High-throughput Screening to Identify Inhibitors of Dengue Virus (DV) Entry

Principal Investigator: Priscilla Yang, PhD, Harvard Medical School

Co-Investigator: Amal Rameh, PhD, Harvard Medical School

Dengue virus (DV) is the most widespread mosquito-borne viral disease affecting humans today. DV causes a broad spectrum of disease ranging from the asymptomatic to classical dengue fever and can progress to more severe and life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). As with other viral hemorrhagic fevers, such as those caused by Ebola virus, there is no vaccine and the only treatment for DHF/DSS is supportive care. An estimated 500,000 cases of DHF/DSS occur annually with estimated 2.5% fatality although fatality rates can exceed 20% if untreated. The diversity of DV serotypes and propensity of non-neutralizing antibodies to exacerbate disease have limited success in vaccine development. Efforts to develop antivirals targeting conventional viral polymerase and protease targets have also been unsuccessful. We have discovered compounds that potently inhibit DV in cell culture by binding to the envelope protein, E, on the virion surface and blocking membrane fusion during viral entry. Despite considerable medicinal chemistry efforts, we have thus far been unable to improve our existing lead compounds sufficiently for *in vivo* validation studies. Here we propose a one year HTS effort to identify alternative scaffolds against this target. Our long-term plan is to develop DV entry inhibitors that can be advanced as preclinical candidates. We have developed a screening platform and infrastructure (i.e., medicinal chemistry, virology, structural biology, PK/PD, ADME/toxicity, and *in vivo* efficacy testing) to enable this goal.