FORMULATION OF NANOTECHNOLOGIES FOR THE DELIVERY OF NUCLEIC ACIDS

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Over the past years, the delivery of small nucleic acid sequences in target cells using nanoparticles has been proven challenging. To improve the selectivity and delivery of anticancer therapeutics, and reduce side effects, it is necessary to design an effective strategy. Nanotechnologies can be engineered and formulated to enhance target-ligand interactions, promote internalization and intracellular release to effectively address the clinical need.

In the recent years, we have developed and optimised ternary nanocomplexes to deliver small nucleic acid sequences to cancer cells. Polycations varying in physicochemical properties were complexed with siRNA, or mRNA. Nanoparticles were decorated with hyaluronic acid (HA) to exploit the interaction with CD44-expressing cancer cells. We evaluated the role of chitosan macromolecular properties (e.g. molecular weight; degree of deacetylation) and correlate it with nanoparticle properties (e.g. complexation strength, nucleic acid protection, internalization rate).

The interaction between chitosans and siRNA showed protection of the cargo, regardless the chitosan used. Chitosans with higher deacetylation degree showed higher avidity towards encapsulated siRNA. Interestingly, such avidity of chitosan for RNA lead also to higher transfection efficiency. We further characterised the selected chitosan/HA formulation (higher transfection efficiency), and demonstrated that the decoration of nanoparticles with HA, not only promote the internalisation in CD44-expressing cancer cells, but also improved the stability and efficacy of siRNA transfection after storage (one-week, 4°C). We finally demonstrated nanoparticle internalization (flow cytometry), siRNA cytosolic release (confocal microscopy) and gene silencing (RT-qPCR) in CD44+/KRAS+ colorectal cancer cell line, HCT-116. Further we demonstrated that the uptake of HA-decorated nanoparticles in cancer cells is higher when co-cultured with fibroblasts and when tested under perfusion.

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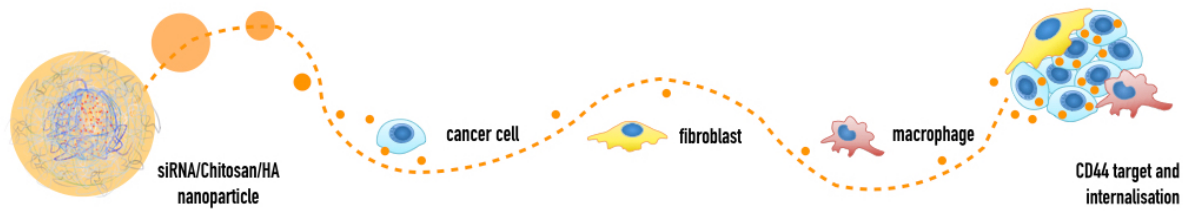

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