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Targeting bacterial stringent response

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Bacteria employ an array of systems to sense their environment and respond to various stimuli. One of such systems is mediated via changes in the intracellular levels of alarmone nucleotides guanosine tetraphosphate (ppGpp) and pentaphosphate (pppGpp), collectively referred to as (p)ppGpp. The nucleotides are synthesized by RelA/SpoT Homologue (RSH) enzymes via an in-line nucleophilic attack of the 3'-OH group of GDP (or GTP) on the β-phosphate of ATP. (p)ppGpp is a pleotropic intracellular effector targeting numerous molecular targets. It regulates transcription via direct interaction with two allosteric sites of *Escherichia coli* RNAP; suppresses translation via binding to the GTP-binding pocket of ribosome-associated GTPases, DNA replication via binding to the active site of DNA-dependent RNA polymerase primase DnaG, and nucleotide biosynthesis via direct competition with nucleotide substrates of several enzymes involved in synthesis of GTP and ATP. In addition, (p)ppGpp activates its own production via interaction with ribosome-dependent *Escherichia coli* RSH RelA.

An acute increase in (p)ppGpp concentration – referred to as 'the stringent response' – orchestrates a survival program leading to increased virulence and antibiotic tolerance. Due to the central role of the (p)ppGpp in regulation of bacterial virulence and recently proposed connection to formation of antibiotic-tolerant persister cells, (p)ppGpp-mediadted signaling constitutes a promising target for development of novel antibacterials.

Although ppGpp itself is an activator of the ribosome-associated ppGppsynthetaseRelA, several ppGpp mimics have been developed as RelA inhibitors. However promising, the currently available ppGpp mimics are relatively inefficient, with IC_{50} in the sub-mM range. In an attempt to identify a potent and specific inhibitor of RelA capable of abrogating (p)ppGpp production in live bacterial cells, we have synthesized and tested a targeted nucleotide library using a biochemical test system comprised of purified *Escherichia coli* components.

Biography:

My research interests are chemistry and biological properties of modified nucleic acid components. Currently I am working on several projects: 1. Stringent response modulators, 2. Lipophosphonoxins – novel antibacterial compounds, 3. Phosphonate azanucleotide inhibitors of HGXPRT as potential antimalarial and antibacterial agents.

1992-1996: Department of Organic Technology, UCT, Prague

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