Research Profile:

Viruses cause debilitating and life-threatening infections, as well as a variety of human cancers. They also reveal the beauty of biology and illuminate the delicate balance that exists at the interface of pathogenesis and immunity. Host and viral factors influence pathogenesis and infection outcomes, and targeting the cellular mechanisms at the host-virus interface represents an innovative therapeutic strategy that is widely applicable to a variety of diseases. Through her work, Dr. Lange hopes to increase understanding of mechanisms at the host-virus interface that dictate biological outcomes, highlighting the molecular tug-of-war between host and virus and the complexity underlying co-evolution.

Dr. Lange's experience in virology, RNA biology, cellular and molecular biology, innate immunology, and cellular and molecular engineering provides a unique opportunity for her laboratory to develop innovative strategies to further understanding of the complexity of host-virus interactions. Dr. Lange's laboratory seeks to identify and understand critical events, molecular interactions, and cellular signaling mechanisms that drive viral biology and pathogenesis, host biology, and anti-viral defenses to aid in the rational design of anti-viral and immunomodulatory strategies. Currently, she utilizes nucleic acid technologies, including aptamers and the CRISPR/Cas9 system, to explore virus and host biology, identify novel host targets, modulate innate immune and cell death signaling pathways, and the probe the host response to viral infection. The current projects within her laboratory are discussed below:

Aptamers are functional, structured nucleic acids that bind targets with high affinity and specificity, and have access to binding sites that are often inaccessible to larger molecules (e.g. antibodies).

Project 1 (NIH 1R21AI127195) is focused on the role of the HIV capsid protein in HIV infection and pathogenesis. Capsid is a highly dynamic protein that is involved in almost every step of the HIV life cycle. However, researchers do not yet understand the contribution of capsid to many critical life cycle steps or how capsid's interactions with host factors influence its' activity. Dr. Lange's laboratory uses aptamers that target various capsid assembly states (e.g. the mature, assembled capsid lattice, capsid hexamer, or capsid pentamer) to identify protein interaction sites and signaling partners, allow investigation of these interactions to assess their impact on host and virus biology, and inform drug development.

Project 2 seeks to identify aptamers with both agonistic and antagonist functions targeted to nucleic acid-sensing pattern recognition receptors (PRRs). PRRs are involved in a variety of host defenses, including anti-viral defenses, and are associated with a variety of diseases. The goal of this project is to define sequence and structural requirements for induction of PRR-mediated signaling and differences in signaling mechanisms and outcomes. Eventually, this project will incorporate CRISPR/Cas9 technology for identification of genes involved in context-dependent signaling outcomes. This work will contribute to development of tunable immunomodulatory strategies involving PRRs.

Project 3 utilizes CRISPR/Cas9 technology to identify key players contributing to HIV pathogenesis. CRISPR/Cas9 technology allows unbiased, large scale genetic screening (genome-wide) to identify important regulators in diverse experimental systems. Many of these regulators could represent novel aptamer and therapeutic targets, as well as lead to a detailed, mechanistic understanding of host-virus interactions underlying HIV pathogenesis. Here, Dr. Lange's applies this technique using the fully infectious virus, as well as viruses engineered to express specific HIV proteins, to identify and characterize host co-factors that facilitate HIV replication.

The combination of aptamer and CRISPR/Cas9 technologies constitutes a powerful and complimentary strategy for investigating host-virus interactions, and will increase our understanding of virus and host biology. Importantly, the experimental strategies under development in her laboratory will be widely generalizable to a variety of pathogens of critical importance to public health. In the long term, Dr. Lange will expand her work to other viral models, including other retroviruses, lytic viruses, and those with unmapped capsid architecture (functional and structural), cellular models where dysregulation of cell death pathways plays a critical role in disease pathogenesis (e.g. cancer), and additional PRR-related targets.