Each year, tens of thousands people died at seasonal "flu" epidemics caused by influenza virus infection. In a 20~30-year cycle, global influenza pandemics, such as the one in 1918 that killed ~40 million people, can occur when an influenza strain changes so dramatically that people have no immunity against it. Although available for many years, vaccines against influenza virus do not completely subdue influenza infection in humans due to the extraordinary ability of the virus to change its genetic makeup and subsequently to evade human immune system. Moreover, the effectiveness of vaccines depends heavily on the accurate prediction of which strains are most likely to circulate in a given epidemics or pandemics. Thus, vaccination offers limited protection, especially when facing a highly virulent pandemics strain. There exist two types of anti-influenza drugs: the M2 channel blockers amantadine and rimantadine, and neuraminidase inhibitors zanamavir and oseltamivir. However, clinically resistant influenza virus strains are quickly developed where these drugs have been extensively used over time, suggesting that their future usefulness will be very limited. Therefore, urgently needed are new antiviral drugs that will help protect us in impending pandemics and seasonal epidemics. These new antivirals will also protect us against deadly influenza virus-based bioweapons that can be easily produced by bio-terrorists.

One of the two major glycoproteins on the surface of influenza virus is hemagglutinin (HA). HA mediates the fusion of viral membrane with endosomal membrane, resulting in release of the viral genetic materials into host cell for replication. Membrane fusion is coupled to an extremely large-scale conformational change of HA from the metastable pre-fusion state to the highly stable post-fusion state, triggered by the low pH in endosome. The fusion mechanism caused by HA appears to be a fairly common and ancient process shared by a diverse range of viral fusion proteins including human immunodeficiency virus type 1 (HIV-1) and ebola virus.

A new strategy for antiviral drugs is the development of fusion inhibitors blocking the large-scale conformational transition of HIV-1 gp120/gp41. Just like the post-fusion state of HA, the post-fusion gp41 has a rod-shaped six-helical bundle structure, with a central three-helical bundle formed by the N-terminal region and three outer-layer helices by the C-terminal region. Peptides derived from the C-terminal region of gp41 were found to inhibit HIV-1 infection at nanomolar concentration. Moreover, efforts to target a prominent pocket on the surface of the central three-helical bundle have led to discovery of small, cyclic D-peptides and small organic molecules that inhibit HIV-1 infection. In our preliminary study, we have successfully identified a highly conserved pocket on the surface of the central three-helical bundle of HA, and peptides binding to this pocket displayed micromolar inhibition against HA-mediated membrane fusion. In this proposal, we will extend our study to screen for high-efficacy small organic molecules using high-throughput approach. Successful identification of promising lead molecules in this pilot study will drastically enhance our ability to attract major federal funding for developing high-potency antiviral drugs that would ultimately benefit the entire humanity.