On the Amyloid-β transcytosis across the blood-brain barrier

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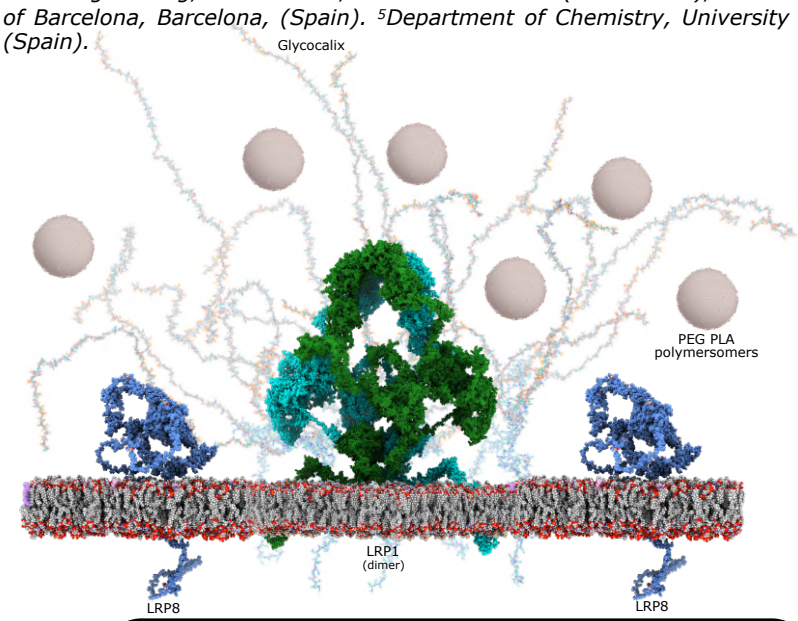
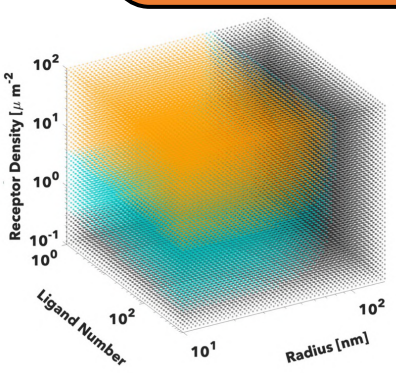


Background

Our group has discovered that the blood-brain barrier (BBB) plays a crucial role in regulating the transport of misfolded proteins to and from the Central Nervous System (CNS). We have found that the BBB controls the trafficking of macromolecular cargo by its affinity towards receptors like the low-density lipoprotein receptor-related protein 1 (LRP1) and the low-density lipoprotein receptor-related protein 8 (LRP8). LRP1 primarily transfers amyloid-β (Aβ) across the BBB, while LRP8 requires further studies. We have developed functionalised polymeric nanoparticles that mimic the in vivo process by having multiple ligand-receptor affinities to encourage this process. These investigations are essential in determining how polymeric nanoparticles can enhance the clearance of Aβ from the CNS, which could lead to the development of novel therapies.

On the polymersomes' avidity

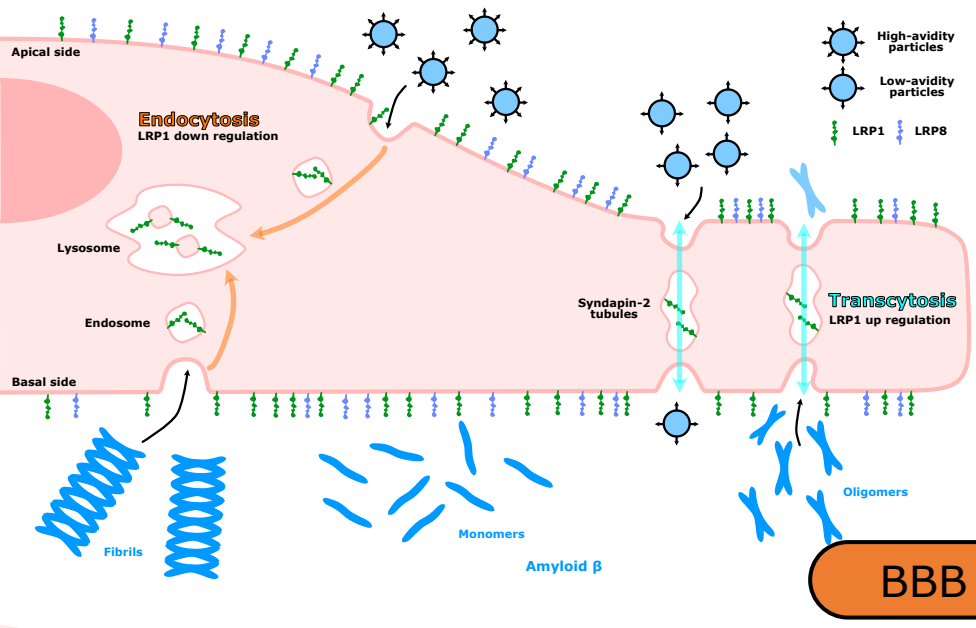


The cargo avidity mainly depends on receptor density, ligand number, and radius. We aim to tune these parameters to understand how LRP1 and LRP8 control trafficking.

$\beta E_{binding} = -\ln(\rho_0 K_a)$

30 20 10 0 -10 -20 -30 -40 -50 -60 -70

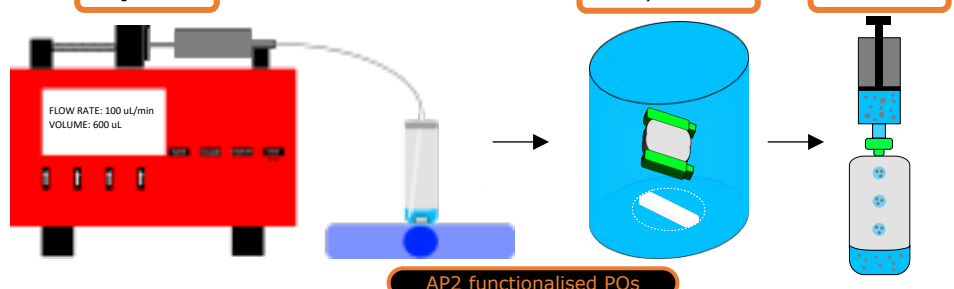
No interaction | Transcytosis | Endocytosis



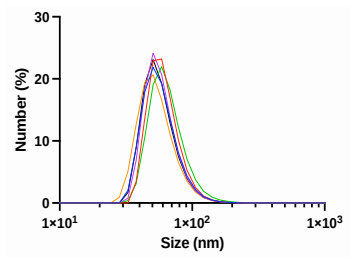
PEG PLA Polymersomes

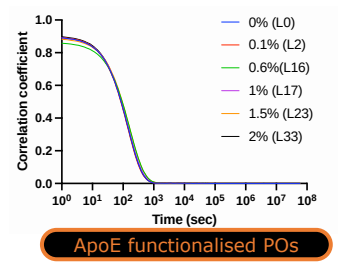
Solvent displacement approach

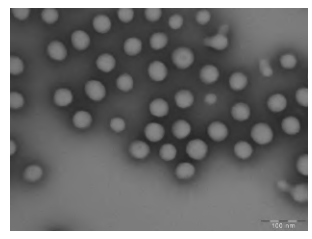
Injection → Dialysis o.n. → Filtration



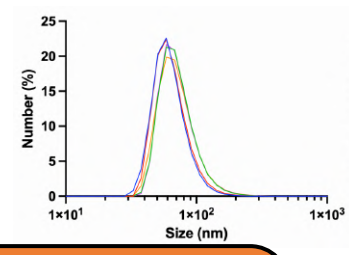
AP2 functionalised POs

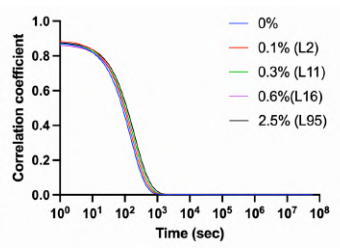


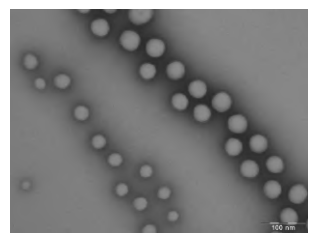




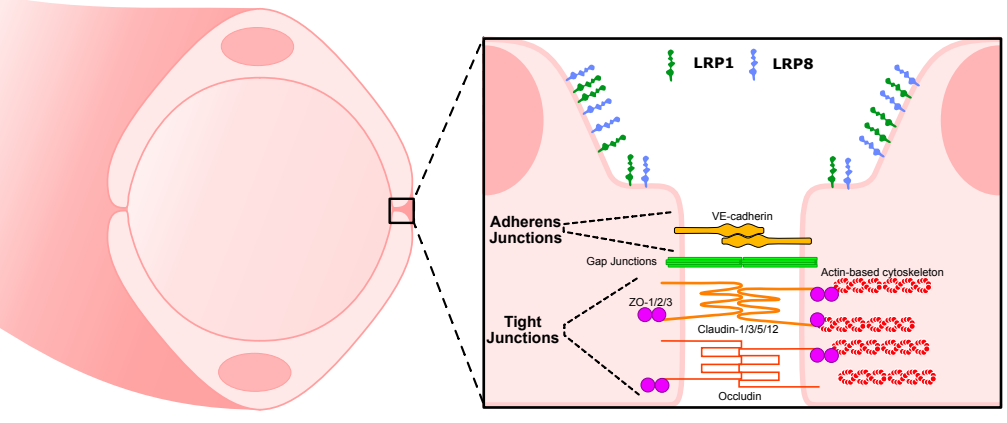
ApoE functionalised POs



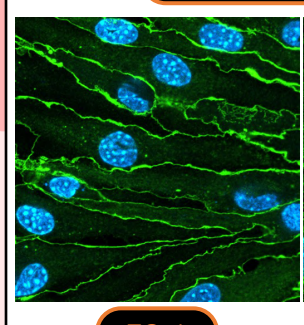




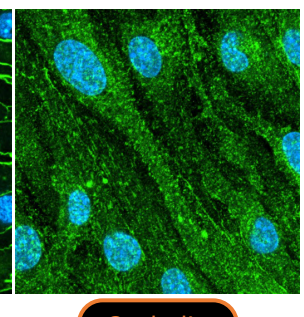
BBB characterisation



Tight Junctions

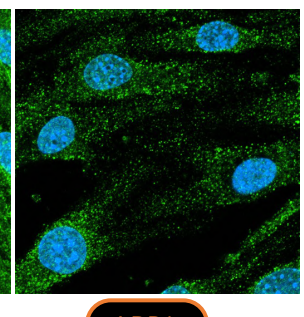


ZO-1

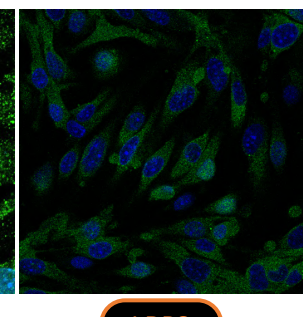


Occludin

Receptors



LRP1

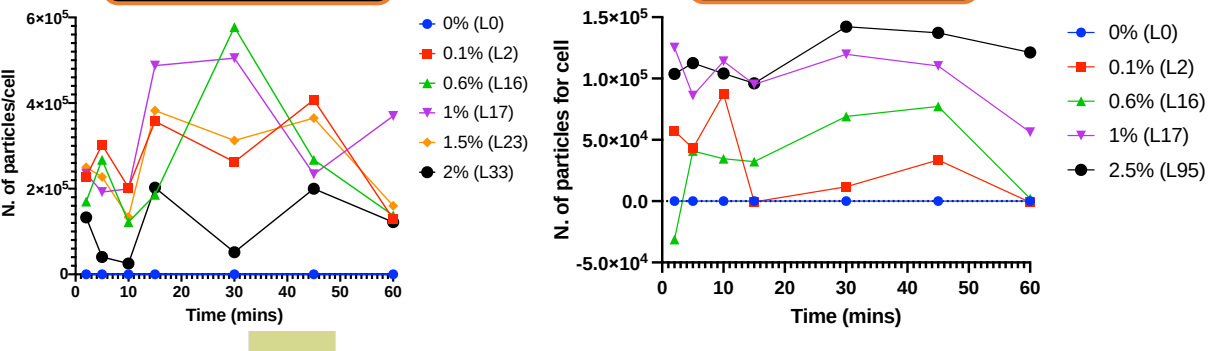


LRP8

Binding assay

Polymersomes incubation → Supernatant collection → Fluorescence analysis

AP2 functionalised POs



ApoE functionalised POs

Future prospective

These findings have opened the door for more in-depth investigations into the gene and protein expression of LRP1 and LRP8, as well as for a deeper exploration of the molecular mechanisms underlying the transcytosis of these receptors.

Acknowledgement

"la Caixa" Foundation

"The project that gave rise to these results received the support of a fellowship from "la Caixa" Foundation (ID 100010434). The fellowship code is "LCF/BQ/DI22/11940010".