Discovery of Small Molecules to Inhibit Human Cytomegalovirus Nuclear Egress

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Human cytomegalovirus (HCMV) is a ubiquitous herpesvirus that causes severe disease in immunocompromised individuals such as transplant and chemotherapy recipients and patients with HIV. HCMV is also a major cause of birth defects, with deafness and mental retardation frequent outcomes. Current anti-HCMV treatments are limited by toxicities, drug resistance, and/or poor oral bioavailability. Our proposal addresses the need for new anti-HCMV drugs by focusing on the HCMV nuclear egress complex (NEC) as a novel target for drug discovery. The NEC, which is unique to herpesviruses, orchestrates the process of nuclear egress in which viral nucleocapsids transit from the nucleus into the cytoplasm. The NEC is composed of a single-span transmembrane protein, UL50, and a nucleoplasmic protein, UL53. Our on-going structural and biochemical studies on the complex indicate that UL50 has a novel protein fold that includes a groove that serves as a binding site for UL53. The groove should also be a ready binding site for small drug-like molecules. Single substitutions of residues in this groove ablate subunit interactions and viral replication. We therefore hypothesize that we can identify small molecules that would eliminate UL50 and UL53 interactions and thus have selective antiviral activity. We have developed an assay suitable for high throughput screening. We aim to utilize this assay and the small molecule libraries available at ICCB-Longwood to screen for inhibitors against the NEC. We will conduct follow-up assays to identify compounds with selective anti-HCMV activity. These compounds can serve as starting points for new, much-needed anti-HCMV drugs.