Development and in vitro Evaluation of Peptide-based Stealth Nanoparticles for Enzyme Replacement Therapy

*Melissa Santi**[1,2], *Antonella Cecchettini*[3], *Giuseppe Maccari*[2], *Stefano Luin*[1], *Giovanni Signore*[1,2]

[1]NEST, Scuola Normale Superiore and Istituto Nanoscienze-CNR, Pisa, Italy.
[2]Center for Nanotechnology Innovation@NEST, Istituto Italiano di Tecnologia, Piazza San Silvestro 12, Pisa, Italy
[3]Institute of Clinical Physiology-CNR, Pisa, Italy

Melissa.santi@sns.it

Delivery of large therapeutic payloads to the central nervous system is challenging owing to the presence of the blood brain barrier (BBB) that inhibits uptake of virtually any macromolecule. Targeted nanostructures could overcome this issue, allowing delivery of otherwise impermeant payloads without suffering serum protein adsorption during circulation in the bloodstream. Here we present our results on the realization of a rationally designed targeted nanostructure tailored to in vivo use.

Our strategy relies on the development of a stealth shell that inhibits serum protein adsorption without using immunogenic PEG derivatives. A zwitterionic peptide (EKEKEKE) with known stealth properties was conjugated with lipid tails and used to prepare liposome-like self-assembled structures that outperform PEG in terms of serum protein adhesion, being stable up to 8 hours in pure serum.[1]

These structures were decorated with a targeting sequence that exploits transferrin receptor pathway. Transferrin (Tfn) is a promising target for delivery to the central nervous system (CNS) due to the overexpression of its receptor on the BBB. We designed and validated experimentally a new peptide aptamer (Tf2) able to recognize with good affinity transferrin without altering binding properties of the latter to its receptor.[2] We shall show that the presence of Tf2 on the surface of a nanoparticle induces extensive modulation of the protein corona composition, with significant overrepresentation of Tfn. We will also show that Tf2-decorated nanoparticles are efficiently assimilated by the cells in a transferrin-dependent fashion.[2]

Finally, we shall present the applicability of our structure to enzyme replacement therapy for the treatment of Batten disease. Our nanostructures can be loaded with recombinant protein palmitoyl thiotransferase 1 fully retaining its activity. We shall discuss the effect of this administration on enzymatic activity recovery and on the phenotypic rescue in primary healthy and patient-derived fibroblasts.

References

1. Ranalli, A., Santi, M., Capriotti, L., Voliani, V., Porciani, D., Beltram, F., Signore, G. (2017) Peptide-Based Stealth Nanoparticles for Targeted and pH-Triggered Delivery. Bioconjugate Chem.
2. Santi, M., Maccari, G., Mereghetti, P., Voliani, V., Rocchiccioli,S., Ucciferri, N., Luin, S., and Signore, G. (2016) Rational Design of a Transferrin-Binding Peptide Sequence Tailored to Targeted Nanoparticle Internalization. Bioconjugate Chem.

View publication stats