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Trans-translation pathway inhibitors have broad-spectrum antibiotic activity and sterilize *M. tuberculosis*

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In bacteria, ribosomes that have stalled during translation are recognized by a ribonucleoprotein complex consisting of tmRNA and the small protein SmpB. tmRNA-SmpB release the stalled ribosome and target the nascent polypeptide for proteolysis through a pathway known as *trans*-translation. Genes encoding tmRNA and SmpB have been found in all bacterial genomes, but not in higher eukaryotes. Components of the trans-translation machinery are essential for virulence and viability in many pathogenic bacteria, so this pathway is a potential target for antibiotic development. High-throughput screening using a cell-based assay identified inhibitors of both the ribosome release and proteolysis steps of the *trans*-translation pathway. These inhibitors have broad-spectrum antibiotic activity, with MIC values in the range of 0.1–3 μg/ml for species including *Shigella flexneri, Bacillus anthracis,* and *Mycobacterium tuberculosis*. More detailed investigation of the requirement for trans-translation in *M. tuberculosis* revealed that the pathway is essential for growth in culture and during macrophage infection. *Trans*-translation inhibitors efficiently killed both growing *M. tuberculosis* cells and non-proliferating persister cells, suggesting that these compounds could be useful in the treatment of tuberculosis. Overall, these studies validate the use of *trans*-translation as a target for development of new antibiotics.

Biography

Kenneth C. Keiler is an Associate Professor of biochemistry and molecular biology at Penn State University. He earned his Ph.D. in biology from the Massachusetts Institute of Technology. He completed post-doctoral fellowships at the Institut de Genetique et de Biologie Moleculaire et Cellulaire in Illkirch, France, and at Stanford University. He studies bacterial development, looking at regulation of gene expression and localization of RNA and protein in bacteria.

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