University of Massachusetts UMASS Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

M.D./Ph.D. PROGRAM IN BIOMEDICAL SCIENCES

M.D., Ph.D. THESIS DEFENSE

ASHLEY N. MATTHEW

MENTOR: Celia Schiffer, PhD

TUESDAY, 4/10/18 9:30 a.m.
LRB 816

"Targeting Drug Resistance In HCV NS3/4A Protease: Mechanisms And Inhibitor Design Strategies"

The Hepatitis C virus (HCV) NS3/4A protease inhibitors (PIs) have become a mainstay of newer all-oral combination therapies. Despite improvements in potency of this inhibitor class, drug resistance remains a problem with the rapid emergence of resistance-associated substitutions (RASs). In this thesis I elucidate the molecular mechanisms of drug resistance for PIs against a resistant variant and apply insights toward the design of inhibitors with improved resistance profiles using structural, biochemical and computational techniques. Newer generation PIs retain high potency against most single substitutions in the protease active site by stacking on the catalytic triad. I investigated the molecular mechanisms of resistance against the Y56H/D168A variant. My analysis revealed that the Y56H substitution disrupts these inhibitors' favorable stacking interactions with the catalytic residue His57.

To further address the impact of drug resistance, I designed new inhibitors that minimize contact with known drug resistance residues that are unessential in substrate recognition. The initially designed inhibitors exhibited flatter resistance profiles than the newer generation PIs but lost potency against the D168A variant. Finally, I designed inhibitors to extend into the substrate envelope (SE) and successfully regained potency against RAS variants maintaining a flat profile. These inhibitors both pack well in the enzyme and fit within the SE. Together these studies elucidate the molecular mechanisms of PI resistance and highlight the importance of substrate recognition in inhibitor design. The insights from this thesis provide strategies toward the development of diverse NS3/4A PIs that may one day lead to the eradication of HCV.

Mentor(s)

Celia Schiffer, PhD

Dissertation Exam Committee

Dan Bolon, PhD (Chair)
William Royer, PhD
Paul Thompson, PhD
Kendall Knight, PhD
Stefan Sarafianos, PhD