Poster Presentation
Inter-Disciplinary Explorations in Chemistry (I-DEC 2018)

PNA mediated inhibition of bacterial signal recognition particle system: A novel antibacterial strategy

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The development of antibiotic resistance in pathogenic bacteria has posed a serious threat to the mankind.[1] To address this problem, there is an urgent need to identify new antibacterial strategies which are not subject to existing resistance mechanism. In search of a new antibacterial target, we have identified the bacterial signal recognition particle (SRP) pathway as a potential target.[2] Bacterial SRP consists of a protein-RNA complex (Ffh protein - 4.5S RNA) which along with its receptor, FtsY protein (SRP Receptor), is crucial for transporting the newly synthesized membrane and secretory proteins to their respective cellular destinations[3], also essential for bacterial cell survival.[4] In our study, we inhibited the bacterial 4.5S RNA-Ffh protein interaction to disrupt the functional SRP cycle in bacteria. A specific antisense peptide nucleic acid (PNA) molecule was designed to target 4.5S RNA at the Ffh binding site. *In vitro* studies confirmed the sequence-specific interaction of designed PNA and 4.5S RNA, resulting in disruption of the 4.5S RNA-Ffh interaction. The PNA molecule when conjugated with a cell penetrating peptide (CPP) showed dose-dependent inhibition of bacterial cell growth. The PNA mediated bacterial cell growth inhibition was rescued by over-expression of 4.5S RNA suggesting the specificity of PNA molecule for 4.5S RNA *in vivo*. For the first time, this study supports SRP as a promising antibacterial target via inhibition of 4.5S RNA-Ffh interaction.

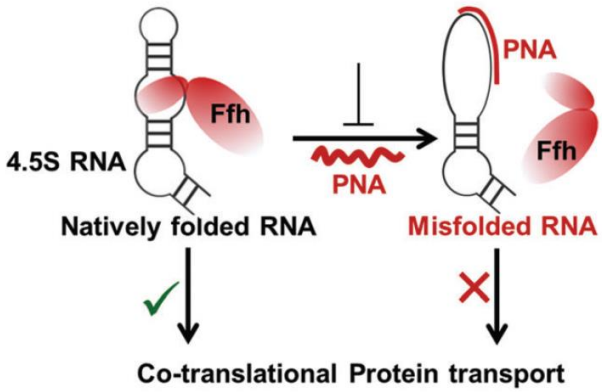

Figure: Schematic showing the PNA mediated inhibition of 4.5S RNA function.

References and Notes:

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(3) Keenan, R. J.; Freymann, D. M.; Stroud, R. M.; Walter, P. The Signal Recognition Particle. *Annu. Rev. Biochem.* **2001**, *70*, 755–775.

(4) Brown, S.; Fournier, M. J. The 4.5 S RNA Gene of Escherichia Coli Is Essential for Cell Growth. *J. Mol. Biol.* **1984**, *178* (3), 533–550.