Subject: Dissertation Defense - Michael D. Barrera, PHD Biosciences
Date: Friday, April 5, 2024 at 11:10:09 AM Eastern Daylight Time
From: SSB Faculty List on behalf of Diane St. Germain
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Dissertation Defense Announcement
To: The George Mason University Community

Candidate: Michael D. Barrera

Program: PhD Biosciences

Date: Thursday April 18, 2024

Time: 2:00 PM Eastern Time (US and Canada)

Location:
In person - conference room 1004, IABR, Science & Tech campus
Also via Zoom
Join Zoom meeting:
https://gmu.zoom.us/j/92631899380?pwd=aVBIV3E3T1N0dWNKcGJ2VW9oYXg0QT09

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Committee chair: Dr. Aarthi Narayanan
Committee members: Dr. Mariaelena Pierobon, Dr. Alessandra Luchini, Dr. Farhang Alem

Title: “Targeting a Non-Structural Viral Protease That Plays an Essential Role in Alphavirus Infection to Develop a Broad-Spectrum Therapeutic Strategy Against Alphaviruses”

Abstract:
Alphaviruses, including Venezuelan equine encephalitis virus (VEEV), eastern equine encephalitis virus (EEEV), western equine encephalitis virus (WEEV), Chikungunya virus (CHIKV), and Sindbis virus (SINV), are mosquito-transmitted viruses that cause disease in humans. VEEV, EEEV, and WEEV are endemic to the western hemisphere and cause encephalitis, while CHIKV and SINV cause arthralgia. CHIKV and SINV are endemic to the eastern hemisphere, but CHIKV has spread to the Americas and has become endemic in Central and South America. There are currently no FDA-approved vaccines or antiviral therapeutics to treat disease caused by these alphaviruses. We have worked testing small molecule inhibitors that target the alphaviruses nsP2 protease via the covalent mode of action. The nsP2 protease is critical for viral replication. Without it, the non-structural polyprotein is not processed into functional components for viral replication. Here we examined five compounds that inhibit the nsP2 protease in a preclinical pipeline which tests efficacy *in vitro*, in an organ-on-a-chip model (OOC) of the blood-brain-barrier (BBB) and in an *in vivo* mouse model. Initial *in vitro* studies of cytotoxicity and antiviral efficacy against VEEV TC-83 led to down selection from five compounds to two with the highest selectivity index. Mechanism of action studies confirm that the nsP2 protease inhibitors prevent processing of the nonstructural polyprotein and inhibit negative-strand RNA synthesis required for productive infection. These two inhibitors also show broad-spectrum activity against new-world and old-world alphaviruses. In our OOC of the BBB, these compounds reduce permeability of the barrier and reduce VEEV TrD replication in the brain and vascular compartments. Additionally, these compounds reduce proinflammatory cytokines and chemokines at the protein and genes expression levels in the OOC and prevent the downregulation of tight-junction proteins during infection. During *in vivo* studies, these compounds were found to be non-toxic in mice and provide protection from infection in a VEEV TC-83 lethal mouse model. Treatment with the nsP2 protease inhibitors also result in a reduction in viral load in the brain and lung tissues of infected mice. Overall, preclinical assessment of the nsP2 protease demonstrates their ability to inhibit alphaviruses *in vitro*, VEEV TrD in a human OOC model of the BBB, and VEEV TC-83 in a lethal mouse model.

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