NOVEL APPROACHES TO OVERCOME THE BLOCK IN HIV VACCINE DEVELOPMENT

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Although there are no correlates of protection from HIV, the induction of broad neutralising antibodies (bNAb) is considered to be the most desirable outcome for a HIV vaccine, but a vaccine able to elicit such antibodies has not yet been developed. Furthermore, HIV employs multiple strategies to evade NAb and cell to cell transmission is effective. This suggests that an effective HIV NAb vaccine regimen should also elicit cell-mediated immunity (CMI), most likely against viral antigens which are more conserved than Env. However, a vaccine that can elicit effective NAb and CMI is not available for use in humans, and this study represents a paradigm in shift in vaccine strategy to achieve this goal. Nevertheless, we developed a novel cytolytic DNA vaccine which encodes a cytolytic protein in addition to the immunogen that is more effective than a canonical DNA vaccine against challenge with EcoHIV, a chimeric virus which infects mice.

We also developed a novel DNA vaccine encoding Tat to elicit anti-Tat NAb that inhibited the function of Tat in an *in vitro* transactivation assay and reduced the titre of nascent virus in cell culture studies. We combined the cyolytic DNA vaccine with the anti-Tat NAb vaccine and showed that this controlled EcoHIV infection most effectively. However, perhaps the most urgent need is to develop a vaccine able to induce immunity at genitorectal mucosa. To address this we developed a series of recombinant human rhinoviruses (recHRV) which encode gag and tat, and showed that a recHRV/DNA prime/boost regimen induced humoral immunity and CMI in gut, vaginal mucosa and systemically. This strategy is an important step towards preventing HIV infection by vaccination.