Protease-Resistant Cell-Penetrating Oligomers for Improved Drug Delivery

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Technology description

This technology describes a new class of non-charged cell-penetrating oligomers and their uses in drug delivery. These synthetic oligomers far surpass current charged peptide standards in performance and exhibit numerous advantages supportive of use beyond cell culture.

Cell-penetrating peptides (CPPs) have been studied for several decades revealing numerous advances in the transport cargo including DNA, proteins and small molecules, as well as in the abilities of synthesized CPPs to enter cells. Effective use of CPPs beyond tissue culture, however, is still a significant challenge due to the presence of CPP-degrading proteases. Moreover, CPPs exhibit extensive non-specific interactions with extracellular matrix (ECM) proteins, further reducing their efficacy. Other significant obstacles for therapeutic use of CPPs include immune response and CPP accumulation in the kidneys due to their charged nature.

To overcome these obstacles, a team at Cornell synthesized a novel class of non-charged cell-penetrating oligomers that supports mimicry of traditional CPP functional groups while allowing fine-tuning of backbone flexibility and pendant group spacing. These sequence-defined cell-penetrating **oligothioetheramides** (OligoTEAs/CPOTs) have so far been shown to be up to **six times** more effective than current standards during cell internalization. The team has produced five or more compounds that have outperformed the standard for charged CPPs (R9 peptide), and have conducted further studies on their lead compound in at least three cell types. The lead compound has so far been shown to be capable of supporting rapid cargo internalization at concentrations as low as 500nM and is minimally cytotoxic.

Publications

Phan, N., Li, C. and Alabi, C. (2018). Intracellular Delivery via Noncharged Sequence-Defined Cell-Penetrating Oligomers. Bioconjugate Chemistry, 29(8), pp.2628-2635 .

Related invention: D-6762 “ Method for Synthesis of End-functional Sequence-Controlled Polymers ” .

Application area

Transport of small and macromolecular cargo into cells.

Advantages

New class of uncharged cell-penetrating oligomers that outperform charged CPP standards.
Not susceptible to protease-mediated degradation.
Do not support non-specific interactions with extracellular matrix or serum proteins.
Synthetic scaffold reduces propensity for first-pass immune response and clearance.

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