

P001 Peptide-based nanoparticles for *in vivo* delivery of siRNA targeting Cyclin B1

**M.-C. Morris¹, F. Simeoni, G. Aldrian-Herrada¹,
Q. Nguyen², G. McMaster², F. Heitz¹ and G. Divita¹**

¹CRBM-CNRS, Dpt-Molecular Biophysics & Therapeutics, Montpellier, France; ²Panomic-Inc, Fremont, USA

The development of nucleic acid-based therapeutic molecules is limited by their poor cellular uptake, cellular trafficking and the lack of biological activity within the cell. We have designed a short amphipathic peptide: MPG, consisting of a hydrophobic domain and a hydrophilic NLS-containing domain. This carrier forms stable “nanoparticles” with siRNA, through non-covalent interactions, thereby increasing their stability. MPG efficiently delivers siRNA into a wide variety of mammalian cell lines, through a process involving membrane potential and dynamics, independently of the endosomal pathway, which enables rapid release of the siRNA into the cytoplasm and promotes robust downregulation of target mRNA. MPG was used for the delivery of siRNA targeting Cyclin B1 into cancer cell lines and a tumor mouse model. We have demonstrated that when associated with MPG, sub-nanomolar concentrations of siRNA Cyclin B1 efficiently knock down Cyclin B1 protein levels, resulting in early G2 arrest and a block to cancer cell proliferation. Moreover, cholesterol-functionalized-MPG/Cyclin B1 siRNA formulations were found to block tumor growth *in vivo* upon intratumoral or intravenous injection. Given the biological properties of this vector, we believe that MPG-based technologies will contribute significantly to the development of basic research and therapeutic applications