Rationally designed chemokine-based toxin targeting the viral G protein-coupled receptor US28 potently inhibits cytomegalovirus infection in vivo - DTU Orbit (08/11/2017)

Rationally designed chemokine-based toxin targeting the viral G protein-coupled receptor US28 potently inhibits cytomegalovirus infection in vivo

The use of receptor-ligand interactions to direct toxins to kill diseased cells selectively has shown considerable promise for treatment of a number of cancers and, more recently, autoimmune disease. Here we move the fusion toxin protein (FTP) technology beyond cancer/autoimmune therapeutics to target the human viral pathogen, human cytomegalovirus (HCMV), on the basis of its expression of the 7TM G protein-coupled chemokine receptor US28. The virus origin of US28 provides an exceptional chemokine-binding profile with high selectivity and improved binding for the CX3C chemokine, CX3CL1. Moreover, US28 is constitutively internalizing by nature, providing highly effective FTP delivery. We designed a synthetic CX3CL1 variant engineered to have ultra-high affinity for US28 and greater specificity for US28 than the natural sole receptor for CX3CL1, CX3CR1, and we fused the synthetic variant with the cytotoxic domain of Pseudomonas Exotoxin A. This novel strategy of a rationally designed FTP provided unparalleled anti-HCMV efficacy and potency in vitro and in vivo.

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