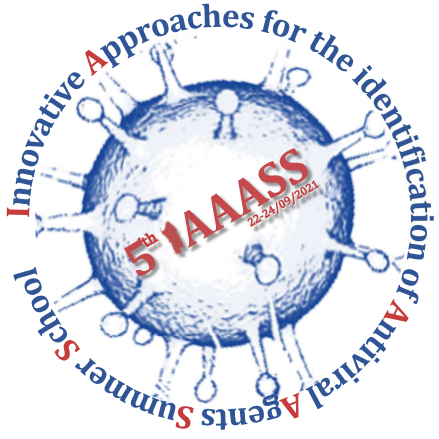

5th Innovative Approaches for Identification of Antiviral Agents Summer School

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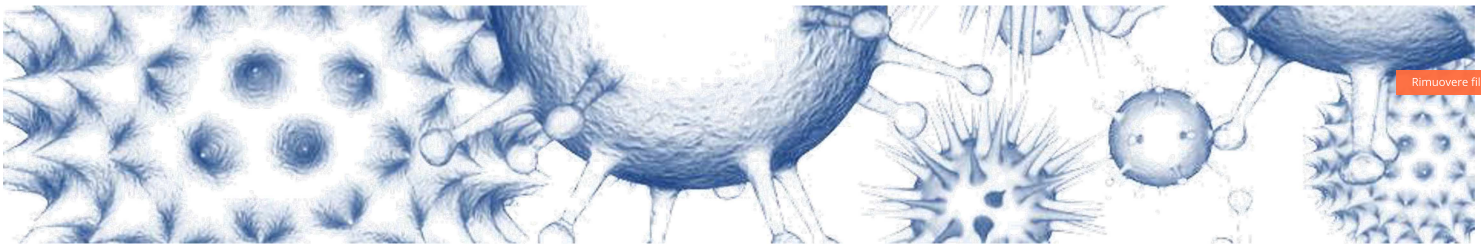

13 – NOVEL ANTIVIRAL ACTIVITY OF PADs INHIBITORS AGAINST BETA-CORONAVIRUSES SARS-CoV-2 AND HCoV-OC43

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Novel coronaviruses (CoVs) have repeatedly attracted the attention of researchers over the past few decades. To date, seven human CoVs (HCoVs) have been identified: among them, HCoV-OC43 and SARS-CoV-2, the causative agent of the ongoing epidemic of atypical pneumonia (COVID-19), belong to beta genus. A recent study described the putative roles of a family of enzymes called peptidylarginine deiminases (PADs) in COVID-19 disease. PADs are a family of cellular enzymes that catalyze the post-translational modification citrullination, a process in which the guanidinium group of a peptidyl-arginine is hydrolyzed to form peptidyl-citrulline, a non-genetically coded aminoacid. PADs dysregulation leads to an aberrant citrullination which is a characteristic biomarker of several inflammatory conditions. Based on these evidences, the aim of this work was to evaluate whether PAD inhibitors were a reliable new class of host-targeted antivirals against coronaviruses.
By using the HCoV-OC43 and SARS-CoV2 strains as models of infection in human lung fibroblasts (MRC-5) and monkey kidney cells (Vero-E6), we observed that the pharmacological inhibition of PAD enzymes led to a significant reduction of viral replication. Furthermore, the overall citrullination profile obtained with the citrulline-specific rhodamine phenylglyoxal (RhPG)-based probe changes consistently during infection. Interestingly, this is associated with an increase of PAD expression, both at mRNA and protein levels. Taken together our results suggested that i) citrullination is a process that can be induced by beta-coronaviruses, as a mechanism to foster their replication, and 2) that increase of PADs activity is central for beta-coronavirus replication.