

NIH COMMON FUND HIGH-RISK HIGH-REWARD RESEARCH SYMPOSIUM

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SPEAKER ABSTRACTS

**Engineering direct control of synthetic protein-RNA interactions for synthetic biology and functional genetics applications**

**Awardee:** Jacquin Niles

**Award:** New Innovator Award

**Awardee Institution:** Massachusetts Institute of Technology

Increasingly, the ease with which RNA and its direct interactions with proteins can be engineered is being exploited in design-oriented, biotechnology applications and the basic life sciences. Using principles inspired by nature, our lab has developed a generalizable framework for achieving direct, small molecule-mediated regulation of protein-RNA interactions. We have demonstrated the use of this approach to directly control several fates of cellular RNA, including its translation and subcellular localization in model organisms (*E. coli* and yeast) and in the human malarial pathogen, *Plasmodium falciparum*. Our application of this technology in the poorly understood and non-model *P. falciparum* context has been valuable in two key ways. First, we have emphasized engineering increased integration of synthetic protein-RNA interactions with native cell regulatory mechanisms as a means of harnessing evolutionarily conserved and optimized mechanisms for regulating cellular RNA processes. Through this approach, we can achieve improved functional robustness and reduced system noise arising from leaky expression during control of translation, for example. This easily generalizable strategy, while counter to the conventional approach of designing regulatory systems agnostic to host cell regulation, should prove broadly useful in synthetic biology and life science applications. Second, we have leveraged our regulatory framework in *P. falciparum* as a novel and much-needed functional genetics tool. Traditionally, few sufficiently robust tools have been available to conditionally perturb parasite gene expression to assess basic biological function or probe the molecular basis for antimalarial drug resistance. By taking advantage of the inter-organism transferability of our system's foundational framework and the principle of host cell integration, we have validated our system as a flexible and robust tool for successfully doing functional genetics in a human pathogen that has been challenging to study.