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Title: Structure based design of aminoacyl-tRNA synthetase inhibitors as anti-parasitic drugs

ABSTRACT: Aminoacyl-tRNA synthetases (AARS), universally essential enzymes for protein synthesis, are a validated molecular target for antimicrobial drugs. AARS inhibitors fatally disrupt protein translation. We propose to apply a strategy of directed library screening coupled with structural studies to find potent inhibitors of parasitic nematode AARS, to develop as potent anti-parasitic drugs. We have initiated this work by cloning and expressing certain AARS from human filarial parasites, such as *Brugia malayi,* to provide milligram quantities of purified enzyme for inhibitor screening and structural studies by X-ray crystallography. The directed screen will focus on AMP and amino-acid analogues which can in principle be coupled together to create aminoacyl-adenylate analogue inhibitors. Readily available, but non species-specific sulfamoyl analogues of aminoacyl-adenylate will be tested against adult *Brugia malayi* to validate the concept of adenylate intermediates as anti-parasite drugs. High resolution structural studies will help in refining lead compounds for nematode specificity. Work will focus on the asparaginyl-tRNA synthetase (for which expression systems for both the *B. malayi* and human enzymes are available) and certain other synthetases such as the tyrosyl-tRNA synthetase. We will collaborate in the screening with one of the number of international pharmaceutical companies currently engaged in the search for AARS inhibitors and thus benefit from the powerful infrastructure already in place for anti-synthetase drug discovery.