PennState

Applied Biological and
Biosecurity Research Laboratory

High Risk/High Reward: Identification of Biomarkers Associated with Dormant Malarial Liver Stage Infections

Minimally invasive approach to identify dormant malaria

Mission Area:
Understanding Pathogen Dynamics and Creating Sustainable Interventions

Type: Hypothesis-Driven Research

Region: Central/South America

Countries: Lima

Status: In Development

Overview

Dormant *P. vivax* parasites ("hypnozoites") can reactivate and be transmitted from returning warfighters at home by native mosquito vectors. Identification of biomarkers for hypnozoites will help to limit the introduction of new parasite strains by providing targeted treatment (primaquine) only to those with a sufficiently high probability of dormant infections. It is completely unknown what causes some *P. vivax* parasites to become dormant hypnozoites in the liver stage while other parasites undergo active development. This study will look broadly for correlates (DNA sequences, RNA abundances, protein abundances, metabolite abundances) that allow/modulate hypnozoite prevalence. This broad screen hedges against the risk that a specific biomarker(s) may not be identified by metabolomic approaches alone.

Objectives / Goals

The goal of this project is the development of a minimally invasive approach to identify returning warfighters that are infected with dormant malaria liver stage hypnozoites or other life cycle stages as a diagnostic test. This requires the identification of molecular markers of commitment to the production of hypnozoites.

Technical Appraoch

To identify diagnostically relevant biomarkers, the team will infect humanized mice with P. vivax sporozoites isolated from the salivary glands of experimentally infected mosquitoes. The hypothesis is that a fraction of these will form hypnozoites, and that this fraction varies between parasite isolates. When active liver stages have cleared (naturally or by drug treatment), blood will be assessed for metabolomic footprints (metaprints) or nucleic acids/proteins derived from human hepatocytes and/or hypnozoites that are discernable from uninfected

humanized mice with comparable liver repopulation and identical primary hepatocyte donor.

To identify commitment factors, malaria-infected blood (from recruited patients in Iquitos) will be fed to mosquitoes (for sporozoite production) and an aliquot of blood will be retained for DNA sequencing of parasites. Purified sporozoites will be used for humanized mouse infections and -omics analyses (RNA-seq, proteomics, metabolomics) to limit the effects of mosquito saliva and microbiome upon analysis. Assuming that there is clear evidence for different active/dormant liver stage ratios in different parasite isolates (e.g. 100% active/0% dormant, 75% active/25% dormant, 50% active/50% dormant, 25% active/75% dormant, 0% active/100% dormant), we will downselect parasites for -omics analysis.

Partners

Funders:

- Pennsylvania State University
- United States Navy

Implementation / Scientific:

- Naval Medical Research Unit 6 (NAMRU-6), Lima and Iquitos, Peru
- Princeton University