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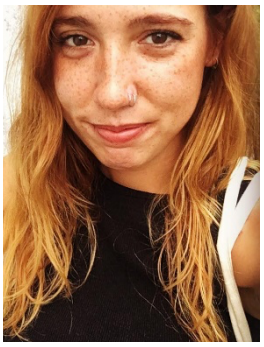

Polyphosphazene nanocarriers for RNA delivery

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Poly(organo)phosphazenes (PPZs) are new, versatile polymers of great interest as biomaterials for medical applications, and concretely for gene delivery [1]. Previous studies from our group showed that 6-mercaptohexanoic acid alkyl carboxylate-poly(phosphazene) (6MHA-PPZ) can enhance transfection efficiency of gene nanocomplexes (NCs) while reducing their cytotoxicity [2].

Herein, we designed three novel prototypes of NCs and explored their potential for pDNA and cmRNA delivery *in vitro* glioblastoma models. To achieve this, we synthesized two new cationic PPZs along with the anionic 6MHA-PPZ using a multistage reaction previously reported by our group [2]. The products were characterized by ^{31}P and ^{1}H NMR. Next, NCs were prepared based on the two cationic PPZs, or the commercial reagent polyethyleneimine (PEI), and their combination with 6MHA-PPZ. All formulations presented sizes between 80 and 150 nm and positive surface charge, which are adequate for their use in gene therapy. Additionally, we observed that all formulations could complex the nucleic acids and release them in the presence of an anionic competitor. Finally, NCs loaded with pDNA and cmRNA were tested for toxicity and GFP expression in the GL261 cell line. The three formulations were non-toxic until a median dose of 250 ng/cm^2. Data from fluorimetry and flow cytometry studies confirmed the possibility to induce efficient GFP expression with formulations loaded with pDNA and cmRNA. In conclusion, our studies highlight the potential of various PPZ-based materials as versatile components to constitute a new generation of nanocomplexes (NCs) designed for efficient gene delivery in brain cancer.

References:

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2. WH. Hsu, *Adv. Ther.* 2019, 2(3), 1800126