NOVEL STEALTH DELIVERY SYSTEMS FOR ODN DERIVATIVES TARGETING PROVIRAL HIV DNA.

Federico Arcamone[1], *Stefano Buttò*[2], *Massimo Capobianco*[1], *Marcella De Champdorè*[1], *Anna Garbesi*[1], *Michele Laus*[3], *Katia Sparnacci*[4], *Luisa Tondelli*[1]

1. I.Co.C.E.A. C.N.R., Via Gobetti, 40129 Bologna, Italy
2. Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy
3. Dipartimento di Scienze e Tecnologie Avanzate, Corso Borsalino 54, 15100 Alessandria, Italy
4. Dipartimento di Chimica Industriale e dei Materiali, Viale Risorgimento 4, 40136 Bologna, Italy

In vivo application of antisense and antigene oligonucleotides (ODNs) is restrained by their poor cellular uptake through lipophylic cell membranes and their short half-life in biologic fluid, as naturally occurring phosphodiester linkages in ODNs are susceptible to degradation by serum and intracellular nucleases. The enhancement of their bioavailability can be faced by their binding to carrier system like polymeric nanospheres, even if clearance by the phagocitic cells of the reticuloendothelial system (RES) can reduce their efficiency. However, it is known that surface modification of particulate carriers with hydrophilic polymers prolongs nanosphere half-life in the blood compared to unmodified nanospheres. Thus we have projected and prepared a novel class of polymethylmethacrylate core-corona type nanospheres whose surface is fucntionalized with cationic groups and PEG chains, leading to an highly hydrophilic outer shell. Ion pair formation occurs between the negatively charged internucleosidic phosphate groups of the ODN and the ammonium cations present on the nanosphere surface. The hydrophilicity of the PEG chains located on the nanosphere surface induces dysopsonic effect, masking the presence of the carriers from the recognition of RES. The reversible adsorption characteristics of ODN on these nanospheres were studied and the surface density of cationic groups was found to be the most important parameter in determining the adsorption behaviour, through a peculiar mechanism involving substantial rearrangements in the outer ionic sphere. Aim of our project is the delivery of a triplex-forming ODN (TFO), capable to recognise and specifically bind the PPT segment of the integrated proviral HIV genome, conjugated with daunorubicine derivatives, through the described core-shell nanoparticles.

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