Peptide-based nanoparticles for *in vivo* delivery of therapeutic siRNA

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The development of nucleic acid-based therapeutic-molecules remains limited by their poor cellular uptake and trafficking. We have designed a short amphipathic peptide: MPG that combines a hydrophobic domain to a hydrophilic NLS-containing domain. MPG forms stable discrete nanoparticles with siRNA, through non-covalent interactions, and promotes their efficient delivery into a wide variety of cell lines. Cellular uptake mechanism of MPG/siRNA nanoparticles is dependent on the size of the particle and involves membrane potential and dynamic, which enables a rapid release of the siRNA into the cytoplasm and promotes a robust downregulation of target mRNA. MPG-carriers were applied to the delivery of siRNA targeting the cell cycle regulatory protein Cyclin B1 into cancer cells and mouse models. In order to control and analyze the kinetics of downregulation of target mRNA, MPG was associated with a light-activated controllable siRNA. We demonstrated that MPG-mediated delivery of siRNA significantly knocked down Cyclin B1 protein levels inducing a cell cycle arrest in G2 and blocked cancer cell proliferation. Cholesterol-functionalize-MPG/Cyclin B1 siRNA nanoparticles were shown to block tumor growth *in vivo* upon intratumoral or systemic intravenous injections.

Given the biological properties of this vector, we believe that MPG-based technologies will contribute significantly to the development of fundamental and therapeutic applications.