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IBRO Workshop



ELTE
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HUNGARIAN
NEUROSCIENCE
SOCIETY

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Budapest, Hungary

Abstract book

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University of Szeged, Albert Szent-Györgyi Medical School, Department of Physiology, Translational Behavioral Neuroscience Group, Szeged, Hungary

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Bálint Varga; Bettina Soós; Balázs Jákli; Eszter Bálint; Zoltán Somogyvári; László Négyessy

Eötvös Loránd Research Network, Wigner Research Centre for Physics, Department of Computational Sciences, Computational Neuroscience and Complex Systems Research Group, Budapest, Hungary; Semmelweis University, János Szentágothai Doctoral School of Neurosciences, Budapest, Hungary

P9.03 Triple ligand-targeted nanoparticles cross the blood-brain barrier in vitro and enter human midbrain organoids

Gergő Porkoláb; Mária Mészáros; Anikó Szecskó; Nóra Kondor; Györgyi Ferenc; Zoltán Kóta; Tibor Páli; Judit P. Vigh; Fruzsina R. Walter; Silvia Bolognin; Jens C. Schwamborn; Jeng-Shiung Jan; Mária A. Deli; Szilvia Veszélka

Biological Research Centre, Institute of Biophysics, Szeged, Hungary; University of Szeged, Doctoral School of Biology, Szeged, Hungary

P9.04 Structural determinants of gap junction channel formation from hemichannels

Ágnes Simon; László Héja; Julianna Kardos

Eötvös Loránd Research Network, Research Centre for Natural Sciences, Institute of Organic Chemistry, Functional Pharmacology Research Group, Budapest, Hungary

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Balázs Barkóczi; Dániel Magda; Arnold Szabós; Pál Maák; Ákos Kusnyerik

Pázmány Péter Catholic University, Faculty of Information Technology and Bionics, Two-Photon Microscopy Laboratory, Budapest, Hungary

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Eötvös Loránd Research Network, Research Centre for Natural Sciences, Institute of Cognitive Neuroscience and Psychology, Budapest, Hungary; Pázmány Péter Catholic University, Faculty of Information Technology and Bionics, Budapest, Hungary

P9.03 Triple ligand-targeted nanoparticles cross the blood-brain barrier in vitro and enter human midbrain organoids

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Nanoparticles targeting transporters of the blood-brain barrier (BBB) are promising candidates to increase the brain penetration of biopharmaceuticals. Solute carrier (SLC) transporters show a specific pattern at the BBB and are highly expressed in brain endothelial cells, which makes them potential targets for drug delivery. Here, we show that the transporter ligands ascorbic acid, leucine and glutathione used as targeting molecules on the surface of nanoparticles can increase the uptake of a 67 kDa protein cargo in cultured brain endothelial cells. Moreover, we demonstrate the ability of our triple-targeted nanovesicles to deliver their cargo into human midbrain organoids after crossing the BBB model. Finally, using a combination of techniques, we reveal that the cellular uptake of nanoparticles is temperature- and energy-dependent, is mediated by both endocytosis and fusion with the plasma membrane and is dependent on brain endothelial surface charge. Our data indicate that labeling nanoparticles with ligands of multiple SLCs can potentially be exploited to deliver drugs across the BBB and into the brain.

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Triple ligand-targeted nanoparticles cross the blood-brain barrier *in vitro* and enter human midbrain organoids

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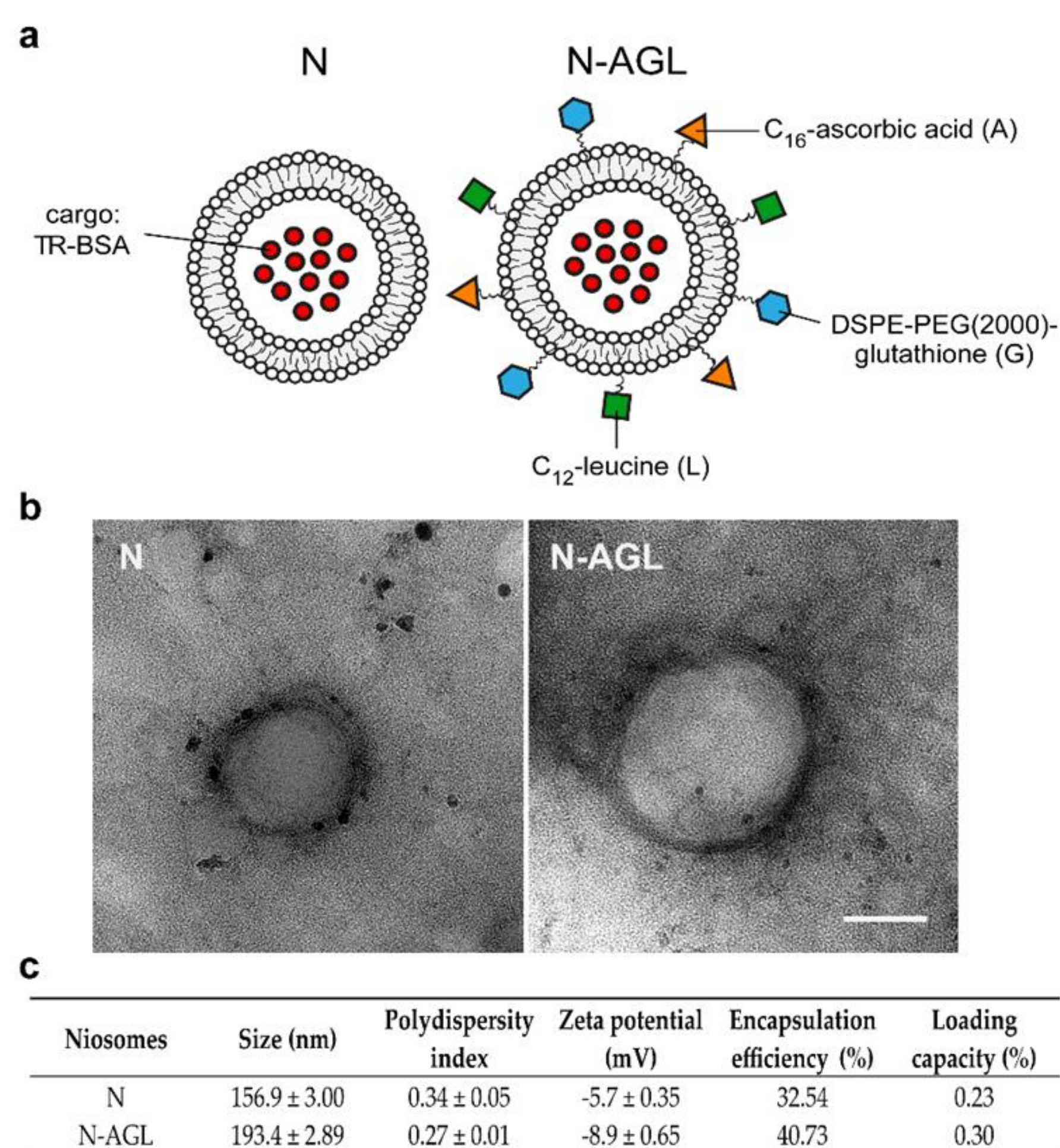


Introduction

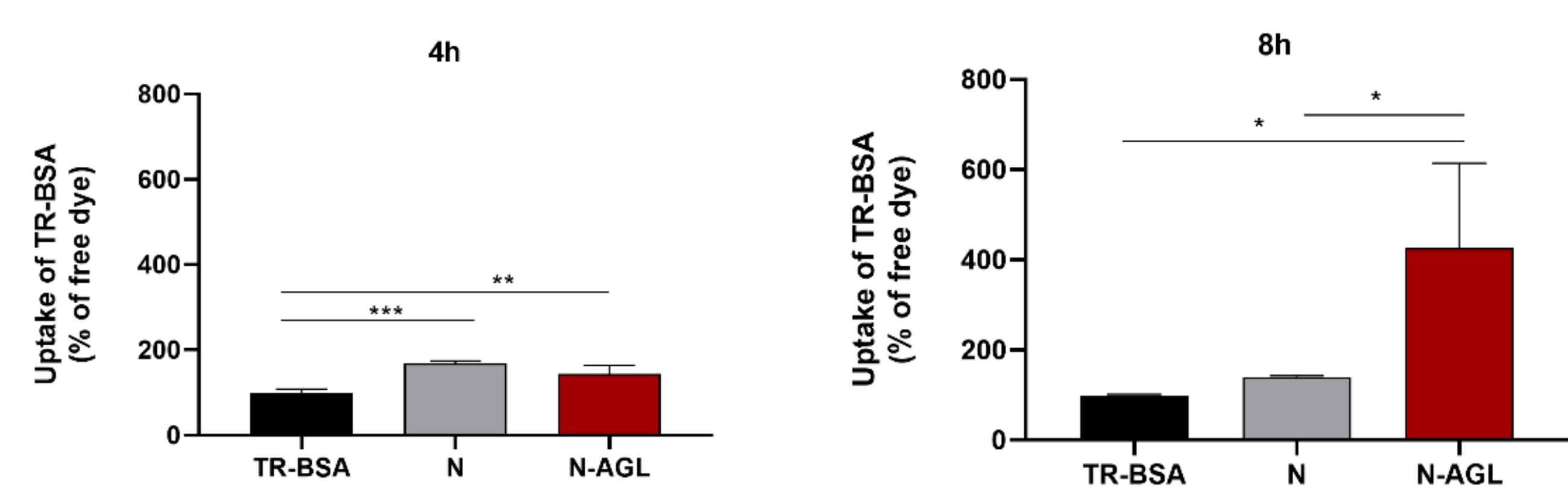
Nanoparticles targeting transporters of the blood-brain barrier (BBB) are promising candidates to increase the brain penetration of biopharmaceuticals. Solute carrier (SLC) transporters show a specific pattern at the BBB and are highly expressed in brain endothelial cells, which makes them potential targets for drug delivery. We hypothesize that an optimal combination of different SLC ligands would lead to better docking of NPs to the surface of brain endothelial cells resulting in the shuttle of NPs and their cargo across the BBB and increased brain delivery. Therefore, we designed nanoparticles with a new triple combination of BBB transporter ligands. We selected leucine, the ligand of LAT1, vitamin C, the ligand of sodium-ascorbate cotransporter (SVCT2/SLC23A2) and glutathione to label the surface of NPs. As model biomolecule cargo, we used bovine serum albumin labeled with Texas Red (TR-BSA).

Results

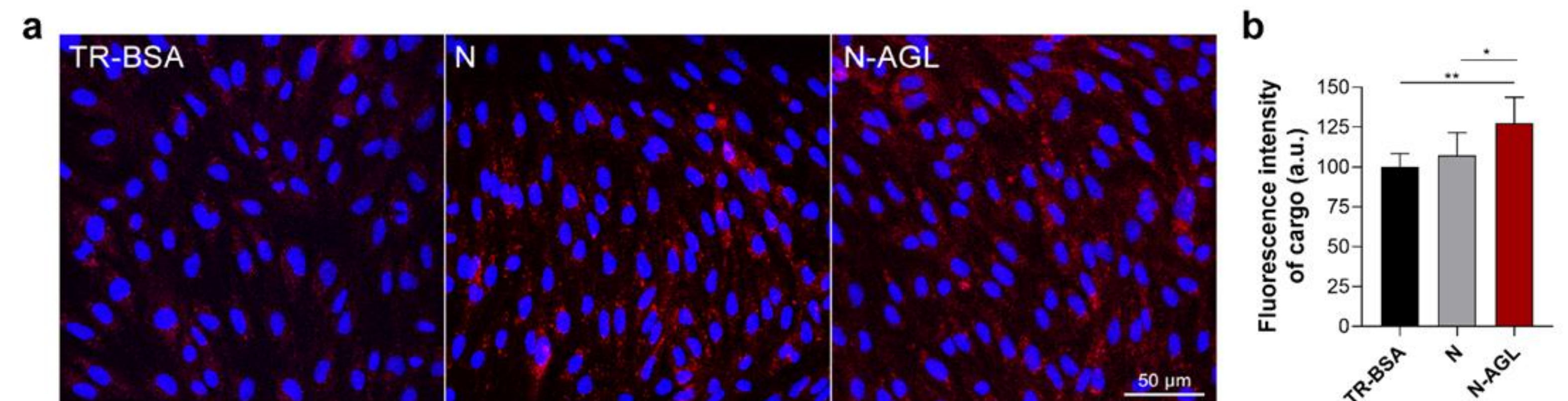
Design and characterization of niosomes



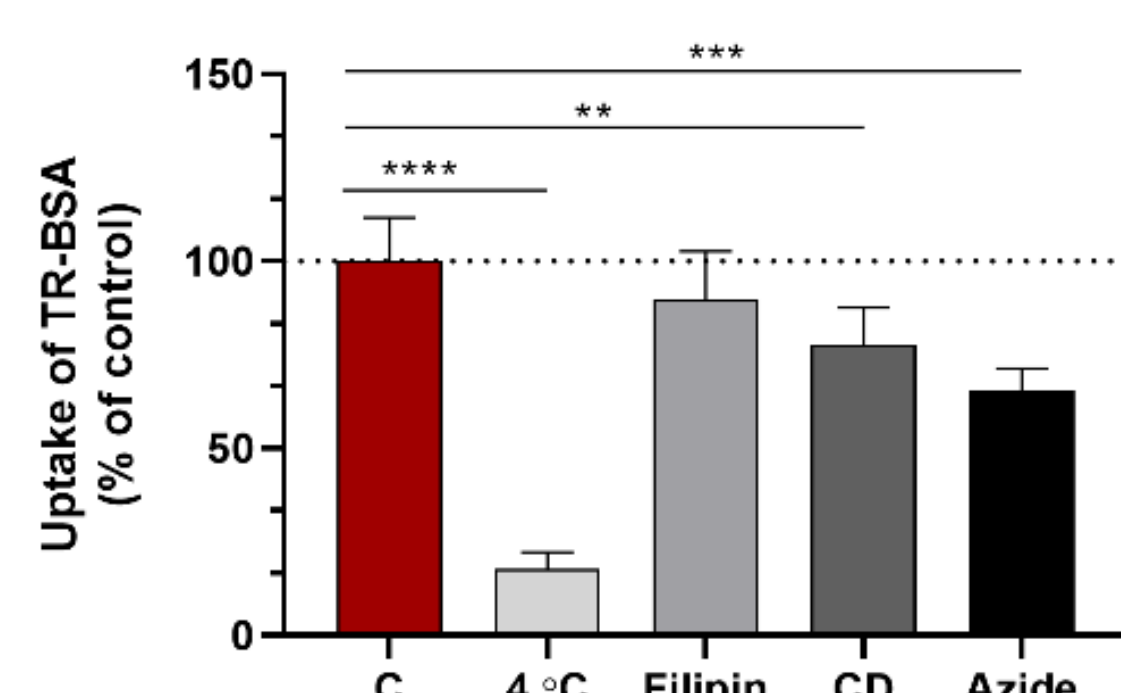
Cellular uptake of TR-BSA



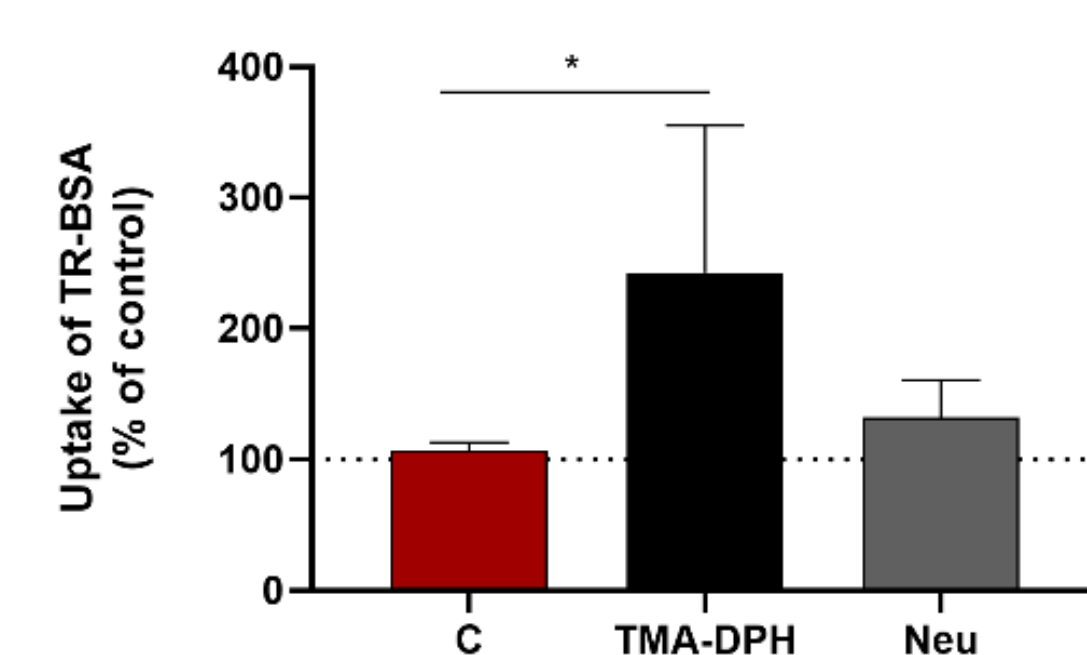
Visualization and quantification of TR-BSA uptake



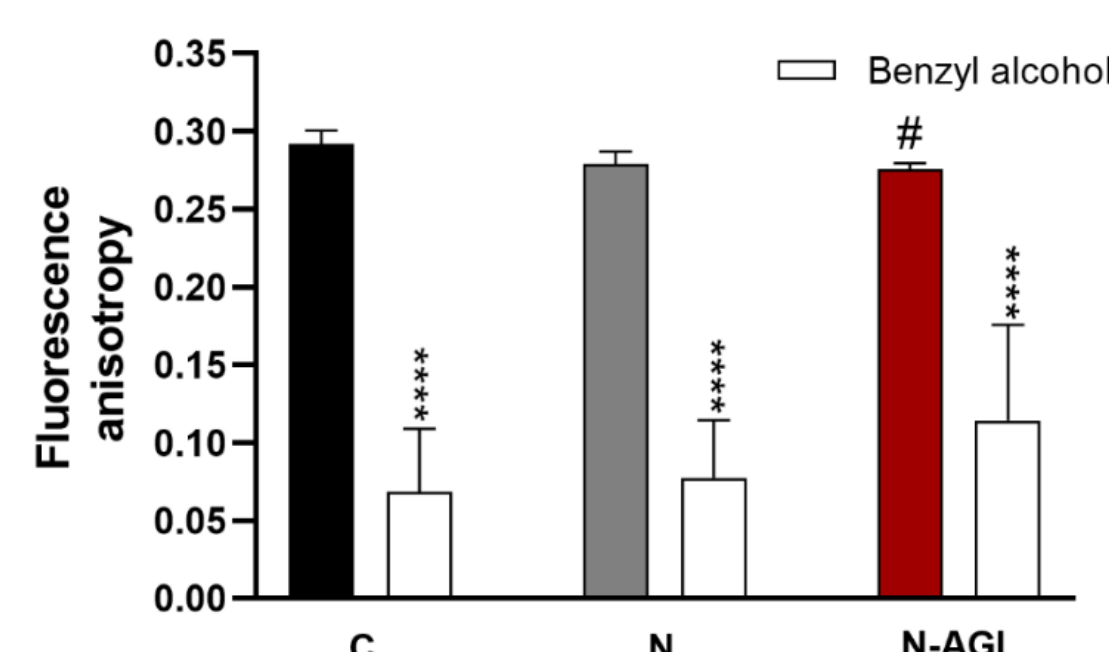
Effect of temperature, endocytosis and metabolic inhibitors on the uptake of TR-BSA



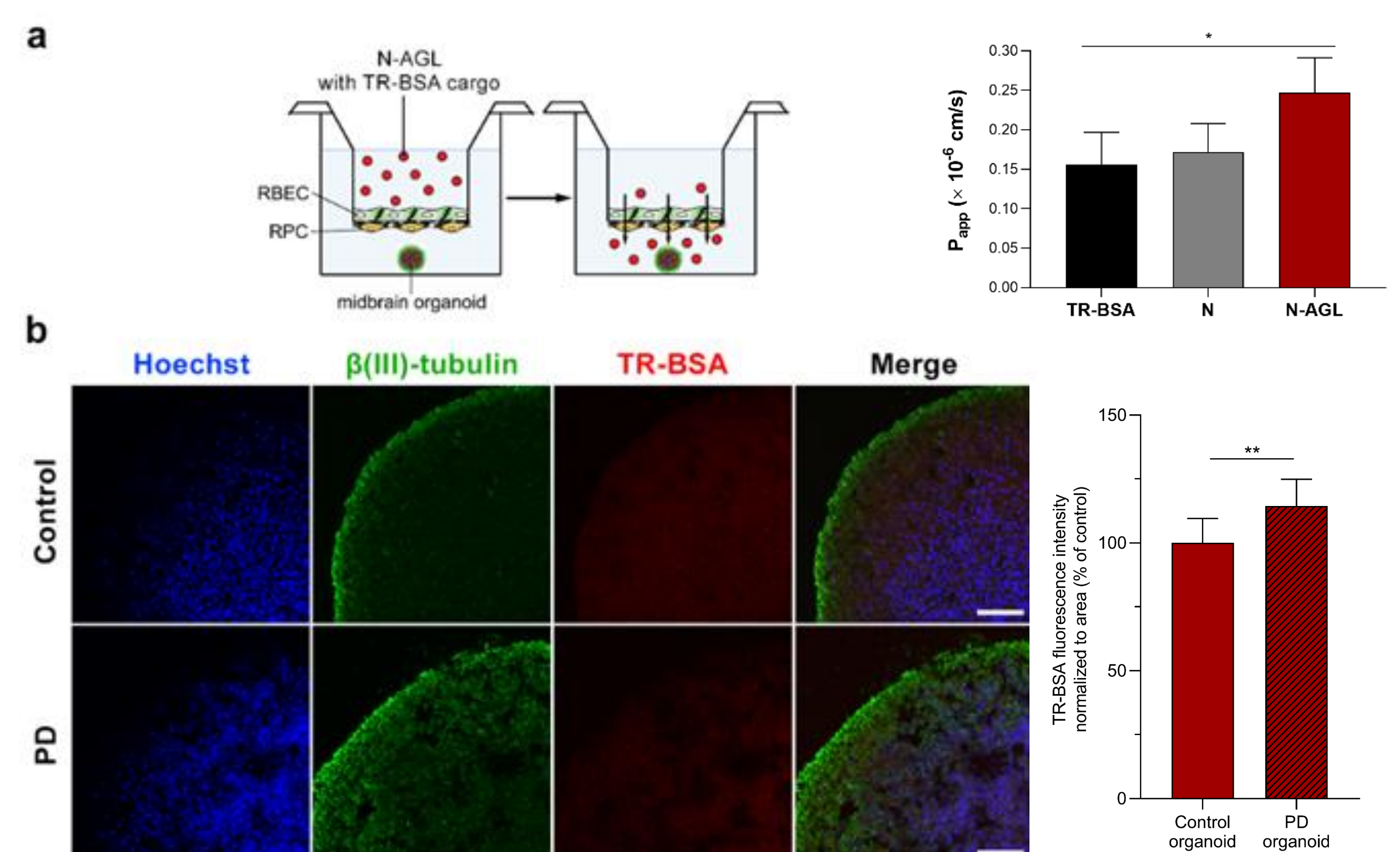
Effect of glycocalyx modification on the uptake of TR-BSA



Effect of niosomes on plasma membrane fluidity of RBEC



Permeability of niosomes across the BBB model and entry into midbrain organoids



Conclusion

Here, we show that the transporter ligands ascorbic acid, leucine and glutathione used as targeting molecules on the surface of nanoparticles can increase the uptake of a 67 kDa protein cargo in cultured brain endothelial cells. Moreover, we demonstrate the ability of our triple-targeted nanovesicles to deliver their cargo into human midbrain organoids after crossing the BBB model. Finally, using a combination of techniques, we reveal that the cellular uptake of nanoparticles is temperature- and energy-dependent, is mediated by both endocytosis and fusion with the plasma membrane and is dependent on brain endothelial surface charge. Our data indicate that labeling nanoparticles with ligands of multiple SLCs can potentially be exploited to deliver drugs across the BBB and into the brain.

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