Delivery of monoclonal antibodies to the brain: The impact of nanocarrier structure

Laura Piñeiro-Alonso

Inés Rubio-Prego, Ana M. López-Estévez, Pablo Garrido-Gil, Rita Valenzuela, José L. Labandeira-García, Pablo Aguiar, Ana I. Rodríguez-Pérez*, María J. Alonso*

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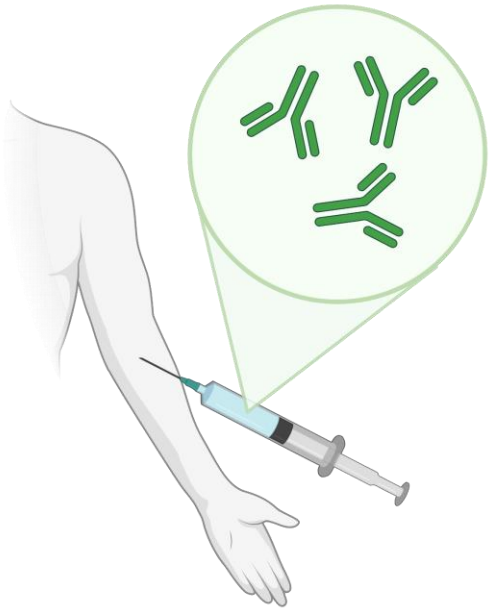
NEXT-GENERATION DELIVERY INNOVATIONS

Monoclonal antibodies for brain delivery



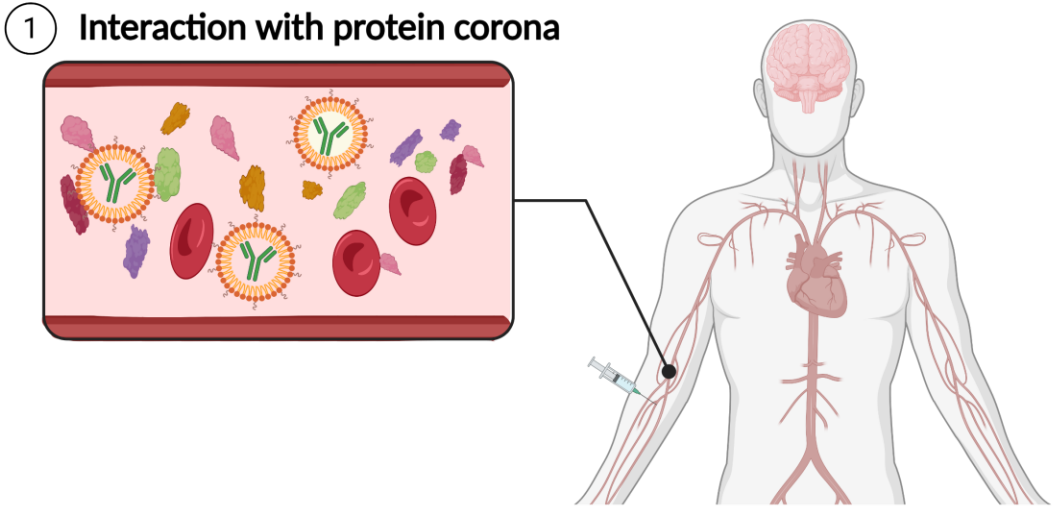
mAbs are transforming brain therapy

- High specificity and potency
- Several FDA approvals: Aducanumab or Lecanemab

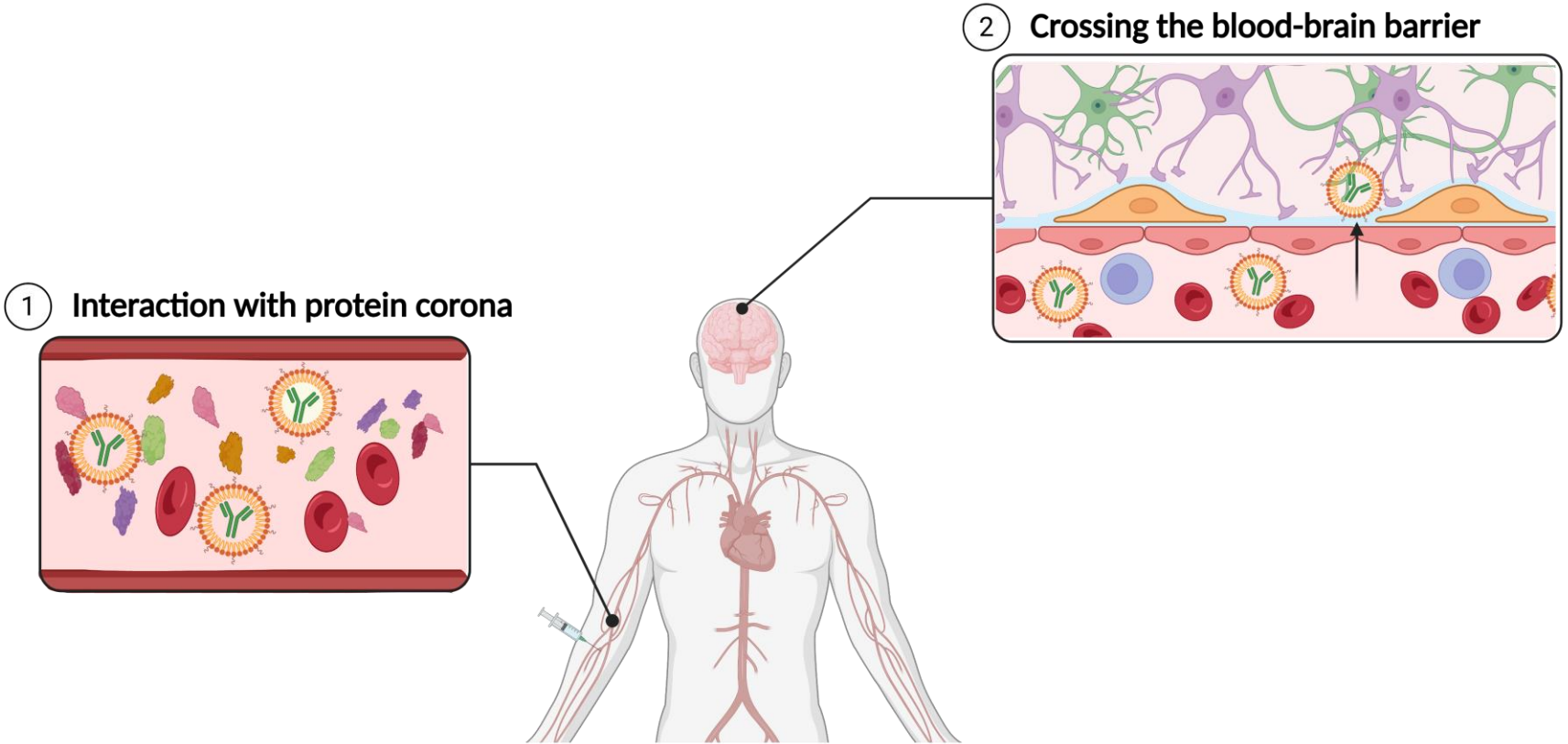
Limited acces and retention in brain tissue

Nanotechnology to enhance mAb delivery to the brain

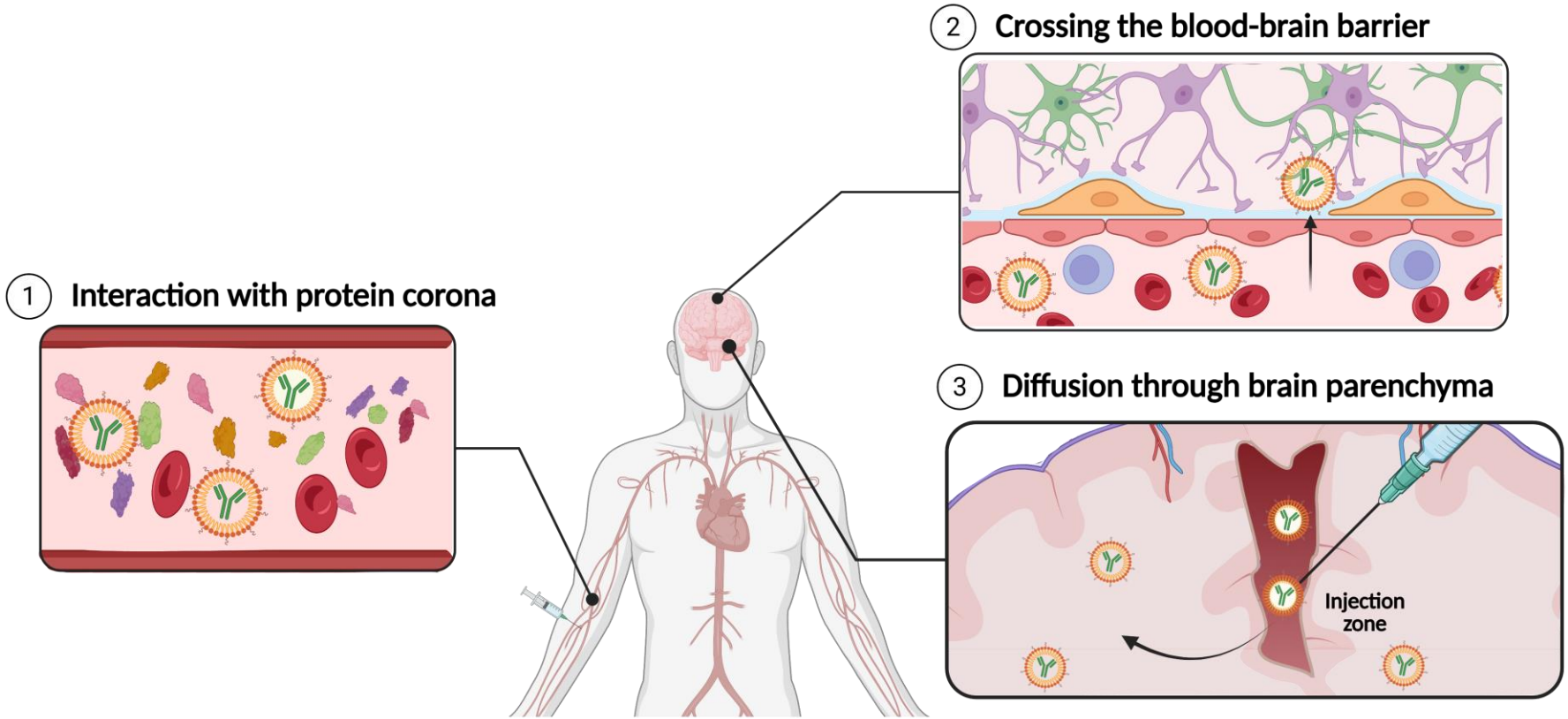
Main challenges for nanocarriers brain delivery



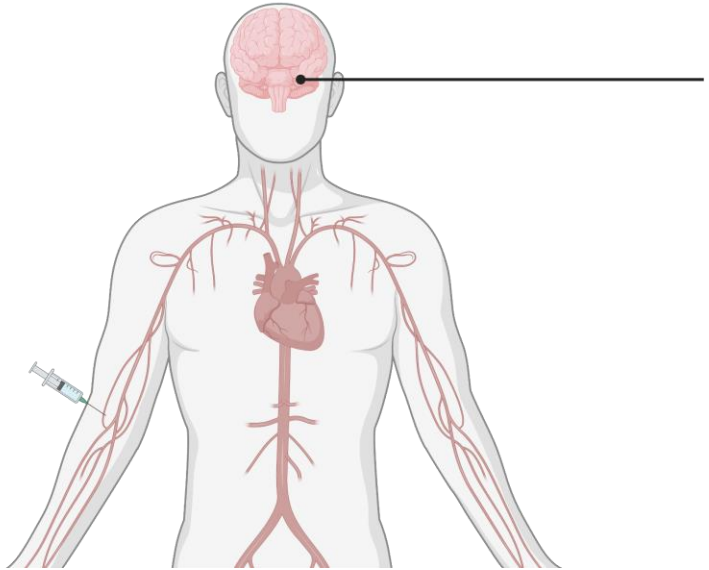
Main challenges for nanocarriers brain delivery

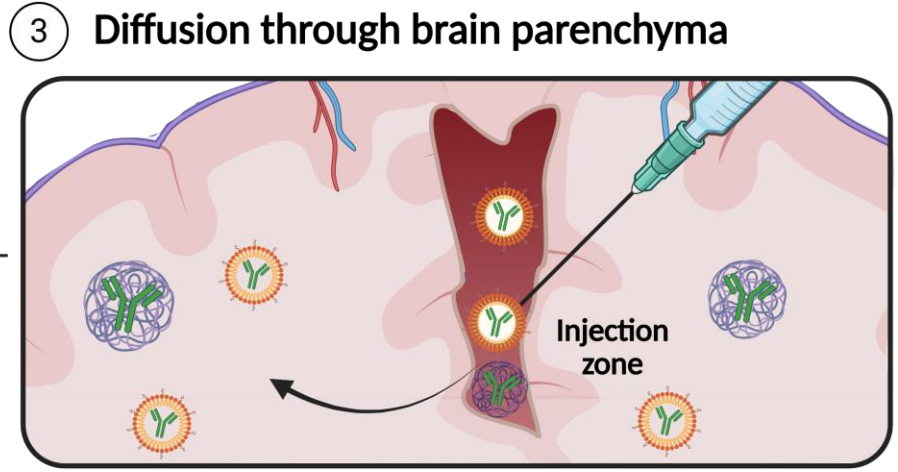


Main challenges for nanocarriers brain delivery



Main challenges for nanocarriers brain delivery

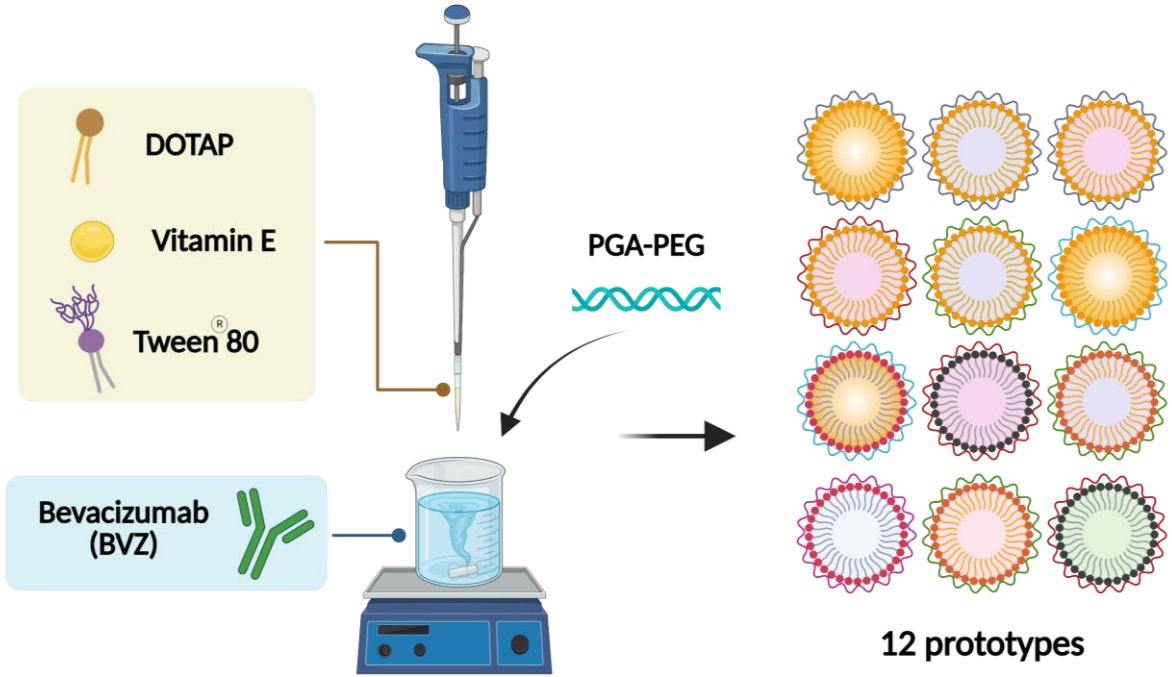




Comparison between two different nanostructures

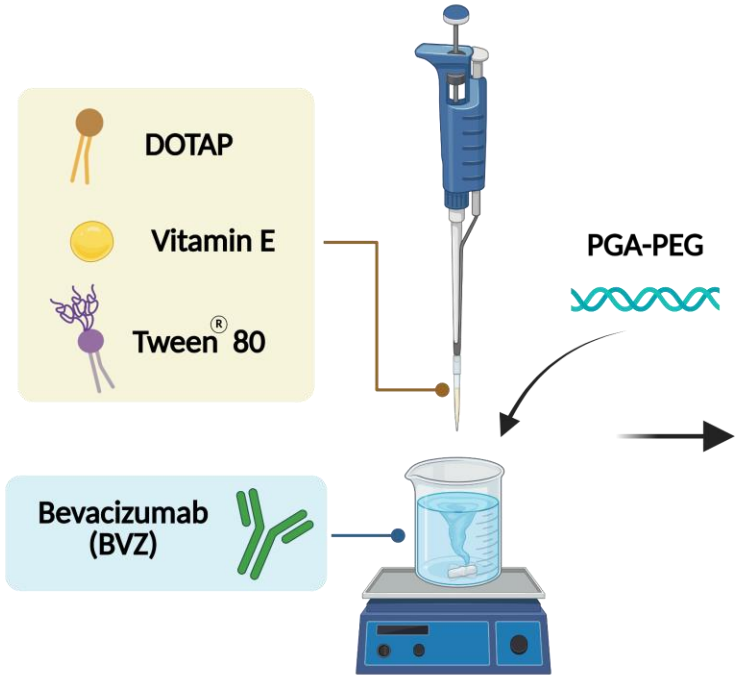
Development of mAb-loaded nanocapsules

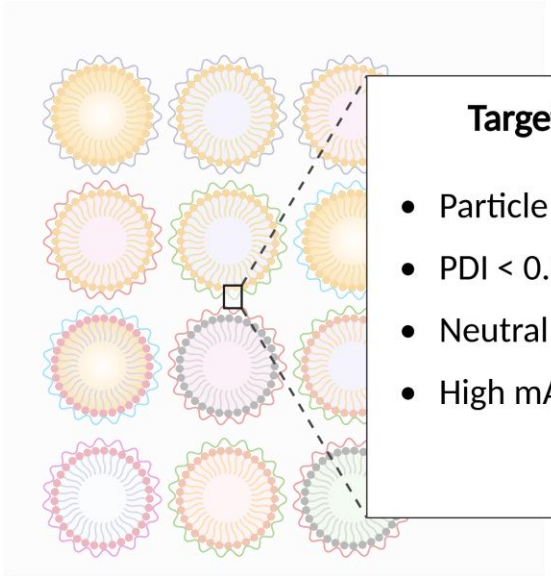
Screening with <u>different concentrations</u> of all compounds



Development of mAb-loaded nanocapsules

Screening with <u>different concentrations</u> of all compounds



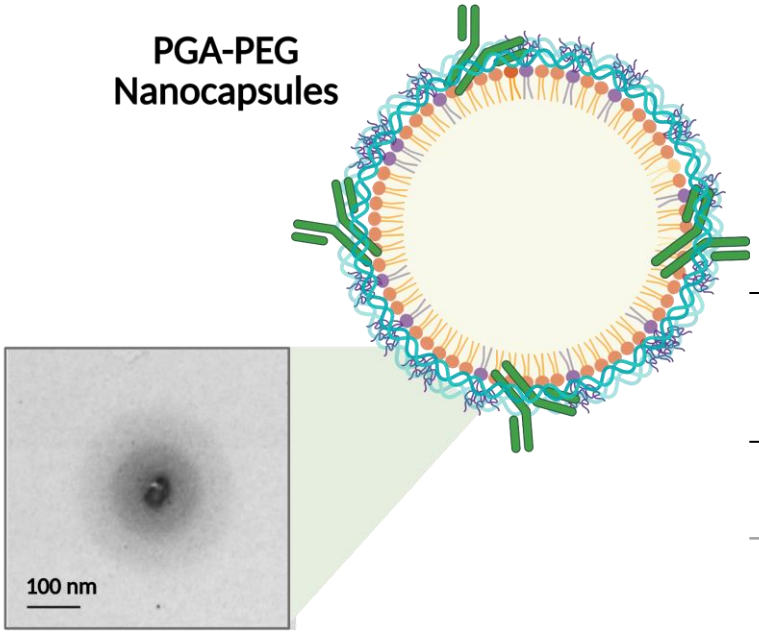


12 prototypes

Target Product Profile:

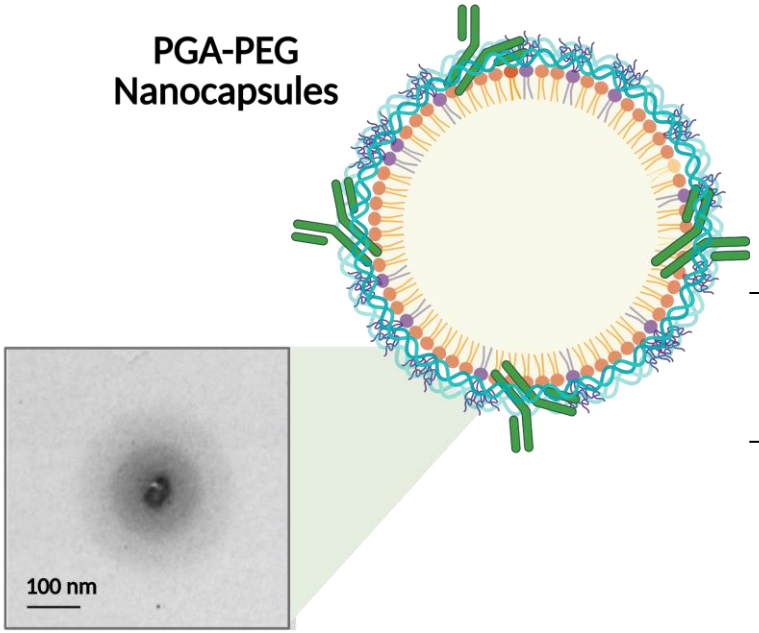
- Particle size < 100 nm
- PDI < 0.3
- Neutral ζ-Potential
- High mAb encapsulation

Development of mAb-loaded nanocapsules

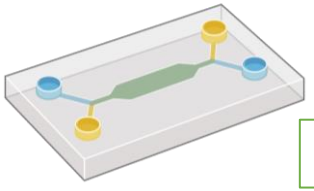


Size (nm)	PDI	ζ-Potential (mV)	mAb encapsulation (%)	Loading capacity (%)
93 ± 6	0.11	-5 ± 4	44 ± 12	2

Development of mAb-loaded nanocapsules



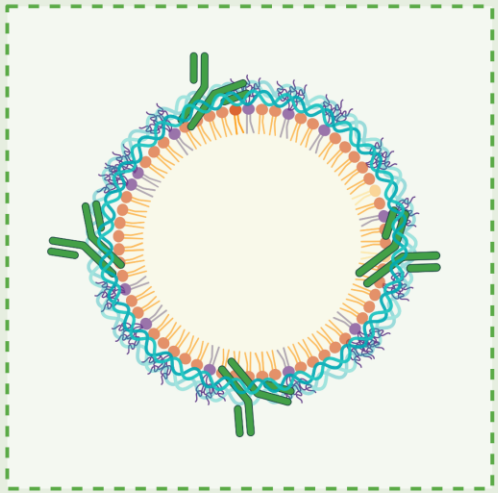
Size (nm)	PDI	ζ-Potential (mV)	mAb encapsulation (%)	Loading capacity (%)
93 ± 6	0.11	-5 ± 4	44 ± 12	2
78* ± 3	0.06**	-1 ± 1	99** ± 14	4



Optimization by microfluidics

Two nanostructures for mAb delivery

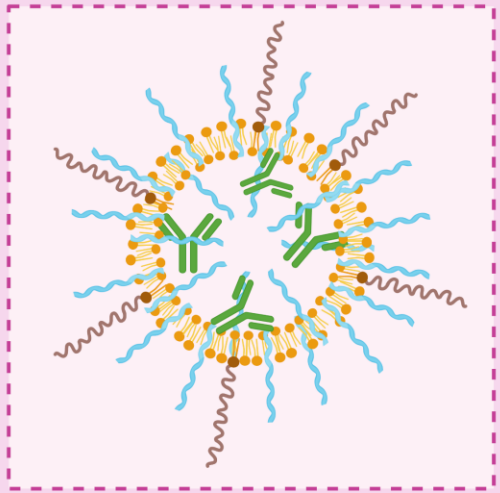
PGA-PEG Nanocapsules



Size: 78 nm
ζ-Potential: -1 mV
AE: 99%
LC: 4%

VS.

PGAC14 Nanoassemblies

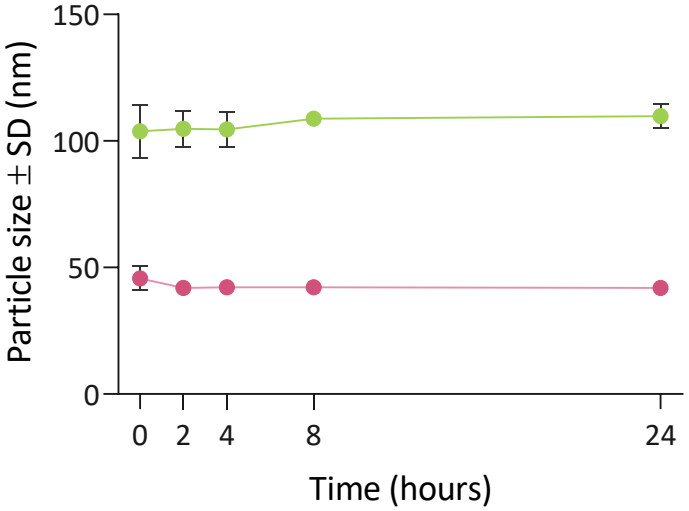


Size: 44 nm
ζ-Potential: -10 mV
AE: 64%
LC: 21%

Two nanostructures for mAb delivery

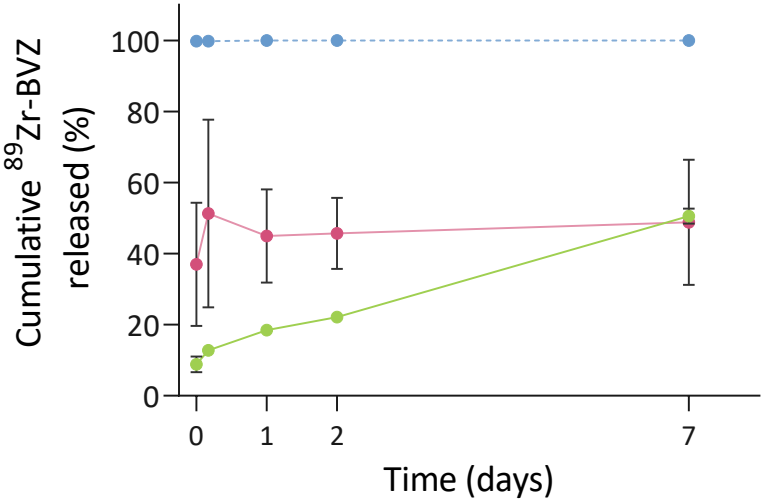
NP stability in simulated biological media

PBS, 37ºC



BVZ release in simulated biological media

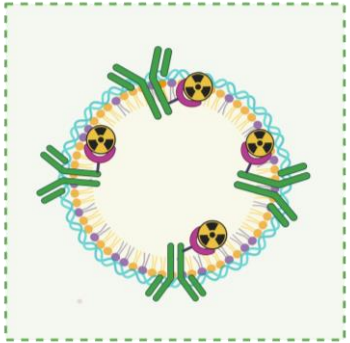
PBS, 37ºC



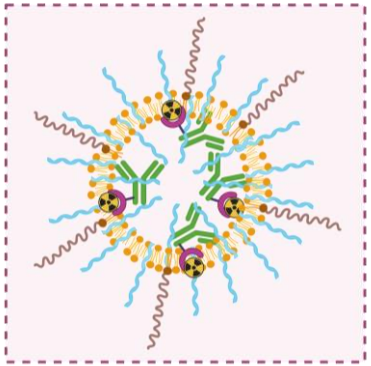
Free BVZ PGA-PEG NCs PGAC14 NAs

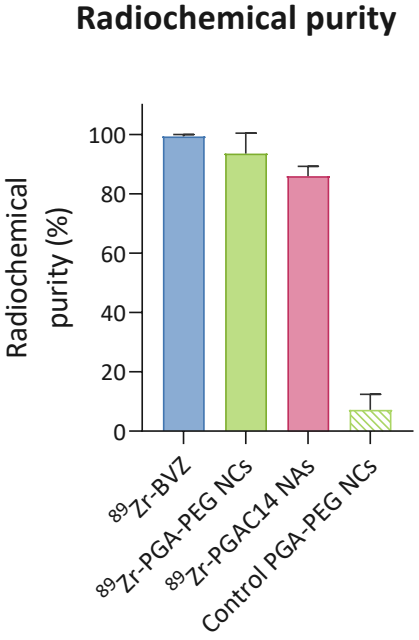
Radiolabeling with ^{89}Zr for PET imaging

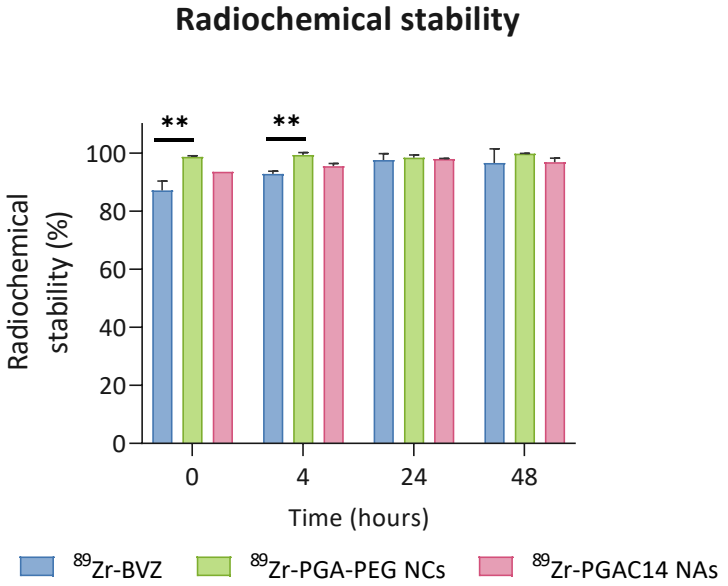
^{89}Zr-PGA-PEG NCs



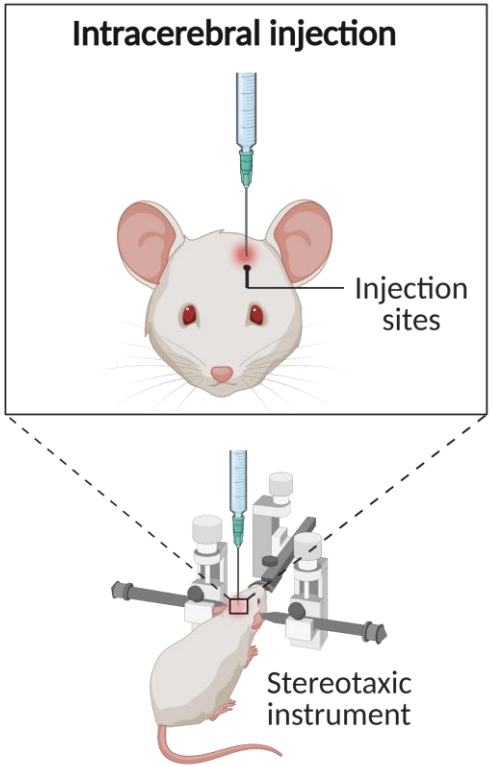
^{89}Zr-PGAC14 NAs





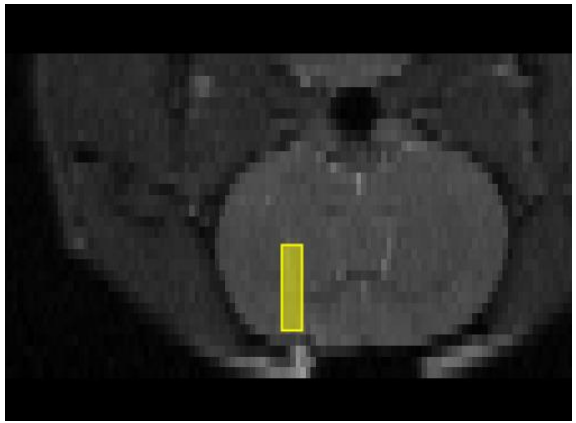


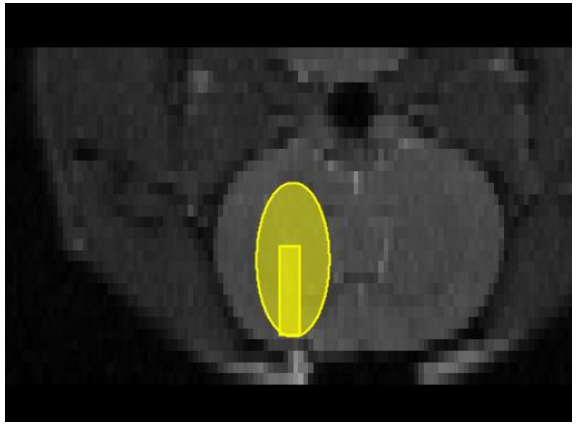
In vivo comparison using PET imaging



① Volume of interest (VOI) of the injection site

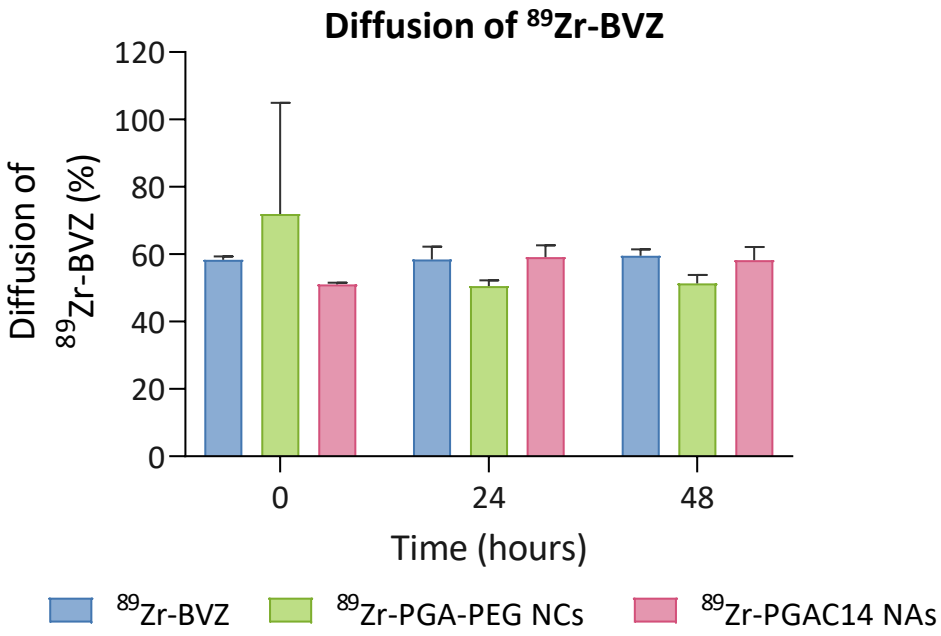
② VOI of the striatum

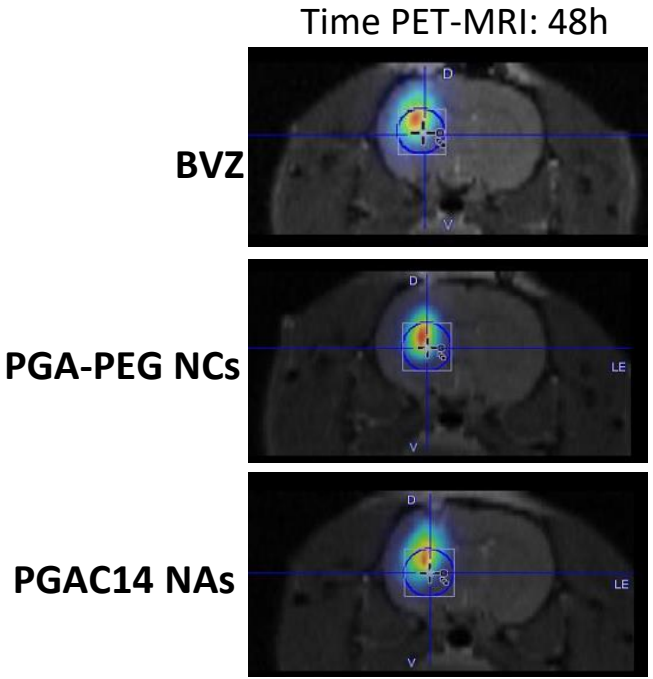




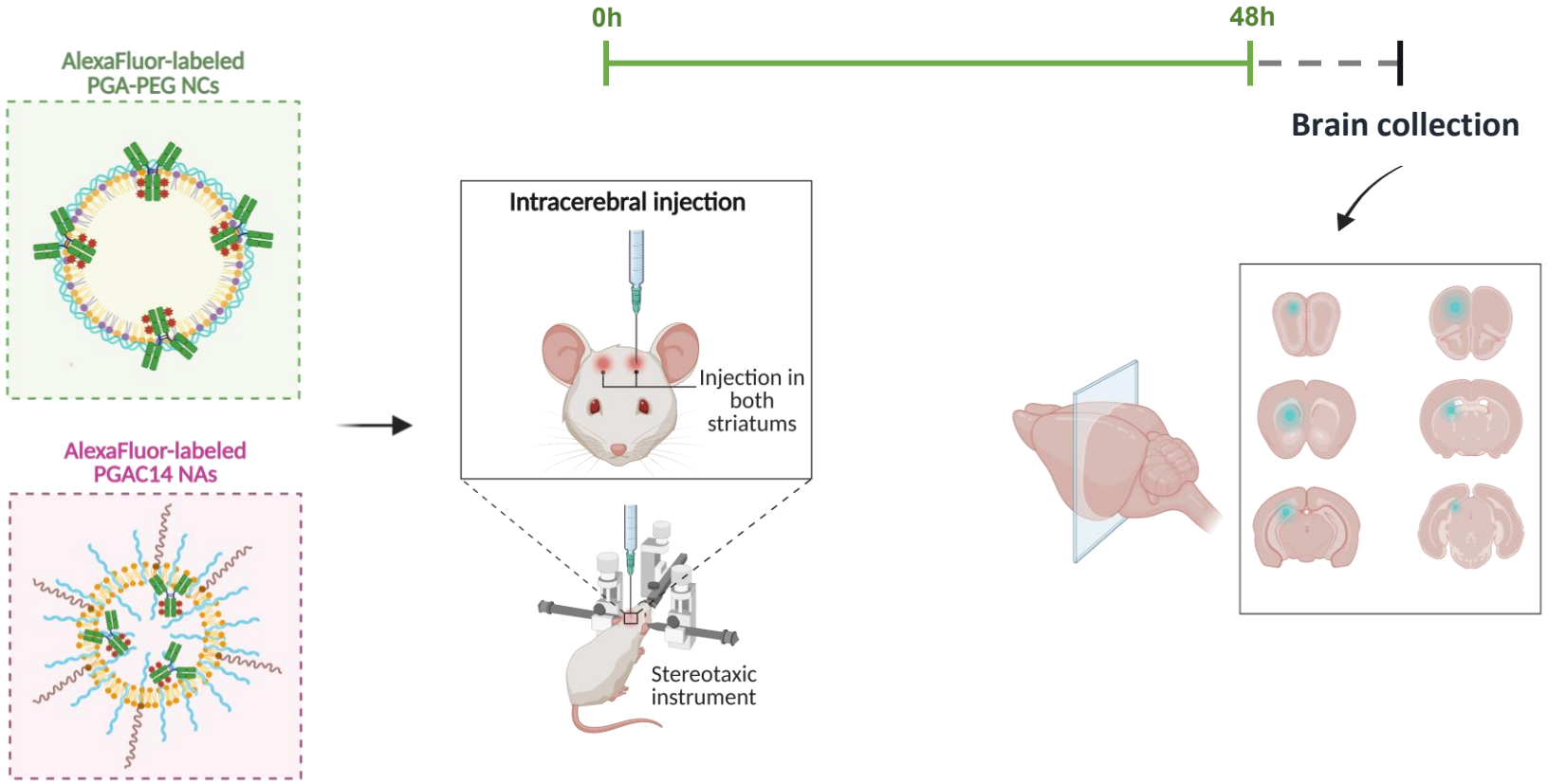
In vivo comparison using PET imaging

PET resolution limitations restricted the ability to study brain diffusion in detail



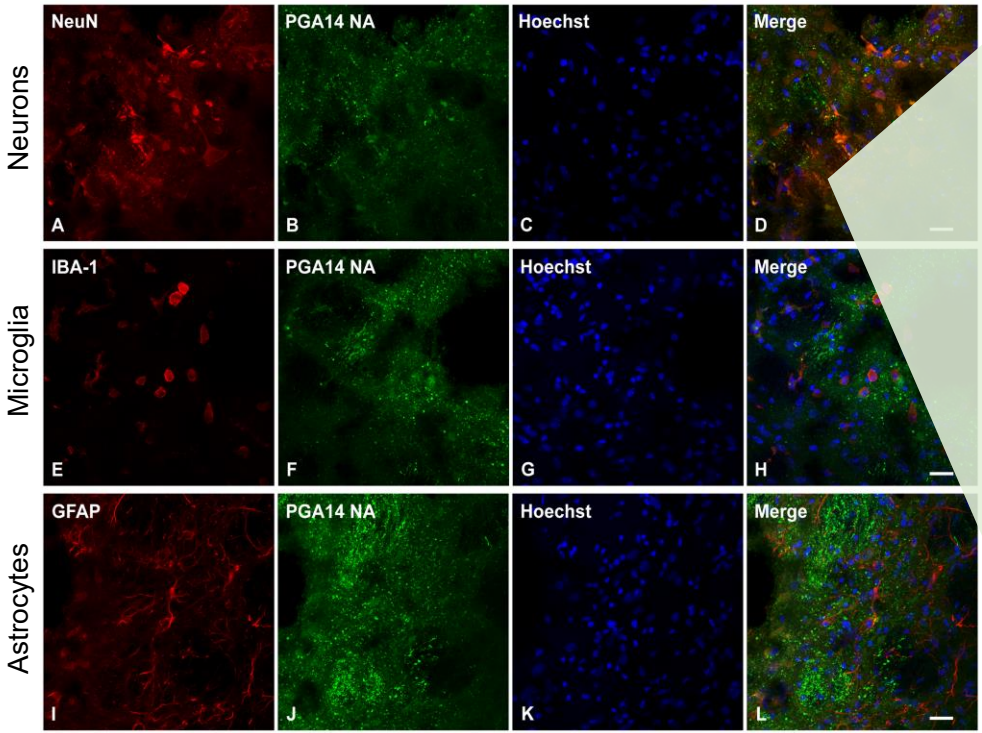


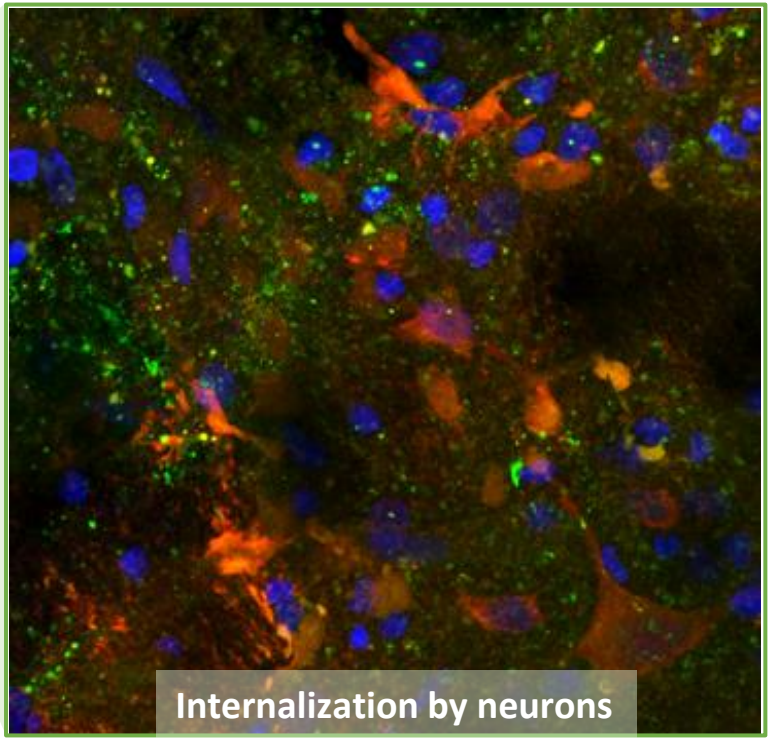
In vivo comparison using fluorescence



In vivo comparison using fluorescence

Colocalization of **PGAC14 NAs** with neurons and astrocytes





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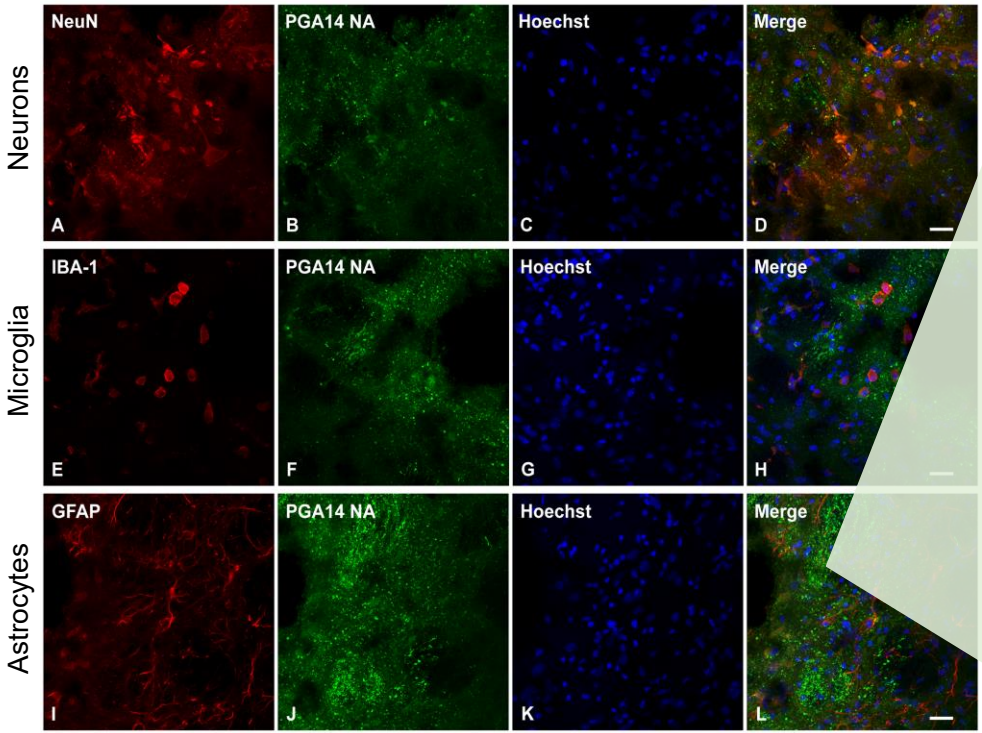
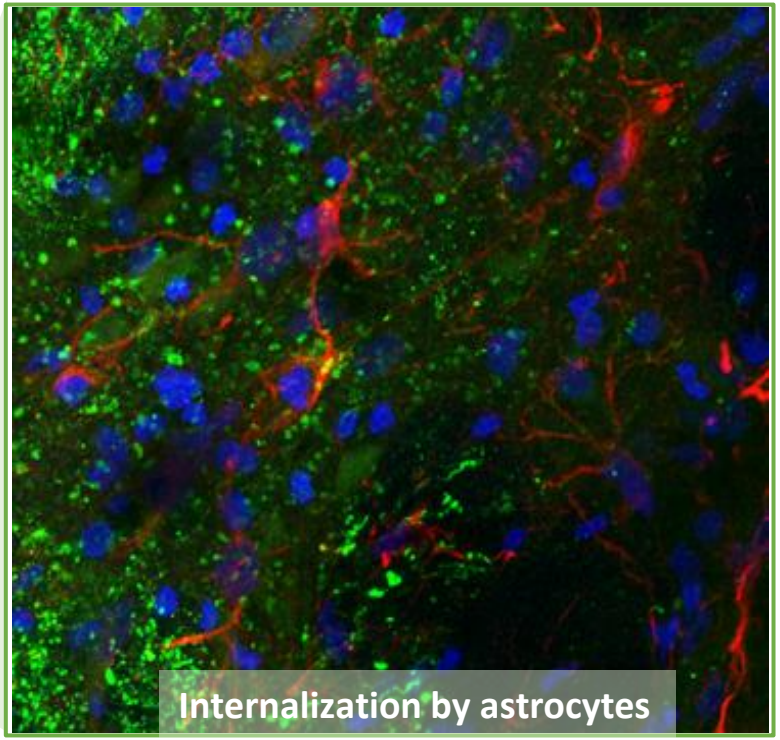
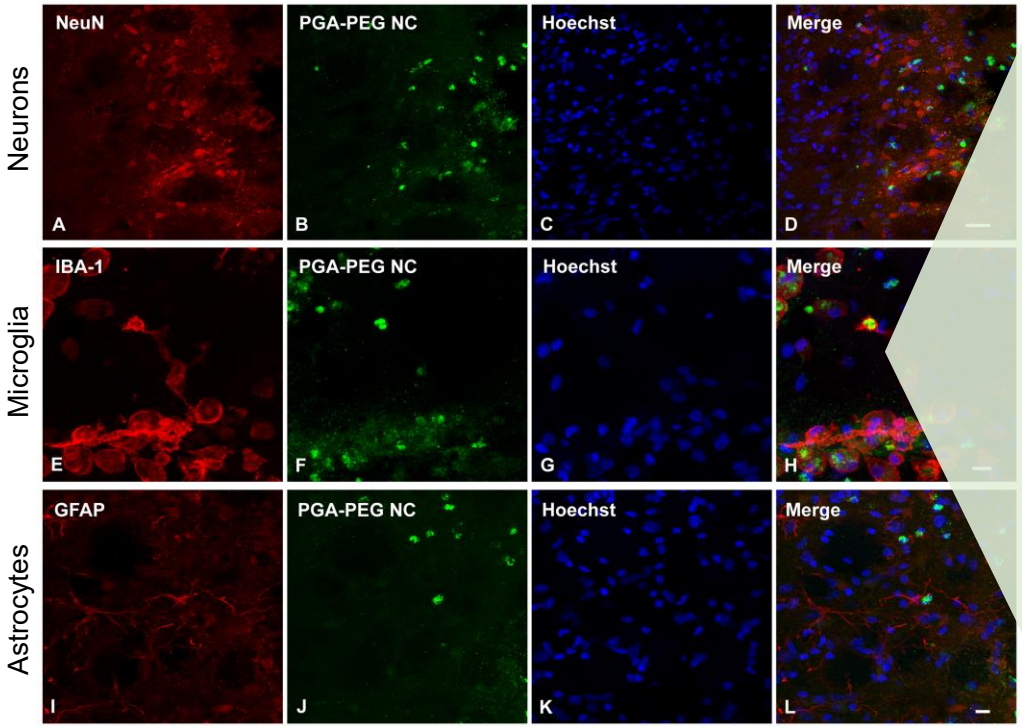
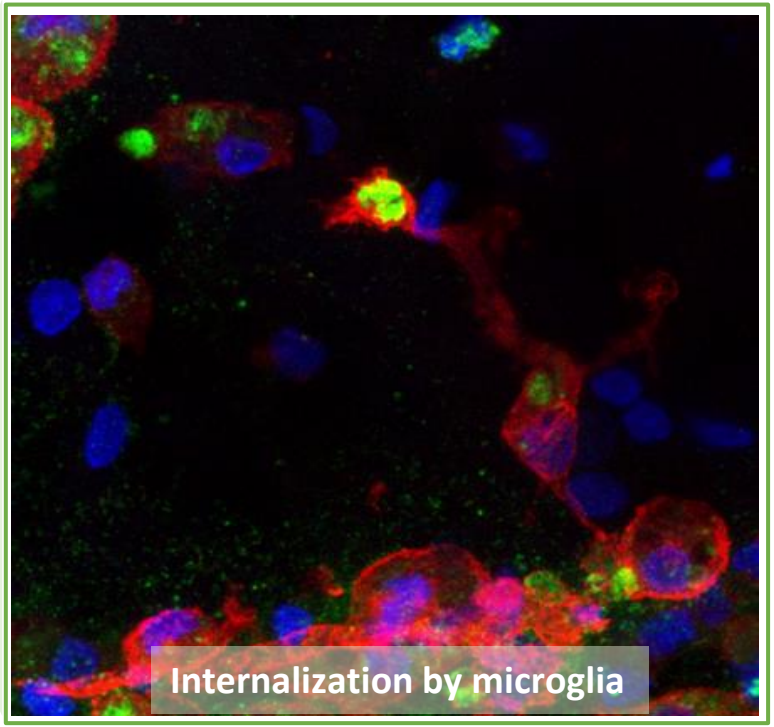




In vivo comparison using fluorescence

Colocalization of **PGA-PEG NCs** with <u>microglia cells</u>

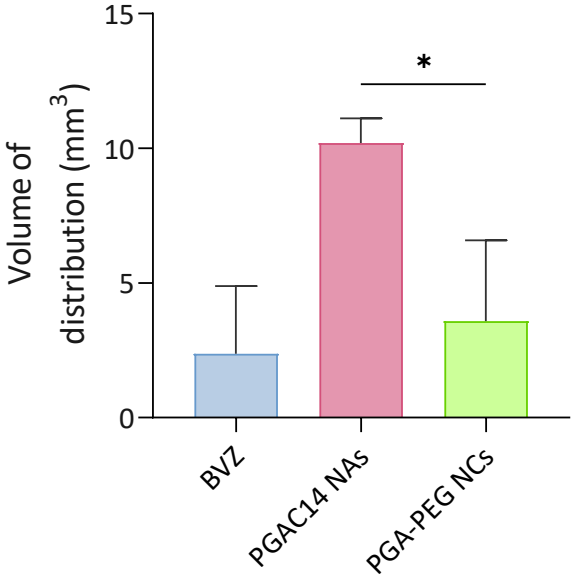


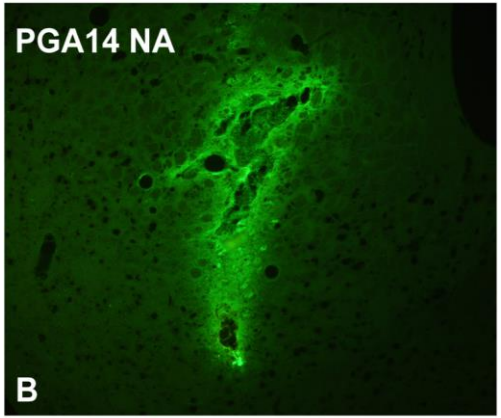


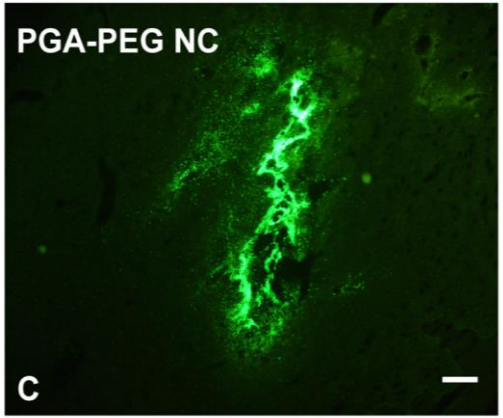
In vivo comparison using fluorescence

PGAC14 NAs exhibited higher diffusion through brain parenchyma

Volume of brain distribution







Conclusions

1. Two nanosystems, PGA-PEG NCs and PGAC14 NAs were produced for the efficient encapsulation of the mAb BVZ.

2. PGA-PEG NCs exhibited high neuronal and astrocytic uptake *in vitro*.

3. A distinct pattern was observed *in vivo* between the two studied nanosystems, with PGAC14 NAs exhibiting higher neuronal uptake and enhanced brain diffusion compared to PGA-PEG NCs.

4. The structure and physicochemical properties of the nanocarriers have significantly influenced their brain interaction and diffusion.

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