

## 5. Summary

The development of an effective HIV vaccine is more than 20 years after the first description of the virus inducing AIDS one of the major targets in international health efforts. Conventional vaccine strategies including attenuated whole virus vaccines or recombinant viral proteins failed due to safety concerns or ineffective immunological responses. Thus the induction of neutralising antibodies against the HIV-1 transmembrane envelope protein gp41 became a major challenge in HIV vaccine development since it is highly conserved within different HIV-1 subtypes and bears epitopes recognised by the broadly neutralising monoclonal antibodies 2F5 and 4E10. Both antibodies were isolated from humans and showed a protection against HIV-1 of humans and primates in passive immunisation studies. However, until today the induction of such antibodies by active immunisation with a variety of antigen constructs in different animal models, including primates, has not been successful.

In this study presented here the aim was to complete a model for the humoral immune response against the transmembrane envelope protein (TM) of retroviruses in order to evolve a strategy for a successful immunisation against HIV-1 gp41. Therefore the immune response against the TM protein p15E of the Feline Leukaemia virus A (FeLV subtype A), a gammaretrovirus, was characterised in different species including cats as its natural host. Two immune dominant epitope regions (E1 and E2) were determined in the ectodomain of FeLV-A p15E shown to be essential for the neutralisation of the virus *in vitro*. Epitopes within this region detected by antibodies from neutralising immune sera were not only localised similar to those of 2F5 and 4E10 in gp41 but also showed a partial homology to the 4E10 epitope. Further more it was observed that immunisation of cats with the FeLV-A p15E can protect them efficiently from a FeLV-A infection showing for the first time the induction of protective immunity against a retrovirus by immunisation with its transmembrane protein. It was also demonstrated that a protective immunity induced by the unglycosylated FeLV-A surface protein p45 or by the transmembrane protein p15E does not require sterilising immunity.

Based on this FeLV-A p15E model we generated two hybrid constructs, consisting of a p15E backbone and the C-terminal part of HIV-1 gp41 and analysed the humoral immune response against these constructs in the laboratory rat model. By one of these constructs neutralising antibodies specific for HIV-1 gp41 were reproducibly induced against the homologous HIV-1 strain as well as against HIV-1 primary isolates. Neutralisation titres similar to those observed for sera from rats immunised with FeLV-A p15E were determined. The epitopes from HIV-1 neutralising antibodies were located within or near by the 2F5 and the 4E10 epitopes. As gp41 derived peptides or gp41 proteins are not able to induce neutralising antibodies against HIV-1, it can be assumed that the conformation of the hybrid antigen must be responsible for this effect. This newly generated antigen might be used as a potential candidate in HIV-1 vaccine studies.