



ID der Kurzfassung : 493

Systematic assessment of cell-penetrating peptides for antisense oligomer delivery in Bacteroides

Inhalt

Cell-penetrating peptides (CPPs) can be harnessed to deliver antisense oligomers (ASOs) into bacterial cells. However, CPPs that are efficiently taken up by Bacteroides—an abundant species of the human gut microbiota—are not currently known. Here, we perform a global screen for CPP uptake by Bacteroides thetaiotaomicron. We perform a global screen for bacterial cell-penetrating peptides (CPPs), identifying MK2i (mitogen-activated protein kinase-activated protein kinase 2 inhibitory peptide) as a suitable carrier peptide with high uptake efficiency and specificity. Our data further propose a TonB-dependent import mechanism and reveal influences of media composition, growth phase, and cell surface structure on CPP uptake efficiency. Building on these results, we design an MK2i-coupled to an ASO peptide nucleic acid (PNA) against fabG, an essential Bacteroides gene involved in envelope fatty acid synthesis. Low micromolar concentrations of this CPP-PNA conjugate evoke a dose-dependent growth inhibition and bactericidal effects. Leveraging a fluorescent B. thetaiotaomicron reporter strain, we monitor the effect of PNA-targeting on GFP transcript, protein, and fluorescence levels. These findings lay the groundwork for delivering ASOs into and leveraging ASO technology in a microbiota keystone species.

Keywords

antisense oligomer; cell-penetrating peptide; peptide nucleic acid; capsular polysaccharide; MK2i; FabG; Bacteroidota

Registration ID

177

Professional Status of the Speaker

PhD Student

Junior Scientist Status

Yes, I am a Junior Scientist.

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Track Klassifizierung: AMR

Typ des Beitrags: Both options possible

Eingereicht von **FRANCO DE CARVALHO, Taís** <taisfc25@gmail.com> am **Mittwoch, 24. Juni 2026**