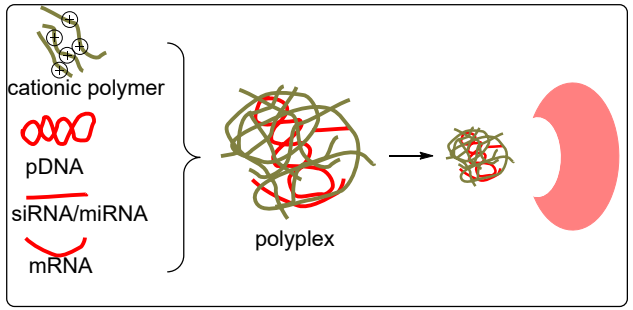
NEW CATIONIC POLYMERS WITH CYCLEN-DERIVED ZINC-CHELATING AGENTS

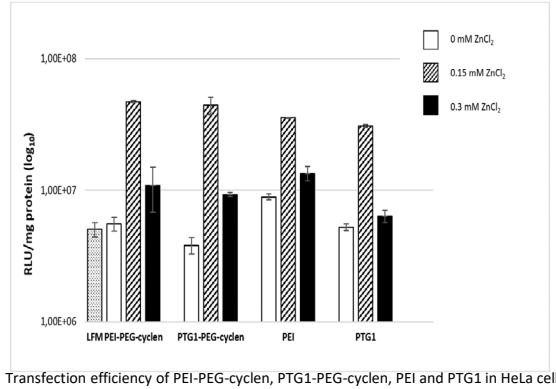
Isabelle Gillaizeau (1), Ismaël Dondasse (1), Chantal Pichon (2), Patrick Midoux (2), Doris Filipović (2)

1) Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, rue de Chartres, 45100 Orléans, France. E-mail: isabelle.gillaizeau@univ-orleans.fr
2) Centre de Biophysique Moléculaire, CNRS UPR 4301, rue Charles Sadron, 45071 Orléans, France. E-mail: Chantal.PICHON@cnrs.fr

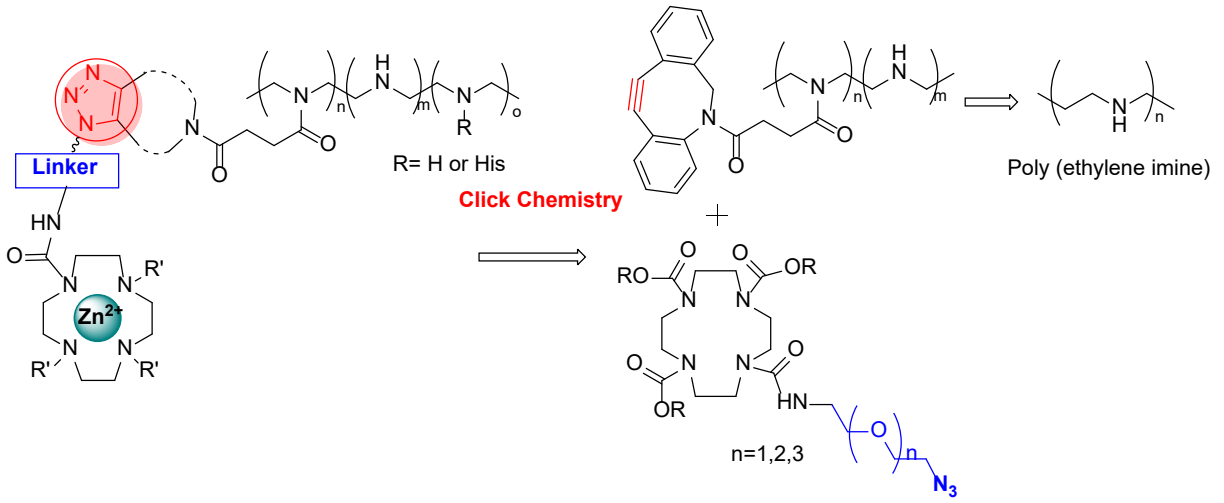
Gene delivery systems are developed to efficiently deliver genetic material to the target site. Naked DNA and RNA exhibit very poor ability to transfect cells due to their easy degradation by nucleases in biological media and their negative charge, from the phosphates they carry, which limits cellular uptake. Nucleic acid vehicles, also known as vectors, are being developed to overcome these obstacles safely and efficiently.

***Cationic polymers (polycations) are attractive candidates for non-viral gene delivery systems due to their easy synthesis as well as their flexible properties**. These polymers are complexed with nucleic acids (pDNA, siRNA, mRNA) via electrostatic interactions at physiological pH, forming nanoparticles (polyplexes) that could be endocytosed by cells and thus facilitate the introduction of nucleic acids. Polyethyleneimine (PEI) and His-IPEI represent one of the most efficient gene delivery vectors. However, low efficiency of pDNA delivery to the cytoplasm represents a major limiting factor for achieving efficient transfection with polyplexes, even with those rich in histidine. A few years ago, it was found that supplementation of the transfection medium with $ZnCl_2$ increases the efficiency of polyfection (polyplex-mediated transfection) of human hepatocarcinoma (HepG2) cells, particularly with histidylated polylysine (His-pLK) assembled polyplexes. This phenomenon is selective to Zn^{2+} among other divalent cations and the data imply that the addition of Zn^{2+} to the transfection medium triggers an increase in the fusion of polyplex-containing endosomes, thereby facilitating better delivery of pDNA into the cytosol. **Our goal was thus to transpose these conditions to mRNA-mediated transfection and investigate whether Zn^{2+} had a similar or even greater effect on transfection efficiency**. Our study demonstrated indeed that supplementation of transfection medium with $ZnCl_2$ (Zn^{2+}) results in an increase of transfection efficiency mediated by mRNA-based polyplexes.*





Transfection efficiency of PEI-PEG-cyclen, PTG1-PEG-cyclen, PEI and PTG1 in HeLa cells at various $ZnCl_2$ concentrations (0 mM, 0.15 mM and 0.3 mM). The cells were transfected in minimum medium with the addition of $ZnCl_2$ to polyplexes after the completion with medium. All values shown are subtracted by RLU values for negative control (2.17×10^6). The figure shows average values ± s.d. of one experiment, performed in triplicate



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5) (a) Dondasse, I. Master Thesis, 2018, Université d'Orléans. (b) Filipović, D. Master Thesis, 2020, Université d'Orléans. (c) Unpublished results.