

S005 Peptide-based delivery of nucleic acids: design, mechanism of uptake and applications to splice-correcting oligonucleotides

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Cell-penetrating peptides (CPP) have given rise to much interest for the delivery of biomolecules as peptides, proteins or nucleic acids.

CPPs and their conjugates were initially thought to translocate through the cell membrane by a non-endocytotic mechanism, but a re-evaluation of their internalisation process has recently been proposed. Basic amino acids-rich CPPs first interact with cell-surface proteoglycans before being internalized by endocytosis (Richard et al, 2003; Richard et al, 2005). Not surprisingly sequestration and degradation in endocytotic vesicles severely limit the cytoplasmic and nuclear delivery of the conjugated biomolecules. Accordingly splicing correction by CPP-conjugated steric-block oligonucleotide (ON) analogs remains poorly efficient in the absence of endosomolytic agents (Turner et al, 2005; Abes et al, 2006).

New arginine-rich CPPs allowing efficient splicing-correction by conjugated PNA or PMO oligomers in the absence of endosomolytic agents have recently been defined in our group and are currently being characterized. They offer promising leads for the development of vectors able to enhance the delivery of therapeutic steric-block ON analogs in clinically-relevant models.