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Peptide mimetic inhibitors fused to human carrier proteins as novel therapeutics for treating respiratory virus infections

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The majority of therapeutic proteins in clinical use today are monoclonal antibodies. Recently, a number of 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 influenza virus using peptide inhibitors fused to various human carrier proteins. Peptide epitope mapping and GST pull-down assays were used to identify essential binding domains on key influenza proteins viz. the replicase subunits. Therapeutic proteins were engineered to contain a HIS tag, a tat nuclear localization signal alone, and peptide mimietic inhibitor fused to Maltose Binding Protein (MBP), Human Serum Albumin (HSA), DARPins or Ig domains as protein scaffolds. These were tested for antiviral activity using shell vial culture and IF staining. These peptides inhibited virus replication at concentrations between 10-20 μM. The PB1 and PB2 peptides engineered onto scaffolds displayed antiviral activities in the 5-20 μM range. Influenza PB1 and PB2 peptides expressed as fusion proteins had extended serum half-lives. 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 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 influenza antivirals in a model of infection.

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