The NF-kappaB-inhibitor SC75741 efficiently blocks influenza virus propagation in vitro and in vivo without the tendency to induce resistant virus var

°*Stephan Ludwig (1), Christina Ehrhardt (1), Karoline Droebner (2), Andrea Rückle (1), Carina Banning (1), Eike Hrincius (1), Katharina Hoppe (1), Johann Leban (3), Stefan Strobl (3), Daniel Vitt (3), Oliver Planz (2)

(1) Institute of Molecular Virology (IMV), Centre for Molecular Biology of Inflammation (ZMBE), Muenster, Germany; (2) Institute of Immunology, Friedrich-Loeffler-Institut (FLI), Tuebingen, Germany; (3) 4SCAG, Planneg-Martinsried, Germany

Influenza is still one of the major plagues worldwide. The appearance of highly pathogenic avian H5N1 viruses in humans and the emergence of resistant H5N1 variants against neuraminidase inhibitors highlight the need for new and amply available antiviral drugs. We and others have demonstrated that influenza virus misuses the cellular IKK/NF-kappaB signalling pathway for efficient replication suggesting that this module may be a suitable target for antiviral intervention. Here we show that the novel NF-kappaB inhibitor SC75741 efficiently blocks replication of influenza A and B viruses, including avian and human A/H5N1 isolates, in vitro and in a mouse infection model in concentrations that do not affect cell viability or metabolism. The underlying molecular mechanism of SC75741 action involves impaired expression of proapoptotic factors, subsequent inhibition of caspase activation as well as block of caspase-mediated nuclear export of viral ribonucleoproteins. Besides this direct antiviral effect the drug also suppresses virus-induced overproduction of cytokines and chemokines, suggesting that it might prevent the so-called cytokine burst that is discussed as an important pathogenicity determinant of infections with highly pathogenic influenza viruses, such as the A/H5N1 strains. Most importantly the drug did not shown any tendency to induce resistant virus variants. Thus, a SC75741-based drug may serve as a broadly active non-toxic anti-influenza agent.

Corresponding author:
Ludwig, Stephan
ludwigs@uni-muenster.de
Phone: ++492518357791
Fax: ++492518357793