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Department of Chemistry

Special Seminar

4:15 p.m. Monday, November 17 • 331 Smith Hall

Associate Professor

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Envelope Glycoproteins of Ebola and Marburg Viruses: Structure, Mechanism, and Inhibition with Synthetic Antibodies

Research interests: understanding principles governing molecular recognition by proteins and antibodies, with the long-term goal of developing new research tools and therapies.
Website: http://www.einstein.yu.edu/faculty/11078/jonathan-lai/

Abstract

Ebola and Marburg viruses comprise the family Filoviridae of enveloped viruses ("filoviruses") that cause severe hemorrhagic fever. Fusion of the viral and host cell membranes is a necessary first step for infection, and is mediated by the envelope glycoprotein (GP). The transmembrane subunit (GP_2) from filoviruses belongs to the "class I" category that is defined by formation of an alpha-helical "trimer-of-hairpins" conformation during the fusion pathway. We have clarified the role of low pH in controlling stability of the GP_2 "post-fusion" six-helix bundle in Ebola, Marburg, and most recently in CAS Virus (CASV), a novel arenavirus from boid snakes that contains a filovirus GP_2. Biochemical studies have demonstrated that the post-fusion conformations for Ebola, Marburg, and CASV GP_2 are stabilized under low pH conditions. The post-fusion structures of the Marburg and CASV GP_2 core domains, reported by our lab, indicate that this pH-dependent stability results from networks of acidic residues. These observations suggest that the pH-dependent stability of filovirus GP2 is such that the post-fusion conformation is promoted only in conditions of appropriately matured endosomal compartments, consistent with a mechanism in which low pH and other endosomal factors are required to trigger membrane fusion. In other work, we have used a novel antibody phage display discovery method ("synthetic antibody technology") to identify antibodies against the glycoproteins of the Zaire (EBOV) and Sudan (SUDV) Ebolavirus species. These antibodies have neutralization potential and, in the case of SUDV, afford post-exposure protection of mice from lethal viral challenge. These antibodies have significant immunotherapeutic potential and demonstrate the applicability of synthetic antibody engineering to address biomedical and public health challenges.

Hosts: Professors Erin Carlson and Will Pomerantz