Title	Smart nanocarriers for oligonucleotide delivery
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Project description:

In the last decades, large efforts have been dedicated for the exploitation of therapeutic oligonucleotides (tON). Indeed, this class of macromolecules has shown a remarkable effect on the treatment of several diseases such as cystic fibrosis, ischemia, neurodegenerative diseases, wound healing and cancer. While oligonucleotide can be designed with high molecular selectivity, they suffer from instability, rapid enzymatic degradation, negligible circulation half-life. Thus, the use of dedicated delivery strategies is mandatory. The use of nanocarriers, in particular, has raised large interest in the scientific community to ensure the delivery of these macromolecules to the site of action. One of the most promising methods for the tON delivery relies on their assembly with polymers, which yields systems named “polyplexes”. We aim here to investigate a new class of cationic polymers with novel structural features that ensure efficient complexation of tONs through coulombic interactions. We expect that this will efficiently prevent their degradation in the blood stream, ameliorate the biopharmaceutical features (i.e. pharmacokinetic and biodistribution profiles). The cationic polymer will be designed to promote also the intracellular access of the tON. A set of star-like shape poly-cationic derivatives will be developed. These derivatives will be conjugated to different natural and biocompatible polysaccharides or polyaminioacid chains to tailor the features of the oligocationic moieties while end functionalization with targeting agents will enhance cancer selectivity.

The ability to condense, protect from enzymatic degradation and release oligonucleotides will be assessed by suitable analytical techniques. To further improve the efficacy of the nano-polyplexes, the co-delivery of oligonucleotides and anticancer drugs will be explored to seek a synergistic effect. Cleavable linkers will be used to conjugate the anticancer drugs to achieve in situ controlled release. I*n vitro* studies will be performed to evaluate the silencing of an intracellular target protein expressed by cancer cells. Nanotoxicity studies will be undertaken with the resulting nano-polyplexes. Finally, the *in vivo* efficacy to induce tumor regression will be performed using appropriate mice tumor models.

The PhD fellow involved in this project will acquired state-of-the-art skills in advanced drug delivery, nanotechnology, bioconjugation/polymer chemistry, in vitro and in vivo screening of novel therapeutic systems. The student will learn the most updated physico-chemical and biophysical techniques for colloid characterization.

This project lays at the interface between material science and biomedicine since the concepts behind the design of these systems stems from the combined knowledge of the physico-chemical features of novel materials and of the physiology of either the tumor tissue and the whole body.

Publications

1. Balasso, A.; et al. (2017) *European Journal of Pharmaceutical Sciences* 103:104-115.
2. Gallon E., et al (2015) *Biomacromolecules* **16**: 1924–1937.

Collaborations/Network

University of Tel Aviv (Israel)

Research funding

The project will be supported by dedicated commercial funds.