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Targeting the influenza A virus M2 proton channel to combat drug resistance

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Each year more people die of flu-related illness than breast cancer, which places influenza virus infection the top ten leading causes of deaths in the U.S. In addition, sporadic and unpredictable influenza pandemics cause even more devastating damages to public health and global economy. Despite this grand challenge, we are limited by the therapeutic countermeasures against flu infection. The only class of drugs that remains effective is the viral neuraminidase inhibitors (NAs), such oseltamivir, zanamivir and peramivir. However, like many other drugs used to treat infectious diseases, NAs are not an exception in terms of drug resistance and flu viruses that are resistant to NAs have been continuously reported. Thus this is a pressing need to develop antivirals to combat multi-drug resistant influenza A viruses. Towards this goal, we explore the influenza A virus M2 proton channel as the drug target. Specifically, we focused on the M2-S31N mutant, which is the predominant drug-resistant mutant among current circulating influenza A viruses. Using an integrated approach involving molecular dynamics simulations, NMR, X-ray, electrophysiology, virology and medicinal chemistry, we were able to design the first-in-class M2-S31N inhibitors. These lead compounds are not only potential drug candidates but also invaluable chemical tools which enable us to address fundamental questions such as: Are M2-S31N inhibitors active against multi-drug resistant influenza A viruses? How is the genetic barrier of drug resistance of M2-S31N inhibitors compared to amantadine? Will mutant viruses similarly evolve resistance to M2-S31N inhibitors? If resistance were to emerge, what is the mechanism? Answers to these questions are pivotal to advance the drug discovery program forward.

Biography

Jun Wang is currently an Assistant Professor at the Department of Pharmacology and Toxicology, College of Pharmacy, the University of Arizona, USA. He also holds an Adjunct Position at the BIO5 Institute. He has received his PhD in Chemistry in 2010 from the University of Pennsylvania, USA. He has spent three years as a Postdoctoral Researcher; first at the University of Pennsylvania and then at UCSF.

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