Peptide Mimetic Inhibitors Fused to Human Carrier Proteins as Novel Therapeutics for Treating Respiratory Virus Infections

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Background/Objective
The majority of therapeutic proteins in clinical use today are monoclonal antibodies. Recently a number of antibody-based therapeutics comprising peptides fused with Fc receptor epitopes have been developed that offer improved tissue penetration and extended half-life. The objective of this study was to develop novel therapeutic proteins for respiratory viruses using peptide inhibitors fused to immunoglobulin domains as carrier proteins.

Method
Peptide epitope mapping and GST pull-down assays were used to identify essential binding domains on key viral proteins including influenza replicase subunits (PA, PB1, or PB2) and RSV phosphoprotein (RSVP). Peptides alone or fusion proteins containing either a maltose binding protein (MBP), human serum albumin (HSA), DARPins or Ig domains as protein scaffolds were engineered to contain a HIS tag and a tat nuclear localization signal (NLS). These were tested for antiviral activity using shell vial culture and direct IF staining.

Result
We developed peptide mimetics targeting the Influenza and Respiratory syncytial virus (RSV) polymerase complex. These peptides inhibited virus replication at concentrations between 10-20 µM. The PB1,PB2 or RSVP peptides were engineered onto various scaffolds and displayed antiviral activities in the 5-20 µM range. Influenza PB1 and RSVP peptides expressed as fusion proteins had extended serum half-lives.

Conclusion
In an age of emerging and re-emerging viral infection including MERS-CoV, avian influenza (H7N9), and Ebola virus, the need for new antiviral therapeutics is paramount. We have used peptide epitope mapping to develop novel therapeutic peptides and engineered these peptides as fusion protein using a variety of carrier proteins. These therapeutic proteins have improved stability, display good antiviral activity, and can be produced in large quantities in E. coli. We are presently testing this novel class of antiviral in animal models of respiratory virus infection.