University of Massachusetts Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

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MENTOR: Celia Schiffer, PhD
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"Viral proteases as drug targets and the mechanisms of drug resistance"

Viral proteases have been shown to be an effective target of anti-viral therapies for human immunodeficiency virus (HIV) and hepatitis C virus (HCV). However, under the pressure of therapy including protease inhibitors, the virus evolves to select drug resistance mutations both in the protease and substrates. In my thesis study, I aimed to understand the mechanisms of how this protease−substrate co-evolution contributes to drug resistance. Currently, there are no approved drugs against dengue virus (DENV); I investigated substrate recognition by DENV protease and designed cyclic peptides as inhibitors targeting the prime site of dengue protease.

First, I used X-ray crystallography and subsequent structural analysis to investigate the molecular basis of HIV-1 protease and p1-p6 substrate coevolution. Co-evolved p1-p6 substrates rescue the HIV-1 I50V protease's binding activity by forming more van der Waals contacts and hydrogen bonds, and that co-evolution restores the dynamics at the active site for all three mutant substrates.

Next, I used aprotinin as a platform to investigate DENV protease–substrate recognition pattern, which revealed that the prime side residues significantly modulate substrate affinity to protease and the optimal interactions at each residue position. Based on these results, I designed cyclic peptide inhibitors that target the prime site pocket of DENV protease. Through optimizing the length and sequence, the best inhibitor achieved a 2.9 micromolar Ki value against DENV3 protease. Since dengue protease does not share substrate sequence with human serine proteases, these cyclic peptides can be used as scaffolds for inhibitor design with higher specificity.

Mentor(s)

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