

P006 (R-Ahx-R)₄ cell-penetrating peptide enhances the delivery of antisense morpholino oligomers

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Phosphorodiamidate morpholino oligomers (PMO) are uncharged steric-blocking antisense compounds that interfere with protein translation, pre-mRNA splicing and viral RNA synthesis. An arginine-rich cell-penetrating peptide (CPP), (R-Ahx-R)₄, enhances the nuclear and cytosolic delivery of PMO and has generated exciting results in the Duchenne muscular dystrophy (DMD) and antiviral fields. Several highlights of our findings with the (R-Ahx-R)₄-PMO conjugates will be presented including 1) its functional biodistribution in mouse, 2) altering pre-mRNA splicing and 3) inhibiting viral replication. The pharmacokinetics and safety profile of an (R-Ahx-R)₄-PMO conjugate in rats will be briefly presented. We attribute the success of this CPP to its greater ability to escape endosomal entrapment and its better enzymatic stability compared to Tat or polyarginine CPPs. Further optimization of the CPP sequence may reduce its endosomal trapping and toxicity.