Biological Design Doctoral Defense

Exploration of aggregation and multivalency as viral inhibition strategies

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Abstract

Scientists are entrusted with developing novel molecular strategies for effective prophylactic and therapeutic interventions. Antivirals are indispensable tools that can be targeted at viral domains directly or at cellular domains indirectly to obstruct viral infections and reduce pathogenicity. Despite their transformative potential in the prevention and treatment of infectious viral diseases, to date, antivirals have been clinically approved to treat only ten different pathogenic human viruses. Unfortunately, for the vast majority of greater than 200 known human viruses, effective antivirals do not exist. Compounding this challenge, many viral pathogens have evolved to evade effective antivirals. As obligate intracellular parasites, viruses rely on unique and tightly controlled biological mechanisms to progress their infection cycle. These mechanisms are often intimately coupled with host cellular processes, which means the development of a clinically relevant antiviral requires extensive insight into these processes. A means to develop virus- or strain-specific antivirals without detailed insight into each idiosyncratic biochemical mechanism may aid in the development of antivirals against a larger swath of pathogens. Such an approach will tremendously benefit from having the specific molecular recognition of viral species as the lowest barrier. Here we modify a nanobody (anti-GFP) that specifically recognizes non-essential epitopes (gM-pHluorin chimera) presented on the extra virion surface of a virus (PRV strain 486). The nanobody switches from having no inhibitory properties (tested up to 50 μM) to ~3 nM IC50 in in vitro infectivity assays using PK15 cells. The nanobody modifications use highly reliable bioconjugation to a 3D wireframe DNA origami scaffold. Mechanistic studies suggest that inhibition is mediated by the DNA origami scaffold bound to the virus particle and enhanced by avidity resulting from multivalent virus and scaffold interactions, which act in concert to prevent virus internalization into the target cells. The assembled nanostructures demonstrate negligible cytotoxicity (<10 nM) and sufficient stability, further supporting their therapeutic potential. If translatable to other viral species and epitopes, this approach may open a new strategy that leverages existing infrastructures - mAb development, phage display, and in vitro evolution - for rapidly developing novel antivirals in vitro.

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Zoom Link: https://asu.zoom.us/my/bionicslab