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Preventing enveloped virus release from cells by targeting budding complexes

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We are developing a novel strategy targeting budding of enveloped viruses to control their infections based upon basic mechanisms discovered in our labs. We have used a multi-tiered high throughput screening strategy to detect small molecule compounds, referred to as viral budding inhibitors (VBIs) which prevent viruses from budding from cell membranes. The VBIs act by blocking the interaction of two cell proteins Tsg101 and Nedd4 with PTAPP and PPPPY L-domain motifs, respectively, in viral structural proteins that facilitates the recruitment of the cellular Endosomal Sorting Complex Required for Transport (ESCRT) machinery, which provides the mechanical means for virus particles to pinch off and separate from cell membranes. There are no clinical therapies to date that target this crucial budding process, so these are first-in-class drugs. Both of these types of drugs effectively block the release of infectious HIV from cells in culture without detectable cytotoxicity. The drugs targeting Tsg101/PTAPP motif also quantitatively block the release of infectious herpes viruses HSV-1 and HSV-2 from Vero cells while the drugs targeting Nedd4/PPPPY motifs were effective in blocking the release of ASLV from 293 and DF-1 cells, again without detectable cell toxicity. Taken together, these observations indicate that VBIs act as broad-based antiviral drugs. In addition, these drugs would complement a known innate immunity mechanism involving interferon-induced ISG15, which disrupts budding complexes to block the virus release process from cells. Tsg101 possesses a ubiquitin (Ub) E2 variant (UEV) domain homologous to Ub conjugating E2 enzymes and can bind Ub but cannot catalyze its transfer to substrates. The UEV domain can also bind PTAPP motifs. It is not known how or whether the UEV Ub-binding function contributes to virus production. Here, however, we show that disruption of UEV Ub-binding by VBIs arrested assembly at an early step distinct from the late stage involving PTAPP binding disruption (Strickland et al., Nature Communications, 8, 1391 (2018)). NMR revealed that the disruption caused by these drugs results from the formation of a covalent adduct near the Ub-binding pocket. We propose that the Ub-binding pocket mediates a chaperone function that permits bud initiation.

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