Tailor-made cell-penetrating peptides with various activity spectra

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Since several years we are interested in the design and application of cell-penetrating peptides (CPPs). CPPs are usually short peptide sequences with an amphipathic or purely cationic nature that supports effective interaction with cell membranes. Notably, CPPs can deliver attached cargoes inside the cell interior including other bioactive peptide sequences. Such chimeric and bifunctional molecules may provide novel cell-permeable peptides with promising new bioactivities and application in various fields.
For instance, tailoring CPPs for targeting intracellular protein-protein-interactions (PPIs) is one area of interest that gained much interest during the last years.[1]
Recently, we have designed cell-permeable peptides to control and regulate collagen secretion.[2] These novel CPPs specifically target the primary interface between TANGO1 and cTAGE5 proteins and act as competitive inhibitors. Different cell models were used to demonstrate their effect like altered collagen secretion and reduced scar formation. Our innovative and new approach might be a promising avenue for therapeutic intervention for currently intractable fibrotic disorders.
Furthermore, we have optimized our CPPs by introducing short amino acid motifs that are recognized by the posttranslational modification (PTM) machinery. Interestingly, such CPPs highly efficiently translocate in cells where they supposedly interact with PTM proteins. Furthermore, our findings let suggest that they interact with and affect different signalling pathways.[3-5]
All in all, the herein highlighted CPPs might represent interesting chemical tools to investigate PPIs, and potentially to selectively alter the PTM machinery.

[1] Stillger K, Neundorf I. *Cell Signal*, **2023**, *109*, 110796. doi:10.10/j.cellsig.2023.110796.
[2] Raote I, Rosendahl AH, Häkkinen AM, Vibe C, Kücüaylak I, et al. *Nat Commun*, **2024**, *1*, 3302. doi:10.1038/s41467-024-47004-1.
[3] Klimpel A, Stillger, K, Wiederstein JL, Krüger M, Neundorf I. *FEBS Journal*, **2021**, *288*, 2911. doi: 10.1111/febs.15612.
[4] Stillger K et al., in revision.
[5] Klußmann M et al., in revision.