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PROGRAM & ABSTRACTS

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We screened a local library of about 19,000 small chemical compounds against HSV1(17+)Lox-GFP. Among the top compounds, PANH_135 and PANH_070 inhibited the formation of infectious virions with an IC50 of 0.6 or 10.1 μM, respectively, and a CC50 higher than 150 μM. PANH_135 inhibited DNA replication, blocked C-capsid formation, and led to overall fewer nuclear and cytoplasmic capsids. In contrast, although the capsids had recruited the large tegument protein pUL36, infection in the presence of PANH_070 led to higher amounts of nuclear and cytoplasmic capsids, suggesting that nuclear capsid egress and secondary envelopment had been inhibited. Both compounds inhibited infection of HSV-1 and HSV-2 acyclovir-resistant strains, and HSV-1 infection of murine skin ex vivo. Importantly, resynthesized compounds and some derivatives maintained their activity against HSV-1. We are currently isolating and sequencing compound-resistant HSV-1 strains, and using derivatives for proteolysis-targeting chimera technology (PROTAC) to identify the viral targets of these PANH compounds.

058. Herpesvirus-mediated Protein Citrullination as a New Target for Antiviral Therapy

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Herpes simplex virus type 1 (HSV-1) is a neurotropic virus that remains latent in neuronal cell bodies but reactivates following a variety of stresses throughout the individual's life. In some cases, individuals can develop adverse reactions such as herpes simplex encephalitis (HSE). In this context, recent evidence suggests the involvement of HSV-1 in the etiology of Alzheimer's disease (AD). The absence of an effective vaccine and the emergence of numerous drug-resistant variants led the need to develop new antiviral agents able to tackle HSV-1 infections. In this scenario, host-targeting antivirals (HTAs) which act on host-cell factors essential for viral replication, are emerging as a promising class of antiviral compounds. Here we show that a new class of HTAs targeting peptidylarginine deiminases (PADs), a family of calcium-dependent enzymes catalyzing protein citrullination, display a potent inhibitory activity against HSV-1. Specifically, we show that inhibition of PADs-mediated citrullination suppresses HSV-1 replication in fibroblasts (HFF), epithelial (ARPE), or neuroblastoma (SHSY-5Y) cell lines. Furthermore, we show that HSV-1 infection leads to enhanced protein citrullination through transcriptional activation of three PAD isoforms: PAD2, PAD3 and PAD4. Interestingly only PAD3 specific inhibitors, CAY10727 or HF4, dramatically curbs HSV-1 replication. Finally, we defined HSV-1-induced citrullinoma that could be useful to understand how citrullination is crucial for HSV-1 replication. Overall, our results demonstrate that PAD inhibitors suppress efficiently HSV infection in vitro which may provide the rationale for their reporpusing use as a HSV-1 antivirals.

059. Combined gB (humoral) and IE1 (cell-mediated) Ad Vector CMV Vaccines Are More Effective Than Disabled CMV DISC Vaccine for cross Strain Protection Against Congenital Cytomegalovirus Disease

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Guinea pig cytomegalovirus (GPCMV) is the only small animal model for congenital CMV. A recent GPCMV DISC vaccine demonstrated the importance of neutralizing antibodies to viral glycoproteins for protection against congenital CMV. Clinical strains of HCMV are highly cell-associated and potentially evade neutralizing antibodies by limiting levels of cell free virus. In convalescent HCMV, the T cell response to IE1 protein is considered important. We verified that GPCMV encodes essential functional homologs of IE1 and IE2. GPCMV IE1 was explored as an adenovirus-based vaccine candidate (AdIE1). Guinea pig specific IFNγ ELISPOT assay to IE1 showed T cell response in vaccinated animals. AdIE1 vaccinated animals challenged with wild type GPCMV (22122 strain) showed reduced viral load in target organs but lacked full protection similar to a previous trimeric capable AdgB vaccine. Although AdgB induced high titer neutralizing antibodies, an AdgB vaccine was less effective against a novel cell associated clinical GPCMV