Development of Vaccines to Emerging / Reemerging Virus: SARS – A Case Study

Konrad Stadler

Chiron Vaccines, Via Fiorentina 1, 53100 Siena, Italy

By the late twentieth century an increase in the emergence and re-emergence of infectious diseases was evident in many parts of the world. Profound changes in human ecology together with improved screening and reporting might explain the accumulated emergence of new diseases but also the re-emergence of old ones. About 30 new diseases have been identified within the last 3 decades, most of them caused by viruses, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), Nipah virus, several viruses causing hemorrhagic fever, avian influenza viruses and most recently, severe acute respiratory syndrome coronavirus (SARS-CoV). The virus appeared for the first time in China in November 2002 and by early 2003 had spread to over 30 countries. The epidemic was contained by quarantine and public health measures, but no specific therapies or vaccines were available. Because vaccines will play a critical role in preventing future cases of SARS, a lot of effort has been put in identifying and evaluating new vaccine candidates.

In our laboratory two independent strategies to develop a vaccine against SARS-CoV infection are pursued. A traditional whole "killed" virus approach, which represents the shortest development path, leveraging decades of experience in developing, manufacturing and administering vaccines based on inactivated viruses. SARS-CoV from the FRA strain was produced in VERO cells, inactivated with beta-propiolactone (BPL) and purified by column chromatography. The immunogenicity and efficacy of this vaccine was evaluated against a challenge with intranasally administered SARS-CoV in a mouse model. Two doses of a BPL-inactivated SARS vaccine with (MF59) adjuvant and 3 doses without adjuvant elicited neutralizing antibody titers of 1:71 and 1:64, respectively in mice, that are comparable to those reported in human convalescent sera. Antibody titers following the third dose of vaccine with MF-59 were >1:500. The vaccine administered in 3 doses 2 weeks apart, with or without adjuvant, provided protection against intranasal challenge with 10^5 $TCID_{50}$ SARS-CoV. Virus was undetectable in the upper respiratory tract and titers were reduced by more than 4.5 $\log_{10}$ in the lower respiratory tract ($p=0.00001$) of vaccinated mice compared to mean titers of 2.8 ± 0.35 and 6.3 ± 0.3 $\log_{10}$ $TCID_{50}$/g in the upper and lower respiratory tract of control mice, respectively.

The second approach is based on the observation that protection from coronavirus infection generally depends on neutralizing antibodies against the "Spike" envelope glycoprotein. By developing a vaccine based on recombinant spike protein expressed in mammalian cells we bypassed the requirement for propagation of infectious SARS-CoV under BSL-3 conditions. Experiments testing the immunogenicity and efficacy of this recombinant vaccine are currently underway.