

NIH COMMON FUND HIGH-RISK HIGH-REWARD RESEARCH SYMPOSIUM
DECEMBER 15 – 17, 2014
POSTER ABSTRACTS – SESSION 1 (DEC. 15, 2014)

Essential gene discovery in the malaria parasite *Plasmodium falciparum*

Awardee: Jeffrey D. Dvorin

Award: New Innovator Award

Awardee Institution: Boston Children's Hospital

Human malaria is a leading cause of death and disease worldwide, resulting in nearly one million deaths each year. The most severe forms of malaria result from infection by the *Plasmodium falciparum* parasite, which causes the vast majority of malaria in Africa. Deaths from malaria disproportionately affect children under five years old and pregnant women. Resistance to existing anti-malarial medications is a constant and continually emerging hurdle to the effective treatment of malaria. A molecular understanding of the fundamental biological process of *P. falciparum* replication will provide the necessary tools to develop new anti-malarial therapeutics. Although the genome of *P. falciparum* has been fully sequenced, the function of more than half of the 5,300 genes in the parasite remains unknown. Many of the genes with unknown function have little or no homology with characterized genes from other organisms. Therefore, existing molecular genetic and bioinformatics techniques cannot be used to efficiently determine the function of many of the genes in the parasite. Furthermore, existing technologies cannot predict which genes are essential for survival of the parasite. We hypothesize that these essential genes, and the proteins that they encode, will be attractive targets for the rational design of new anti-malarial therapeutics. A forward-genetic system to investigate the function of essential genes does not exist currently. We have made significant progress to develop two different and much needed forward-genetic systems in *P. falciparum*. Our first forward-genetic system relies upon a robust and tightly controlled inducible expression system to perform saturating transposon-mediated mutagenesis in *P. falciparum*. We utilize next-generation sequencing following saturating mutagenesis to identify essential genes. The immediate goal of this proposal is to generate a complete list of *all* essential genes in the blood-stage of *P. falciparum*. In a second forward-genetic system, we have designed a novel reporter parasite to allow the selection of clones with temperature-sensitive mutations in essential genes. The long-term objectives and public health implications of these studies are to identify novel targets for new anti-malarial therapeutics. This long-term goal will be achieved as a direct result of our identification of novel essential genes in *P. falciparum* parasites.