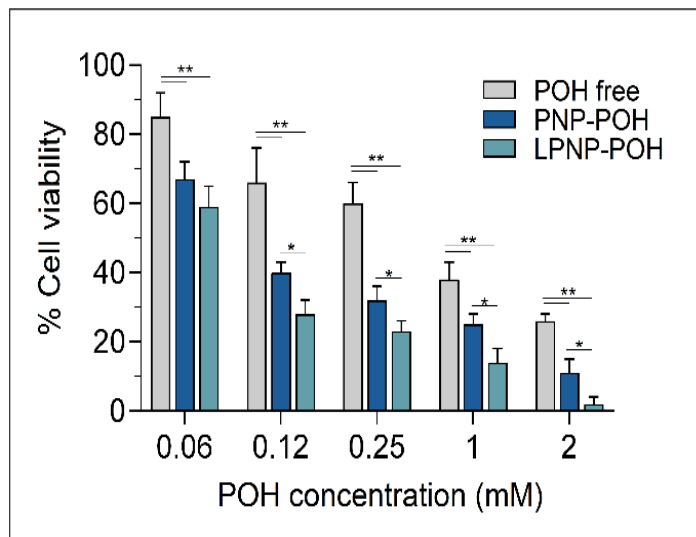


In vivo biodistribution and brain delivery

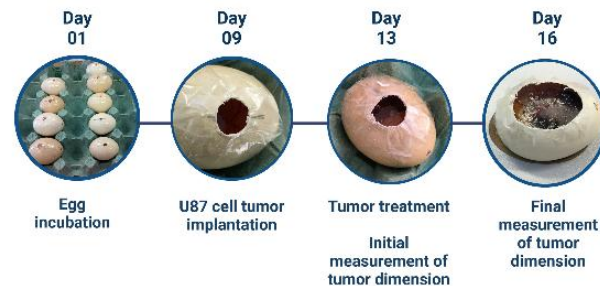


Cytotoxicity against glioma cells and antitumoral activity in CAM model

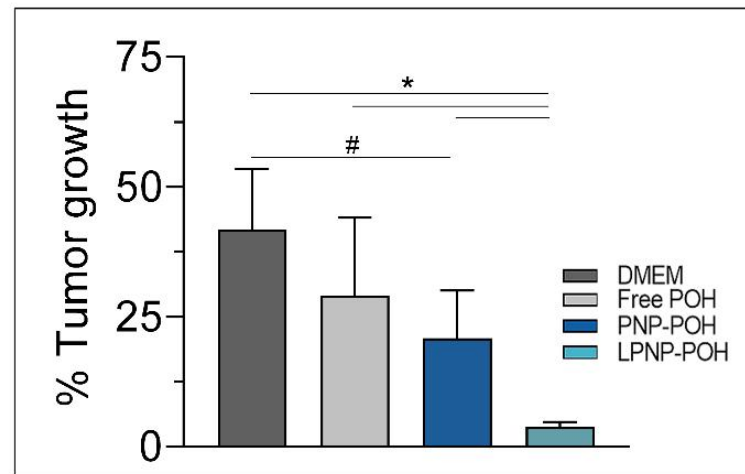
A



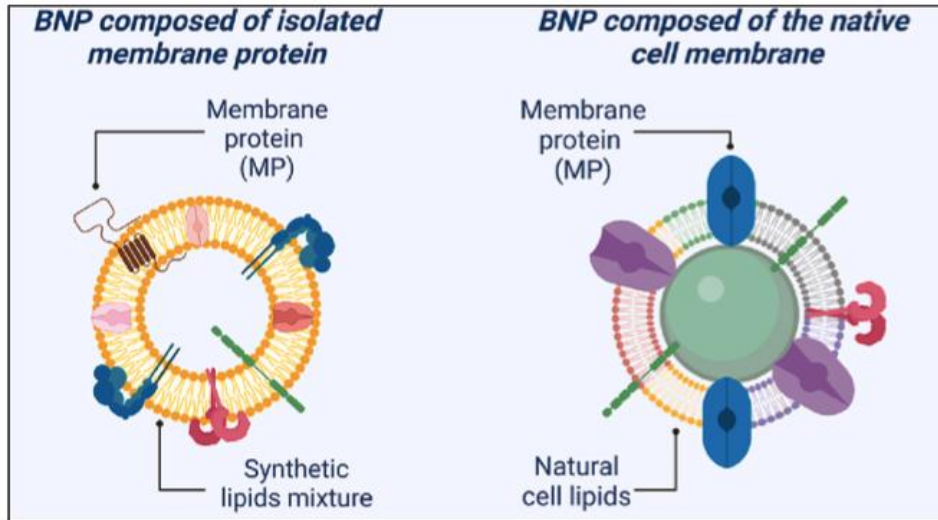
B



C

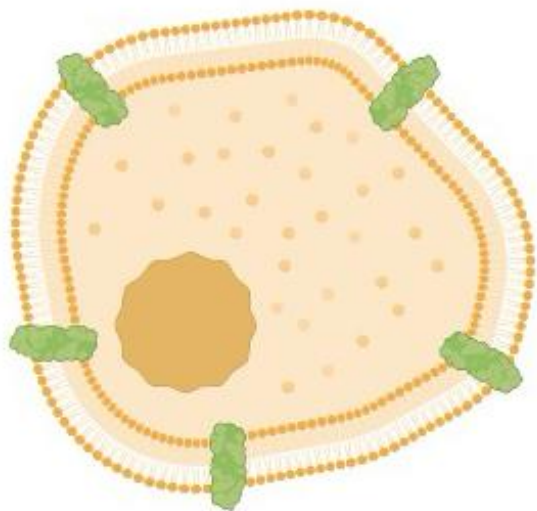


Biomimetic nanoparticles



Cell membrane-based → mimic cells' properties

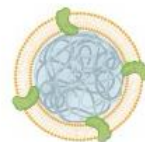
- **Polymeric NP coated with fragments of cell membranes**
- **Hybrid liposomes**
- **Liposomes containing proteins from cell membrane**
- **Cell membrane vesicles**



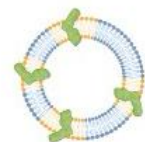
Cell of interest



Conventional liposome



cNP

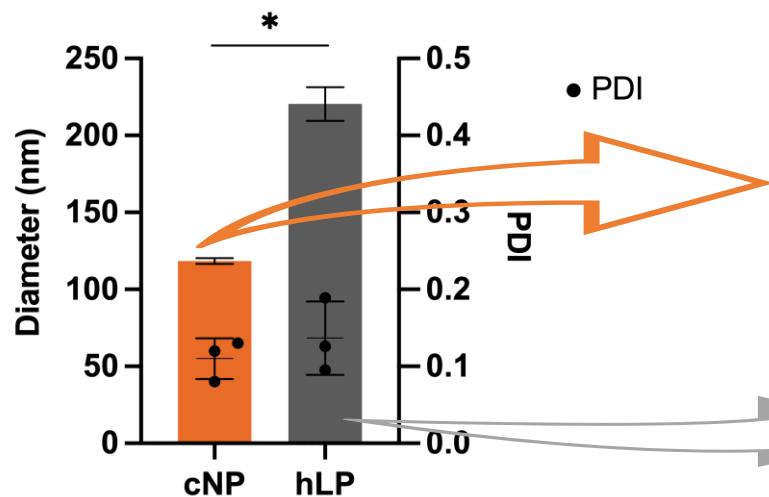


hLP

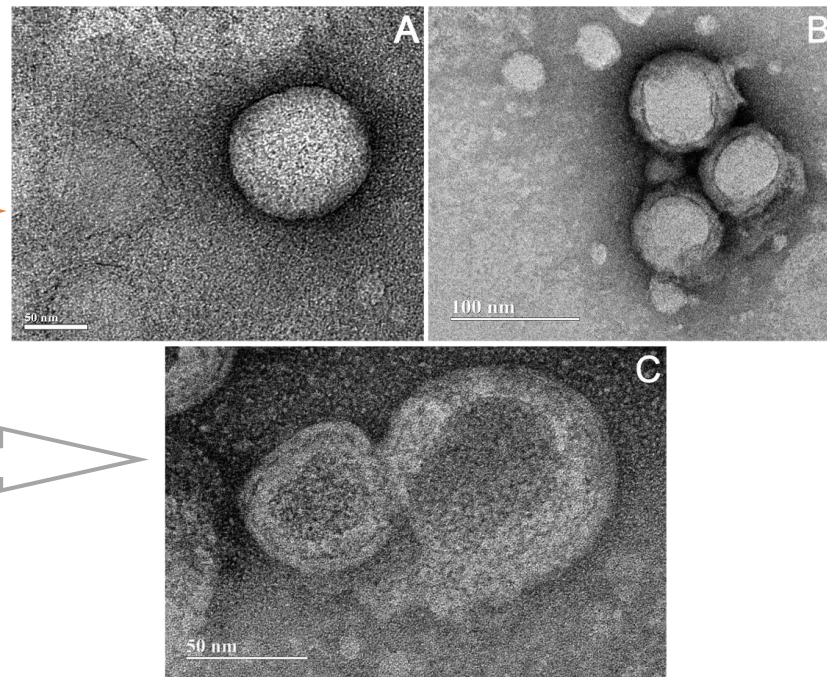


cVS

Nanoparticles (cNP and hLP)



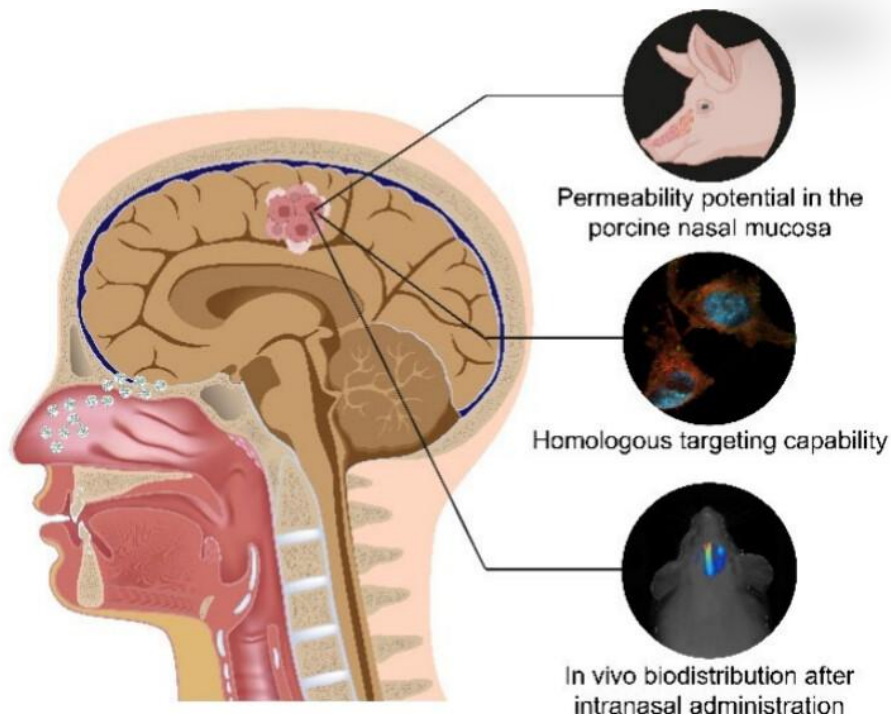
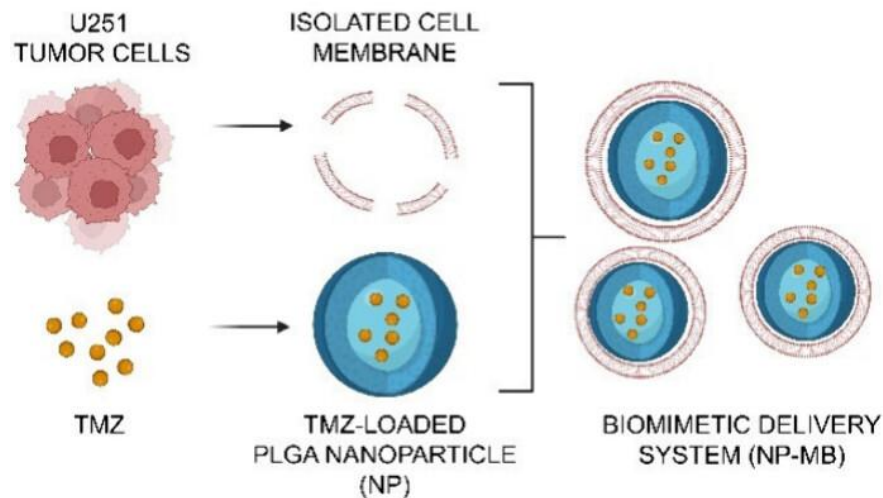
DLS measurements of hydrodynamic diameter (nm) * $p < 0.05$



Transmission electron microscopy of
A) Polymeric core, B) cNP and C) hLP.

Nose-to-Brain Delivery of Biomimetic Nanoparticles for Glioblastoma Targeted Therapy

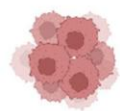
Natália Noronha Ferreira,* Celisnolia Morais Leite, Natália Sanchez Moreno, Renata Rank Miranda, Paula Maria Pincela Lins, Camila Fernanda Roderio, Edilson de Oliveira Junior, Eliana Martins Lima,



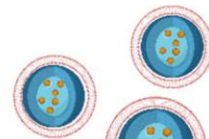
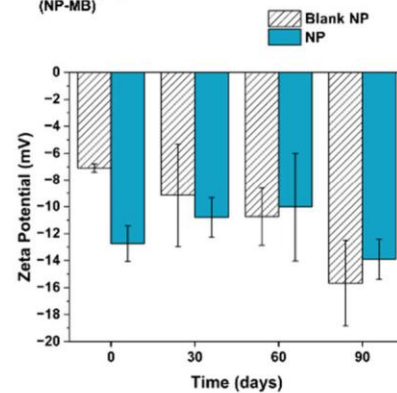
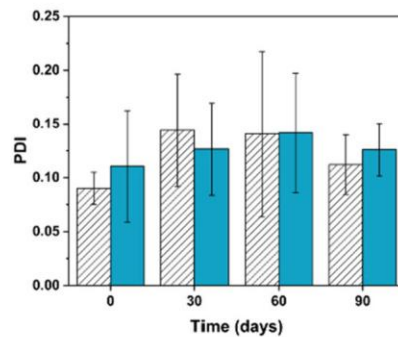
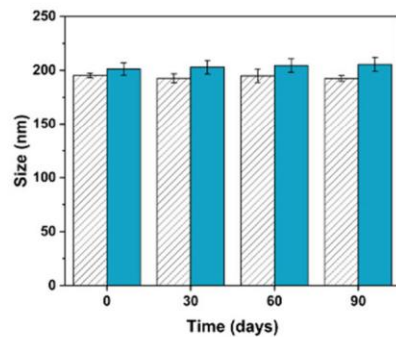
(A)

U251 tumor cells

Isolated cell membrane



TMZ

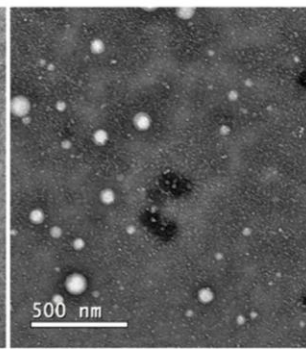
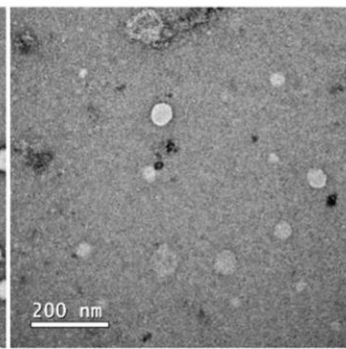
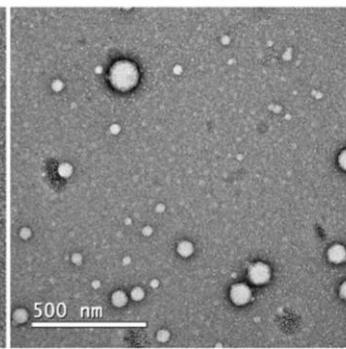
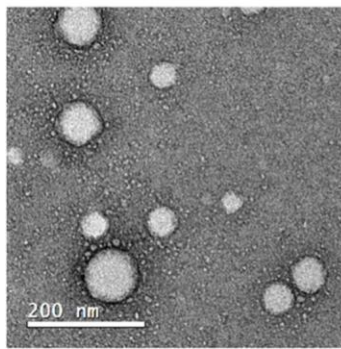
TMZ-loaded
PLGA nanoparticle
(NP)Biomimetic delivery system
(NP-MB)**(B)****(C)**

Blank NP

NP

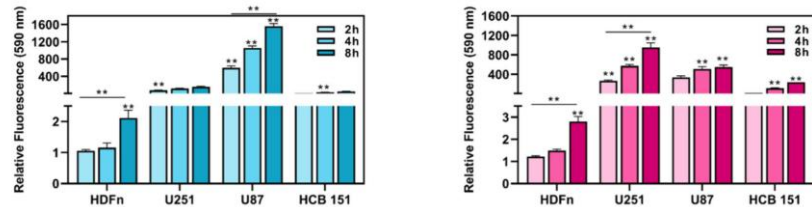
MB

NP-MB

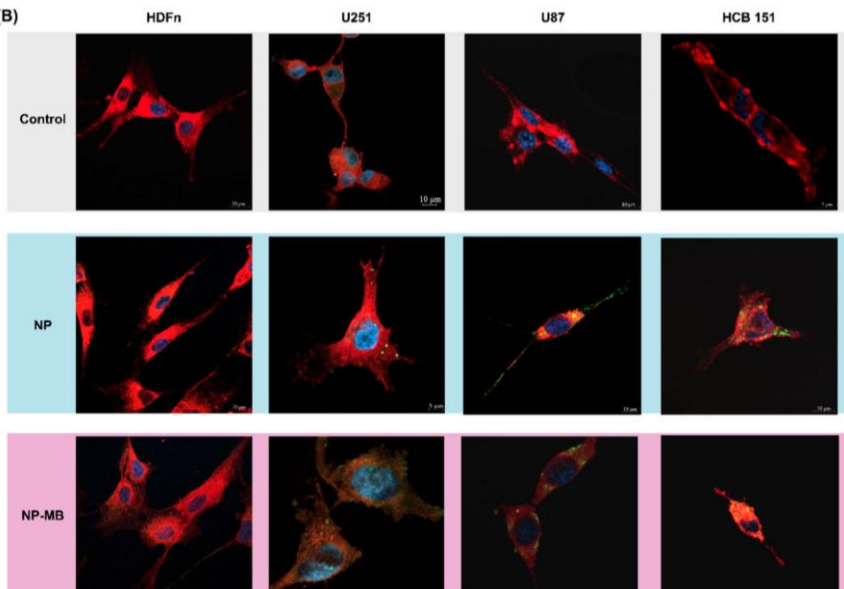


In vitro

(A)

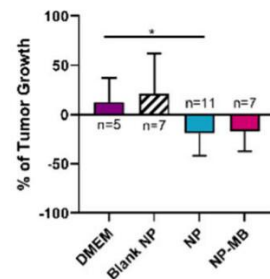


(B)

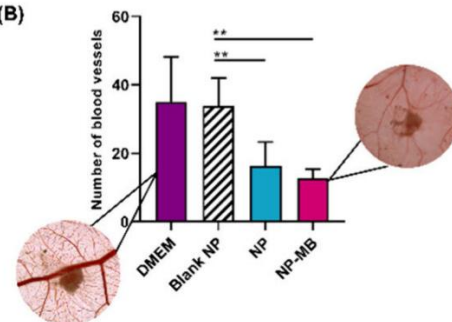


In vivo

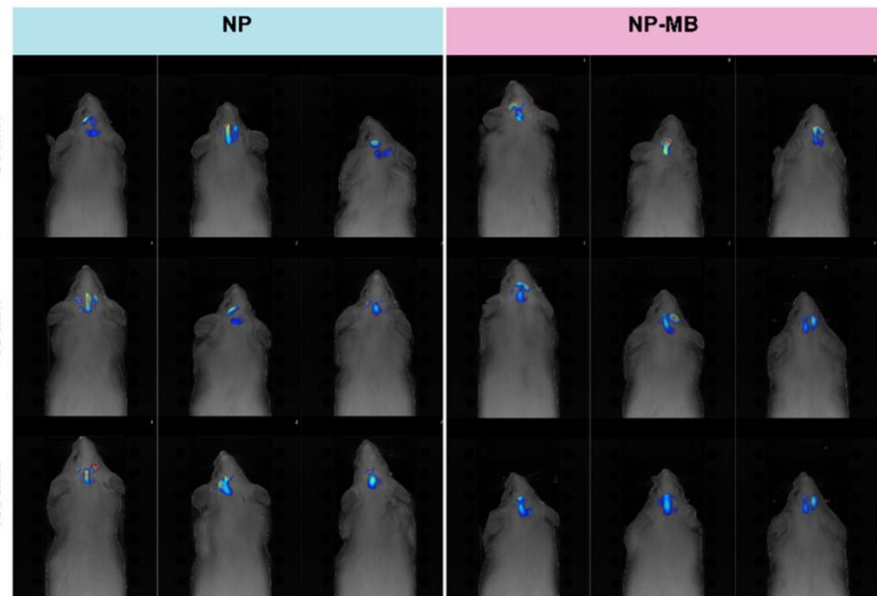
(A)



(B)



(C)

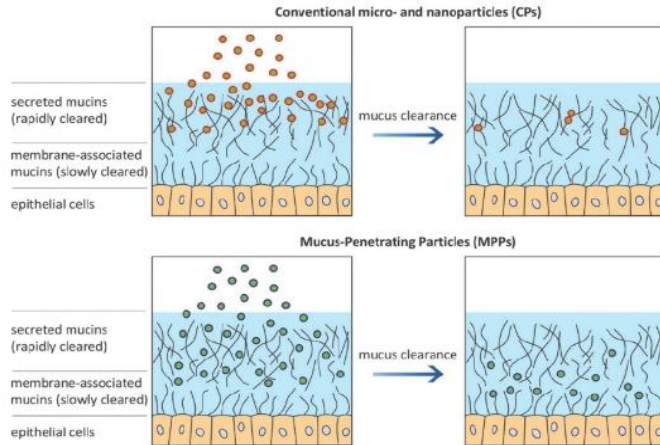


CPPs

PEG

Mucopenetration

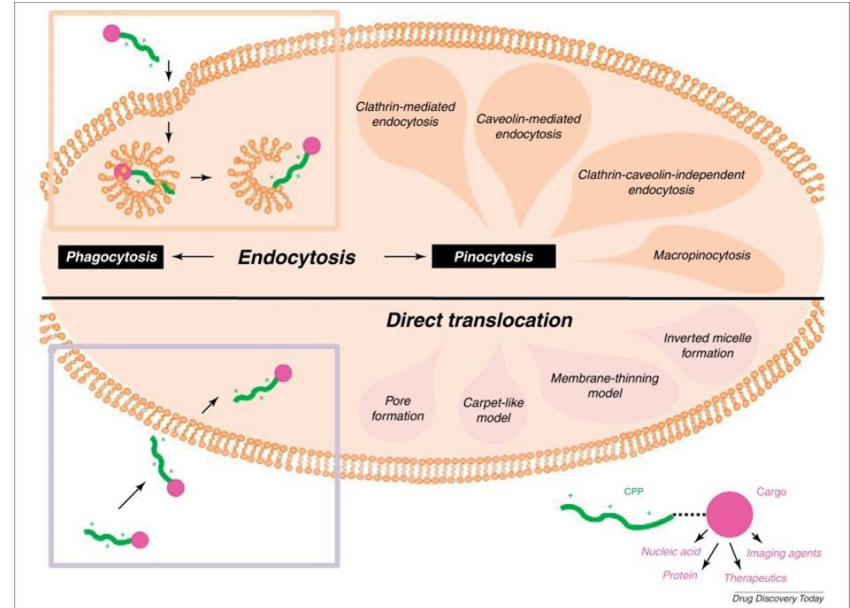
Reduces NP interaction with mucin



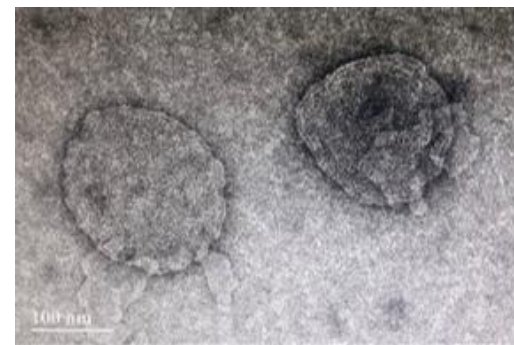
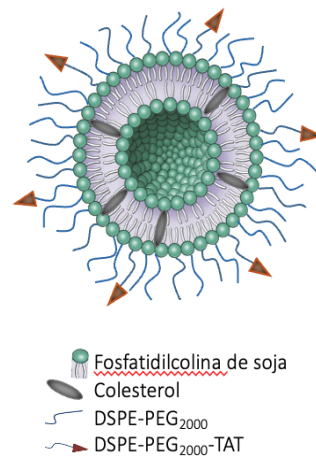
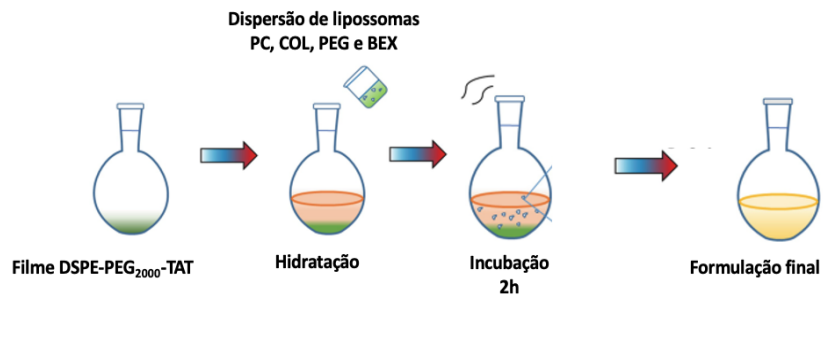
TAT Peptide

Cellular internalization

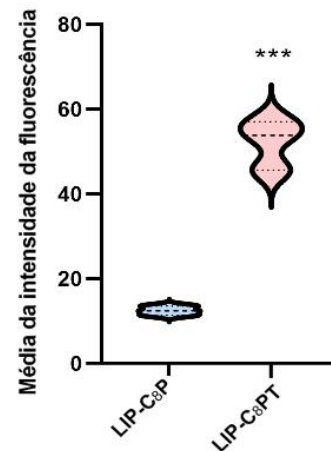
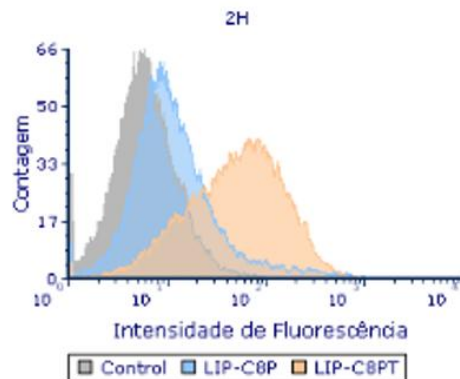
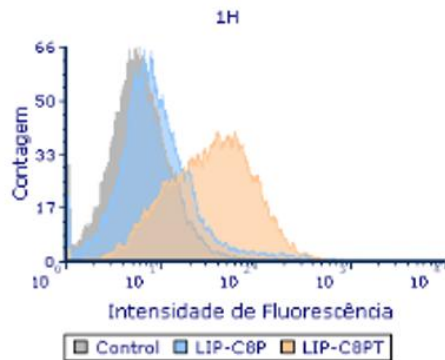
Membrane translocating aa sequence

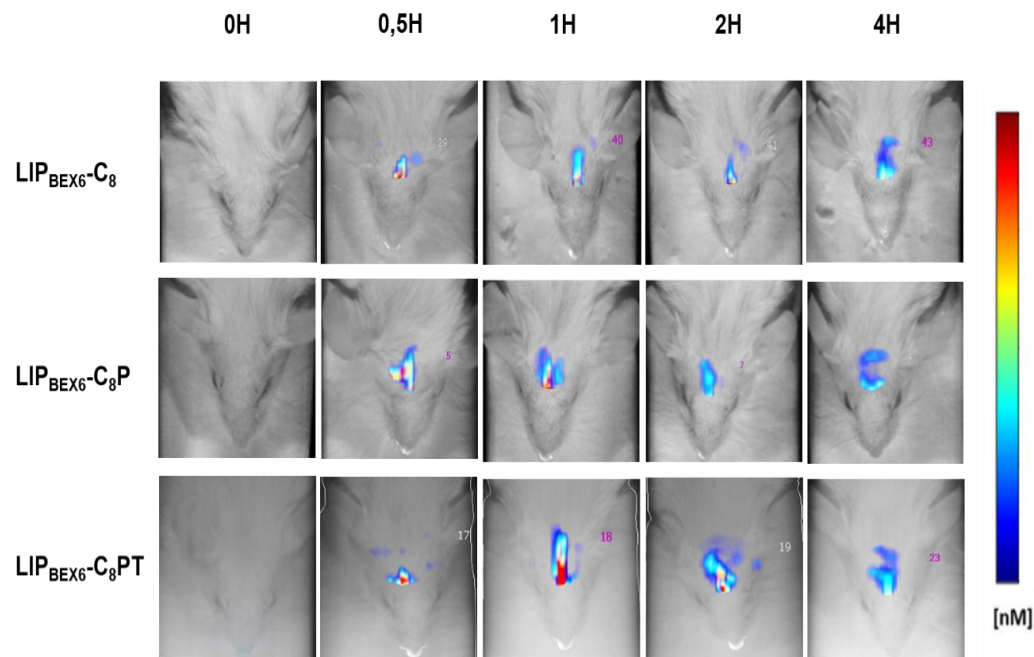


TAT - Liposomes

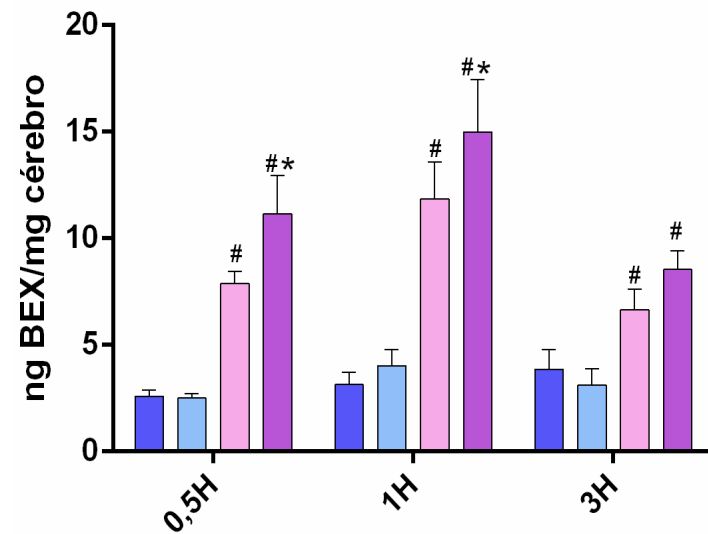


Nasal epithelium internalization





[] in the brain (LC-MS-MS)

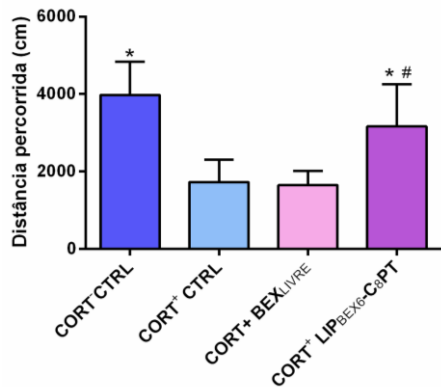
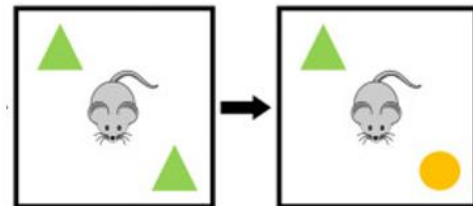
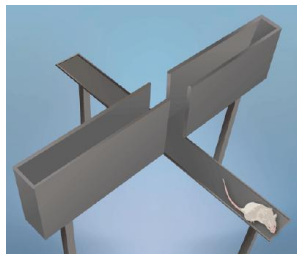
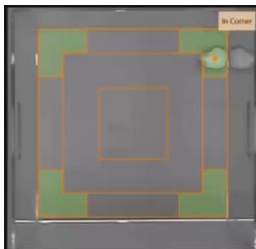


BEX_{LIVRE} ORAL
 BEX_{LIVRE} IN
 LIP_{BEX6}-C₈P
 LIP_{BEX6}-C₈PT

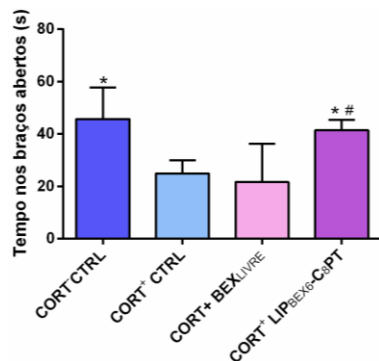
Unpublished data



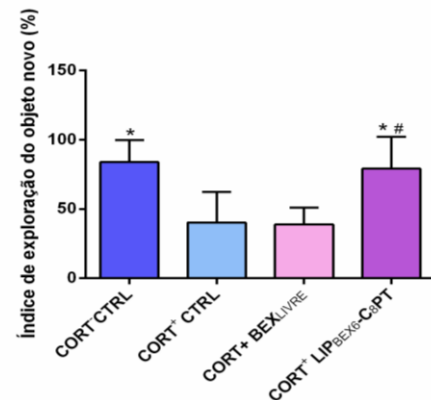
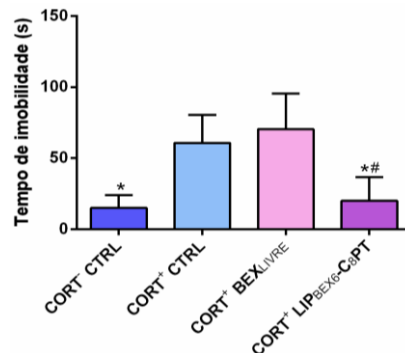
Neurodegenerative patterns / recovery



Mobility
Unpublished data



Anxiety



Memory

When the brain is the target:

- Nanoparticles are efficient in delivering drugs to via N2B
- Nanoparticles surface properties are a key factor to overcome biological barriers
- Sometimes, biological tools are the key to solve biological challenges



Eliana Martins Lima
emlima@ufg.br



@farmatecnano



PhD Candidates, Techs, Post-Docs:

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Bianca Fontanezzi
Naiara Benedetti
Jader Pires
Tácio Hayasaki
Mariana Salomão
Marcília Pavam
Edilson Oliveira Jr
Nathália Oliveria
Kleber Santiago
Carla Santos
Thais Leite



School of Pharmacy:

Danielle Diniz
Luis Antônio Silva
Marize Valadares
Artur Silva

Physics Institute:

Sebastião Mendanha
Andris Bakuzis

USP/São Carlos:

Valtencir Zucolloto
Nathália Noronha



INCT Nanofarma
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Univ. Modena | Regio

Emília:
Eleonora Truzzi
Eliana Leo

USP/São Carlos:

Valtencir Zucolloto
Nathália Noronha

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