# Large-pore silica nanocarriers for antiangiogenic treatment against age-related macular degeneration

**Amelia Ultimo[1]**
Mar Orzaez[2], Maria Jose Santos-Martinez[1], Ramón Martínez-Máñez[3], María Dolores Marcos[3], Félix Sancenón[3], Eduardo Ruiz-Hernández[1]
*[1]School of Pharmacy, Trinity College Dublin, Dublin 2, Dublin, Ireland; [2]Centro de Investigación Príncipe Felipe, 46012, Valencia, Spain; [3]Instituto Interuniversitario de Reconocimiento Molecular y Desarrollo Tecnológico, 46022, Valencia, Spain*
ultimoa@tcd.ie

The main cause of subretinal choroidal neovascularization in wet age-related macular degeneration (AMD) is an abnormal expression in the retinal pigment epithelium (RPE) of the vascular endothelial growth factor (VEGF).[1] Current AMD treatments present considerable issues that could be overcome by encapsulating anti-VEGF drugs in suitable nanocarriers with better penetration, higher retention times and sustained release.[2] The main objective of this work is the preliminary development of a drug delivery system for the topical administration of anti-VEGF siRNA molecules to RPE based on large-pore mesoporous silica nanoparticles (LP-MSNs). siRNA is loaded into LP-MSNs mesopores, while the nanoparticles' external surface is functionalized with polyethylenimine (PEI) chains that allow the controlled release of siRNA and promote endosomal escape to facilitate its cytosolic delivery.[3]
LP-MSNs were functionalised to obtain three different sets of materials. The first one, S1, was loaded with the fluorescent dye rhodamine B and capped with PEI chains, and allowed verifying PEI capping ability; S2 was covalently functionalised with rhodamine B isothiocyanate through 3-aminopropyltriethoxysilane chains, and externally capped with PEI, and employed to study nanoparticles cytotoxicity, cellular uptake and hemocompatibility; finally, S3 was loaded with anti-VEGFA siRNA and capped with PEI, and used for VEGF silencing in ARPE-19 retinal cells. Spherical monodispersed nanoparticles with an average size of 105 nm and center-radial pores of about 17 nm were obtained. The release studies showed that the cargo remains protected inside the pores in the absence of an adequate stimulus. The siRNA-loaded S3 reduced VEGF expression, demonstrating the developed nanocarrier capacity to provide siRNA protection, endosomal escape and consequent cytoplasmic release. Nevertheless, some issues were observed in cells viability.
Our results represent a first step for the development of topically administered nanovehicles based on LP-MSNs for the sustained attenuation of VEGF in the RPE by siRNA delivery systems. The successful results obtained in VEGF silencing in ARPE-19 cells demonstrate that although further modifications are needed for improving their biocompatibility, the designed nanodevices present a great potential for nucleic acid delivery, holding great promise for the next stages of the project.

## REFERENCES

[1] A.F. Moleiro, G. Conceição, A. Leite-Moreira, A. Rocha-Sousa, J. Ophthalmol, 2017 (2017) 1.
[2] R. Bisht, A. Mandal, J.K. Jaiswal, I.D. Rupenthal, Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology, 10 (2018) 1.
[3] T. Xia, M. Kovochich, M. Liong, H. Meng, S. Kabehie, S. George, J.I. Zink, A.E. Nel, ACS Nano, 3 (2009) 3273.

## FIGURES

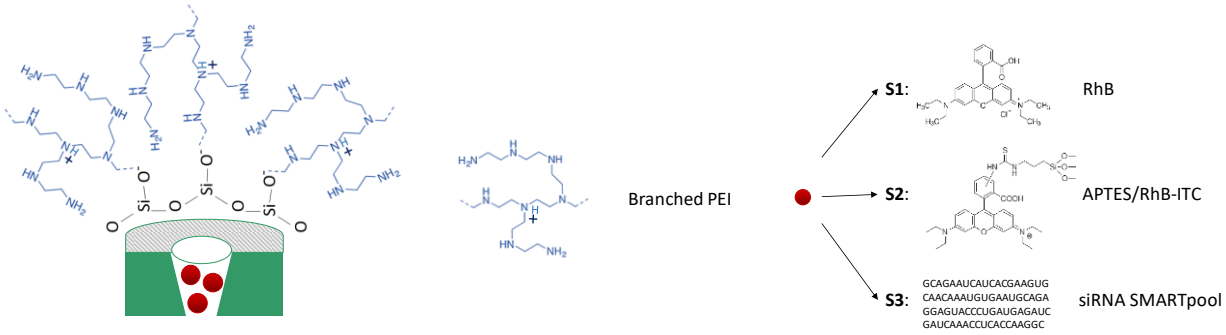


**Figure 1:** Schematic depiction of the synthesized nanodevices. siRNA is loaded into the mesopores, while positively charged PEI chains are attached via electrostatic interaction to the negatively charged silica surface.