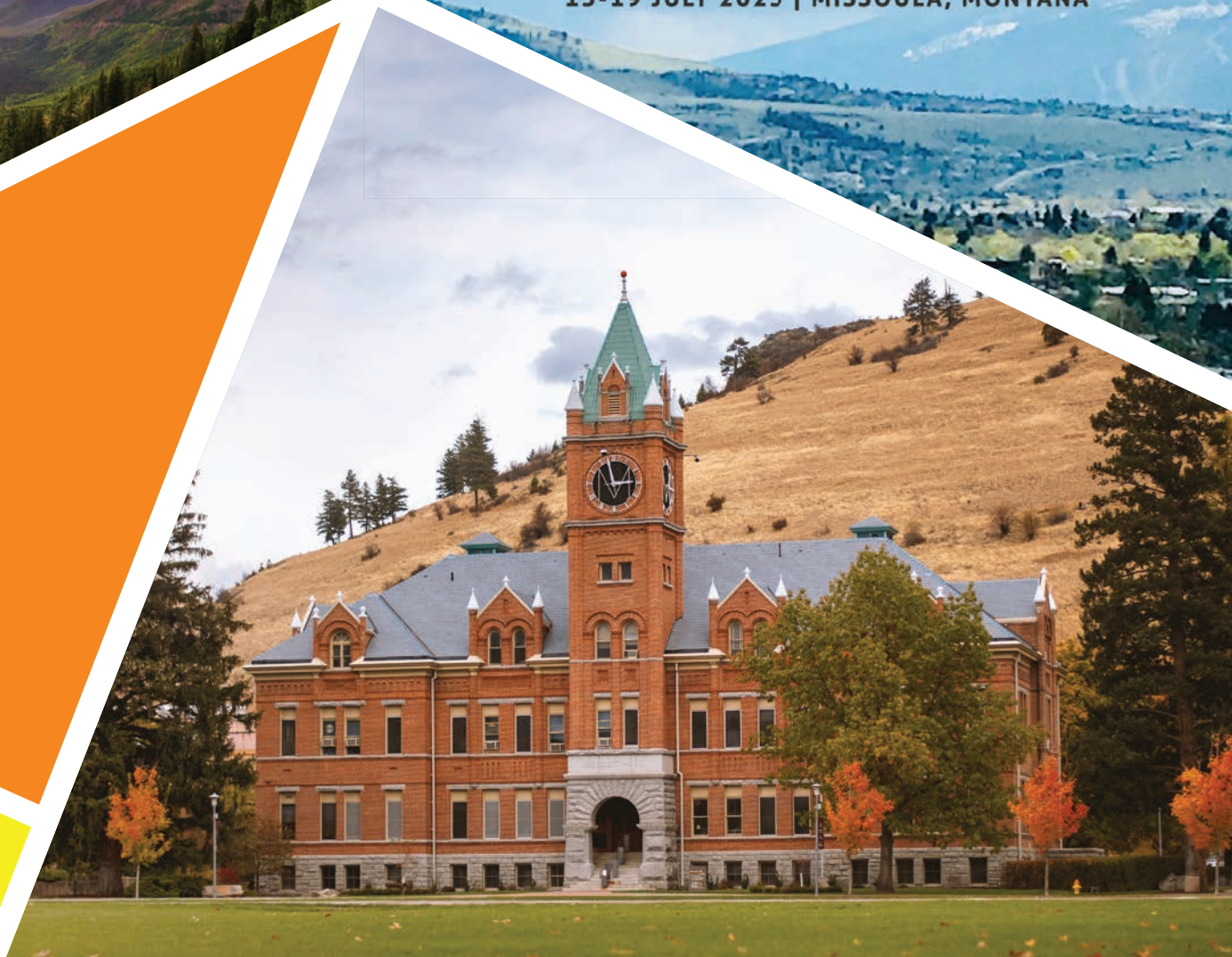
IHW 2023

INTERNATIONAL HERPESVIRUS WORKSHOP

15-19 JULY 2023 | MISSOULA, MONTANA



8.01

HSV-1-induced PAD-mediated Citrullination as a New Target for Antiviral Therapy

Camilla Albano[1] (camilla.albano@unito.it), Selina Pasquero[2], Francesca Gugliesi[2], Gloria Griffante[3], Qiao Yang[1], Valentina Dell'Oste[2], Matteo Biolatti[2], Greta Bajetto[4], Linda Trifirò[2], Bianca Brugo[1], Paul R. Thompson[5], Sen Sudeshna[5], Santo Landolfo[2], Marco De Andrea[2]

[1]University of Turin, Turin, Torino, Italy, [2]University of Turin, Turin, Italy, [3]University of Eastern Piedmont, Novara, Italy, [4]University of Piemonte Orientale, Center for Translational Research on Autoimmune and Allergic Disease-CAAD, Novara, Italy, Novara, Italy, [5]UMass Chan Medical School, Worcester

Herpes simplex virus 1 (HSV-1) is a neuroinvasive and neurotoxic virus capable of entering the brain via peripheral nerves. Like other members of the Herpesvirus family, HSV-1 has developed different strategies, such as the exploitation of post-translational modification (PTM) of proteins, to ensure efficient viral replication and persistent infection. Citrullination is a PTM catalyzed by peptidyl-arginine deiminases (PADs), that convert peptidyl-arginine into peptidyl-citrulline. Here we show that HSV-1 infection triggers PAD-mediated citrullination through transcriptional activation of three PAD isoforms: PAD2, PAD3, and PAD4. Interestingly, the pan-PAD inhibitors, Cl-amidine and BB-Cl-amidine, and the PAD3-specific inhibitor, HF4, dramatically suppress HSV-1 replication. Finally, citrullinome analysis reveals significant changes in several host and viral proteins, with interferon (IFN)-inducible proteins IFIT1 and IFIT2 being among the most heavily deiminated ones. As genetic depletion of IFIT1 and IFIT2 strongly enhances HSV-1 growth, we propose the viral-induced IFIT1-2 citrullination as an HSV-1 evasion mechanism from host antiviral resistance. Altogether, these findings highlight the pivotal role of citrullination in subverting cellular responses to viral infection and demonstrate that PAD inhibitors efficiently suppress HSV-1 replication, suggesting their potential repurposing as HSV-1 antiviral drugs.

8.02

Inhibition of Intracellular Peroxynitrite Production Alleviates CMV Replication

Pragati S. Amratia[1] (SabberwalP@cardiff.ac.uk), Lauren E. Kerr-Jones[1], Morgan Marsden[1], Mathew Clement[1], Richard J. Stanton[1], Ian Humphreys[1]

[1]Cardiff University, Cardiff, South Glamorgan, United Kingdom

There is no licensed vaccine against HCMV, and current therapeutic approaches that target key viral proteins are toxic and/or prone to antiviral drug resistance. Targeting host pathways essential for virus replication provides an alternate strategy for the development of antivirals, which may reduce opportunities for resistance to evolve. Here we show that CMV exploits host oxidative/nitrosative stress responses for efficient viral replication. Oxidative/nitrosative stress is caused by the accumulation of intracellular reactive oxygen/nitrogen species (ROS/RNS). Using a range of ROS/RNS scavengers, we identified that peroxynitrite, a powerful oxidising/nitrating agent, promoted virus replication in both *in vitro* and *in vivo* models of CMV infection. HCMV rapidly induced the generation of intracellular peroxynitrite upon infection, and inhibiting peroxynitrite within the first 24 hours of infection prevented CMV replication in both cell-free and cell-associated infection systems. Thus, peroxynitrite production may impact virus entry and/or the initiation of replication. Interestingly, serotonin, a naturally occurring antagonist of peroxynitrite, also impinged on HCMV-induced production of peroxynitrite and exhibited anti-viral activity. Overall, our study highlights a novel role for intracellular peroxynitrite in CMV pathogenesis and implies that oxidative/nitrosative stress signalling pathways could be targeted as a novel strategy for inhibiting CMV infection.