Novel targeted devices based on Elastin-like polypeptides for diagnosis and gene therapy in breast cancer

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Breast cancer is the principal malignancy diagnosed in women and the second most common cancer overall. Typical treatments for breast cancer are surgery, chemotherapy and radiotherapy; and although they improve the clinical outcome, they do not increase the cure rate [1]. The main problem of the current cancer treatments is the low specificity that translates into systemic toxicity and side-effects. In the last years, immunotherapy has emerged as an outstanding personalized treatment. Other approaches for cancer treatment such as the delivery of therapeutic genes via specifically targeted nanodevices stands out as an alternative therapy. Elastin-like polypeptides (ELPs), biomaterials derived from elastin-mimetic peptide sequences, are promising candidates as carriers for these gene therapies because of their excellent biocompatibility and low toxicity [2].

This work comprises the development of a selectively targeted nanodevice to eliminate tumor cells while keeping healthy ones safe. This devices are based on a polycationic Elastin-like backbone that complexes therapeutic DNA and interacts with the cell membrane allowing the DNA uptake. The device is also targeted to tumoral cell markers, and the expression of the therapeutic DNA is controlled by a tumoral promoter, which makes these nanoparticles doubly targeted to cancerous cells [3,4].

The genes codifying the different ELPs were created using genetic engineering techniques and the ELPs were bioproduced in a bacterial host. They were purified by affinity chromatography and characterized by MALDI-TOF, 1H-NMR, SDS-PAGE and DSC. Nanoparticles based on this ELPs and therapeutic plasmid DNA (pDNA) were formed by electrostatic interactions between the positively charged lysine-rich backbone of ELRs and negatively charged pDNA. The obtained nanoparticles were characterized by Dynamic Light Scattering (DLS). In addition, *in vitro* and *in vivo* experiments have been performed to prove the efficiency of the system.

Our nanoparticles presented a Zeta potential of about +40 mV and a size of about 140 nm. Their positive charge allows the interaction with the negatively charged cell membrane, facilitating the pDNA uptake. When loaded with a pDNA that encodes a fluorescent reporter protein, these nanoparticles can be used as imaging technique for diagnosis and when loaded with toxic pDNA, they can be used as selective gene therapy against cancerous cells. The developed in vitro studies showed transfection ability of the system facilitated mainly by micropinocytosis uptake and selective toxicity against cancer cells without harming the healthy cells. After the development of *in vivo* studies, an inhibition of tumor progression was observed with a decrease of the tumor growth of an 85% in comparison with the placebo group. In addition, a dose dependent reduction in tumor mass was observed, with a better result in the highest concentration of the therapeutic DNA tested which was 70 nM.

This versatile system can be tuned to target different tumoral targets making it a next-generation material with a promising scope.

References

[1] Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN; Adv Exp Med Biol (2007) Ed 608:1-22.

[2] Rodriguez-Cabello JC, Arias FJ, Rodrigo MA, Girotti A; Adv Drug Deliv Rev (2016) Ed 97: 85−100

[3] Piña MJ, Girotti A, Santos M, Rodriguez-Cabello JC, Arias FJ; Mol Pharm (2016) Ed 13:795-808

[4] Piña MJ, Girotti A, Serrano S, Muñoz R, Rodriguez-Cabello JC, Arias FJ; Cancer Lett. (2020) Ed, 470:43-53

Figures

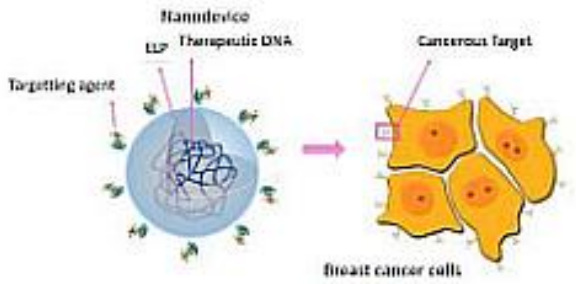

Figure 1: Scheme of the developed nanodevice