# FD028: A Bifunctional HIV-1 Inactivator Acts Before Host Cell Entry

Rasquinha, Giselle (School: Syosset High School)

Most HIV-1 drugs act as passive defenders to inhibit viral replication inside the cell, while a few function as gatekeepers to combat viruses before viral entry. These entry inhibitors are disadvantaged as they require the host cell to function and suffer from low potency and drug resistance. In this study, a new type of HIV-1 inactivator was tested to assess if multiple steps of entry could be targeted to inactivate HIV-1 before interaction with the host cell. The HIV-1 envelope protein consists of gp120 and gp41, which mediate viral attachment and membrane fusion. The inactivator tested, FD028, consisted of two parts- FD016, a CD4-receptor mimetic, and FD017, a membrane fusion inhibitor. ELISA assays and NATIVE-PAGE were used to demonstrate competitive inhibition of gp120 binding and six-helical-bundle formation. Results showed that FD028 binds to gp120 via its FD016 domain, causing a conformational change in gp41. FD028 then interacted with the exposed grooves on the gp41 via its FD017 domain, resulting in a rapid decay of the gp41 fusion intermediate that leads to the six-helical-bundle, potently inhibiting its formation and destroying cell-free virus. Because of the double-hit synergistic and sequential mechanism, the bivalent HIV-1 inactivator FD028 was able to permanently inactivate HIV-1 at nano-molar concentrations on contact with both cell-free HIV-1 and at the cell surface. This was shown through both inhibition and inactivation assays, using a surrogate ELISA assay measuring levels of viral p24 antigen. These results indicate that FD028 has potential for further development as a clinical HIV-1 inactivator-based therapeutic.

**Awards Won:**

Second Award of $2,000

Drug, Chemical &amp

Associated Technologies Association (DCAT): $1,000 scholarship will will be awarded &#x0D

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