Transport of Single-Chain Polymer Nanoparticles across the Blood-Brain Barrier

Jos M. J. Paulusse[1,2]
Jan-Willem Paats, Laís Ribovski[1]

[1] Department of Molecules and Materials, University of Twente, Enschede, The Netherlands
[2] IntriS, Hengelo, The Netherlands

J.M.J.Paulusse@utwente.nl

Neurological disorders, such as brain injuries, infections, stroke and dementia, affect many millions of people worldwide and are the cause of death of nearly 7 million people every year. [1] Therapies to treat these disorders often fail, due to the difficulties encountered with therapeutics delivery. The brain is protected by the blood-brain barrier (BBB), which is extremely effective in keeping foreign substances from entering the brain. A variety of nanocarriers has been developed over the past decades, that exploit the transport systems of the BBB, and promote transport of therapeutics to the brain. However, a reliable, efficient and easy to use nanocarrier for brain delivery is still lacking. [2]

Our research efforts have been focused on developing single-chain polymer nanoparticles as nanocarriers for controlled therapeutics delivery. Single chain polymer nanoparticles (SCNPs) are prepared by intramolecular crosslinking of individual polymer chains into a nanoparticle, and therefore particle size and dispersity originate directly from the employed precursor polymer. As such, SCNPs are highly uniform and display sizes in the 5-20 nm range. This size range is of particular interest, as it matches the sizes of proteins and small viruses, and is therefore likely to display promising behavior in vivo. We developed strategies to easily develop functional SCNPs through post-formation conjugation of different surface ligands. This has enabled us to rapidly prepare SCNPs with increasing content of negative surface charge, allowing targeting of malaria parasites. [3] Further, a series of SCNPs with increasing amounts of tertiary amines provided control over their cellular uptake behavior, even on a sub-cellular level. [4]

Many nanocarriers are based on assembled or crosslinked polymers, utilizing their highly modular nature, and display sizes in the range of 50-200 nm. Interestingly, several studies outlined the importance of particle size on brain transport efficiency, with the smallest 10 nm-sized particles displaying substantially higher transport than larger 100-250 nm-sized particles. [5,6] We therefore reasoned that single chain polymer nanoparticles may display enhanced transport across the BBB.

We report here our investigations into the cellular uptake of SCNPs equipped with varying ratios of 1-aminoglycerol and *N,*N-dimethylaminoethylamine, as well as SCNPs equipped with increasing densities of 1-glucose ligands, by hCMEC/D3 brain endothelial cells, as well as their promising transport behavior across an in vitro blood-brain barrier model.

References

[1] Deuschl, Beghi, Fazekas, Varga, Christoforidi, Sipido, Bassetti, Vos, Feigin, "The Burden of Neurological Diseases in Europe: An Analysis for the Global Burden of Disease Study 2017" *The Lancet Public Health* 5 (2020), e551–e567

[2] Ribovski, Hamelmann, Paulusse, "Polymeric Nanoparticles Properties and Brain Delivery" *Pharmaceutics* 13 (2021) 2045.

[3] Hamelmann, Paats, Avalos-Padilla, Lantero, Spanos, Siden-Kiamos, Fernàndez-Busquets, Paulusse, "Single-Chain Polymer Nanoparticles Targeting the Ookinete Stage of Malaria Parasites" *ACS Infect. Dis.* 9 (2023) 56–64.

[4] Hamelmann, Paats, Paulusse, "Cytosolic Delivery of Single-Chain Polymer Nanoparticles" *ACS Macro Lett.* 10 (2021) 1443–1449.

[5] De Jong, Hagens, Krystek, Burger, Sips, Geertsma, "Particle size-dependent organ distribution of gold nanoparticles after intravenous administration" *Biomaterials* 29 (2008) 1912-1919.

[6] Sonavane, Tomoda, Sano, Ohshima, Terada, Makino, "In vitro permeation of gold nanoparticles through rat skin and rat intestine: Effect of particle size" *Colloids and Surfaces B: Biointerfaces* 65, (2008) 1-10.

Figures

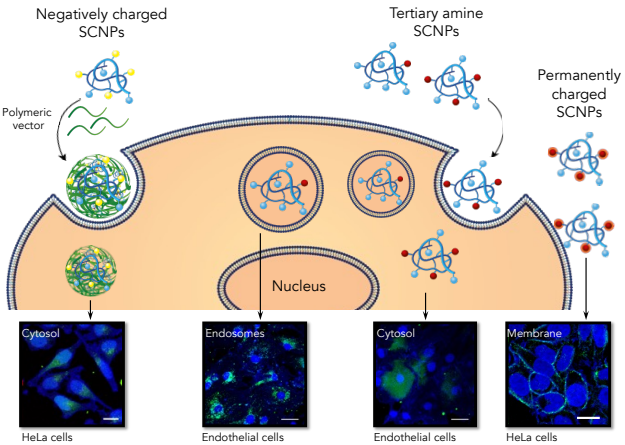

Figure 1. Cellular uptake pathways of single chain polymer nanoparticles depending on their surface functionality.