Life Science

# New Insights into the Major Drug Target of H7N9 Human Infecting Influenza Virus

Between February and March of 2013, the source of avian-origin H7N9 human infection was discovered in Shanghai and Anhui, China. Prior to this, H7N9 has only exhibited characteristics of a low pathogenic avian influenza virus, carried by chickens with no known cross-species transmission.

By the end of August 2013, Chinese mainland reported a total of 134 confirmed cases of H7N9 human infections across 12 provinces and 42 cities, resulting in 45 deaths. In October and November, Zhejiang Province found three new cases and Guangdong found one case of human infection, suggesting the possibility of a comeback in the fall and winter seasons.

Researchers led by Prof. GAO Fu (George Fu Gao) at the Institute of Microbiology, CAS and Beijing Institutes of Life Science, have made progress on understanding the two important H7N9 influenza virus surface proteins, hemagglutinin (HA) and neuraminidase (NA). Their findings on the H7N9 HA protein have been published in *Science*, while the analysis of NA has been published online in *Cell Research*, featured on the issue's front cover.

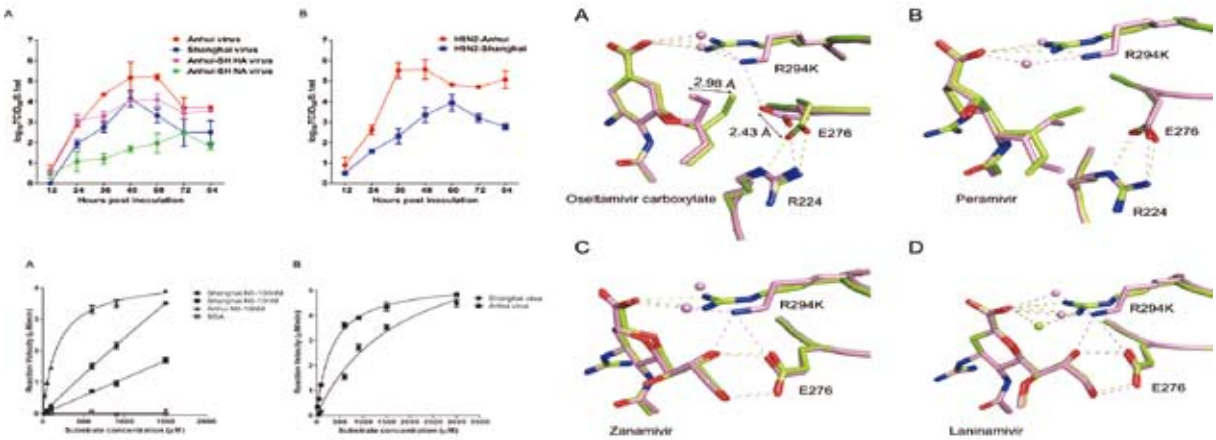
The influenza NA protein is the most important influenza drug target. The antiviral agents Tamiflu, Relenza, Peramivir and Laninamivir are clinically used drugs which target NA. Important variations in the HA and NA proteins were detected in H7N9 patients, with at least two distinct HAs and NAs.

WU Yan, BI Yuhai, Chris Vavricka and their colleagues at CAS analyzed two distinct NA proteins, one from Shanghai, with a Lysine residue at amino acid position 294, and another from Anhui, with Arginine at position 294. Residue 294 plays an important role in binding inhibitors and influenza receptors.

Their study determined that R294K results in drug-resistance to all known NA inhibitors. The drug resistant mechanism of N9 K294 mutant was interpreted by obtaining high-quality N9 protein crystals and determining their three-dimensional structures from X-ray data collected at Shanghai Synchrotron Radiation Facility.

WU Yan *et al* also proved that H7N9 virus carrying K294 impairs viral replication. Although R294K containing H7N9 viruses are resistant to the current arsenal of influenza drugs, they hardly become the dominant virus subtype due to low replication. Therefore, it was concluded that Tamiflu and other commonly used drugs are still important for the treatment of H7N9 patients. The work was published on *Cell Research*.

Prof. K. Y. Yuen from the University of Hong Kong has highlighted this work in a recently published review article "A group of scientists from the Chinese Academy of Sciences led by Gao GF *et al* should be congratulated for giving these important answers by a combination of conventional virology, reverse genetics and crystallography within a period of just six months."




Researchers at IMCAS found that N9 containing K294 (N9 numbering) results in drug-resistance to all known NA inhibitors and impairs NA activity and viral replication.