



# Houk-Jung Organic Colloquium

## “Medicinal Chemistry and Pharmacology of Antivirals Targeting Influenza Virus, Enterovirus D68, and SARS-CoV-2”

**Abstract:** Respiratory viruses pose a persistent threat to public health and global economy. However, there is a lack of effective antiviral countermeasures against many of these highly transmissible pathogens. In this presentation, I will present a few projects on the development of small molecule antivirals against the influenza virus, enterovirus D68 (EV-D68), and SARS-CoV-2. Throughout the talk, I will discuss the experience and lessons learned from academic drug discovery including target identification, hit prioritization, and translational research. For influenza virus project, we have developed antivirals targeting the viral M2-S31N proton channel and the viral polymerase PA-PB1 interactions. The lead compounds have shown potent in vitro and in vivo antiviral activity against both Tamiflu-sensitive and resistant influenza viruses. EV-D68 is a respiratory virus that mainly infect children and cause flu-like symptoms. In severe cases, the infection can lead to neurological symptoms called acute flaccid myelitis. There is currently no antiviral or vaccine available for EV-D68. We have made promising progress in developing antivirals targeting the viral VP1 capsid, the 2A protease and the 2C protein. The lead compounds have shown broad-spectrum antiviral activity against multiple enteroviruses including poliovirus. For the SARS-CoV-2 project, we are among the first to discover structurally diverse compounds as the viral main protease ( $M^{pro}$ ) inhibitors and have solved multiple X-ray crystal structures. Subsequent structure-based drug design led to the discovery of the both covalent and non-covalent  $M^{pro}$  inhibitors with potent enzymatic inhibition and cellular antiviral activity. Overall, the lead compounds we have developed against influenza virus, EV-D68, and SARS-CoV-2 have promising translational potential and continuous development might lead to the first-in-class broad-spectrum antivirals.

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