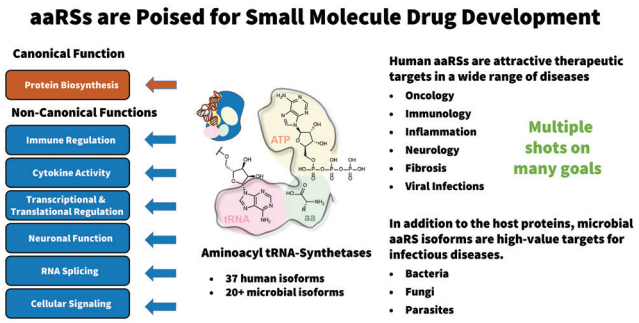


# Unlocking aminoacyl-tRNA-synthetases as novel drug targets for first-in-class therapeutics

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As a chemical biologist, Dr. Mazitschek's research interests center on investigating biological systems at the molecular level using modern chemistry tools. Motivated by Sidney Brenner's famous quote, "progress in science depends on new techniques, new discoveries and new ideas, probably in that order," the Mazitschek lab seeks to develop innovative small-molecule approaches to modulate physiological processes to establish therapeutic strategies for previously unmet medical needs.

Aminoacyl-tRNA synthetase (aaRS) enzymes are central to protein homeostasis, connecting RNA and protein domains in the central dogma. Because of their assumed role as mere housekeeping enzymes, traditional aaRS drug development efforts have primarily focused on antimicrobial agents targeting bacterial, fungal, and parasitic organisms. However, recent advanced omics studies have begun unveiling the many non-canonical roles of individual isoforms in human health and disease, including autoimmune disorders, cancer, and neurological diseases. Unfortunately, despite offering multiple highly-druggable features, the exploration of human aaRSs for translational research has been hindered by an almost complete lack of chemical leads and robust pharmacological tools for systematically interrogating mammalian aaRSs in disease settings - a scenario reminiscent of the kinase field in the 1980s.

To overcome this challenge, we have leveraged our novel CoraFluor high-throughput screening (HTS) assay technology, which has enabled previously elusive experimental designs and provided access to a versatile aaRS discovery platform. Our robust and facile assay strategy is suitable for all 37 human aaRS isoforms and allows for quantitative and comprehensive ligand characterization, eliminating existing bottlenecks and greatly accelerating systematic drug discovery and development. We have validated our approach for multiple aaRS targets, including the rational development of novel prolyl-tRNA synthetase inhibitor classes, and demonstrated their inhibitory efficacy in vivo. We aim to transform this work into a comprehensive and systematic discovery engine, streamlining the process for efficient aaRS-targeted drug development and establishing a direct path to first-in-class therapies, resolving unmet medical needs in various human disease areas.

Figure legend: In addition to their canonical role in protein homeostasis, aminoacyl-tRNA synthetases (aaRSs) exhibit a variety of non-canonical functions that are often isoform-specific and cell-type dependent. These non-canonical functions play critical roles in various cellular processes and have significant implications for human health and disease. The growing understanding of these diverse functions has identified aaRSs as potential therapeutic targets for various diseases, including autoimmune disorders, cancer, and neurological conditions. Along with their microbial homologs, aaRSs represent a large group of underexplored targets with highly druggable features for next-generation therapeutics that can address unmet medical needs.