University of Massachusetts Medical School
UMASS

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

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MENTOR: Brian Kelch, PhD

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Elucidating the structural mechanisms of capsid stability and assembly using a hyperthermophilic bacteriophage

All viruses package their genomes into protective protein shells known as capsids. Capsids self-assemble from repeating protein subunits, which surround the viral genome. Many viruses use a powerful biomotor to pump DNA into preformed capsid shells. Therefore, not only does the capsid protect the genome from environmental stress, it additionally stabilizes against high internal pressure caused by the tightly-packaged genome inside. To understand how capsids remain stable despite extreme conditions, I use thermophilic bacteriophage P74-26 as a model to probe the structural mechanisms that govern capsid assembly and stability. P74-26 capsids have a similar architecture to capsids of mesophilic tailed bacteriophages, allowing direct comparison to elucidate the structural basis of enhanced thermostability. Here I determine the structure of the P74-26 capsid decoration protein, which contains a core beta-barrel domain termed the 'beta-tulip' domain. The beta-tulip domain is conserved in structural proteins from both Herpesviruses and phage, as well as a broad-spectrum Cas9 inhibitor, providing evidence of shared evolutionary ancestry. Additionally, my high-resolution structure of the P74-26 virion capsid reveals unique interdigitated architectural features that contribute to enhanced stability in the thermophile. P74-26 has a significantly larger capsid than related mesophiles yet retains the same icosahedral geometry, demonstrating a novel mechanism for increasing capsid capacity. Furthermore, my thesis work explores capsid assembly and maturation mechanisms *in vitro,* establishing P74-26 as a platform for future development of novel nanoparticles and therapeutic delivery systems. Taken together, this work illuminates the incredible stability of a thermophilic virus and illustrates its utility as a powerful tool for studying viral maturation.

Mentor(s)

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