Adenoviral vectors: a possible road to an HIV vaccine
Lemckert, A.A.C.

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Summary

Approximately 5 million people get infected with HIV and about 3 million people die of AIDS each year, leading to an amount of 39.5 million people living with HIV to date. Therefore, the need for an effective HIV-vaccine is high. However, the development of such a vaccine faces many challenges. It is believed that both HIV-specific NAb and CD8+ cytotoxic T lymphocytes are essential to effectively combat HIV. To date, it still proves difficult to elicit broadly reactive HIV-specific NAb. In contrast, for both plasmid DNA vaccines and recombinant viral vector-based vaccines it has been demonstrated that they elicit potent transgen-specific CD8+ T lymphocytes. Among this latter type of vaccines are the Ad5-based vaccines, which have been proven effective in both pre-clinical as well as clinical studies. A downside of the Ad5-based vaccines, however, is that their immunogenicity is blunted by anti-Ad5 immunity, which is highly prevalent worldwide. Therefore, several research strategies are developed to construct adenoviral-based vaccines vectors that can evade Ad5 pre-existing immunity.

It was demonstrated that both NAb and CD8+ T lymphocytes are involved in the anti-Ad5 immunity, with the NAb playing the main role. In chapter 2 of this thesis we investigated the major immunodominant target of anti-Ad5 NAb. In vitro neutralization assays utilizing both human and mice sera illustrated that the anti-hexon NAb titers were higher compared to the anti-fiber NAb titers. In addition, we demonstrated by performing adoptive transfer studies in mice that primarily the anti-hexon NAb were able to abolish the immunogenicity of an rAd5-based vaccine. Together, these data have shown that the immunodominant target for the anti-Ad5 NAb is the hexon protein. This knowledge has proven pivotal, since recently a hexon chimeric Ad5-based vector (Ad5HVR48) is developed, which is able to escape from anti-Ad5 immunity successfully.

A total of 51 different human adenovirus serotypes have been identified. Seroprevalence surveys among healthy adults worldwide have been initiated to find adenoviral serotypes with low seroprevalence and low NAb titers in positive individuals. Several of such adenoviral serotypes have been identified, including Ad11, Ad35, Ad50 (subgroup B) and Ad26, Ad48 and Ad49 (subgroup D). Ad35-based vaccines have already been investigated for HIV/SIV, malaria, and tuberculosis and proved potent in eliciting transgen-specific CD8+ T lymphocytes in pre-clinical studies. However, the immunogenicity of Ad35-based vaccines was less compared to Ad5-based vaccines in Ad5-naïve settings. Since inbred mice do not express the cellular receptor CD46 that is utilized by Ad35, we investigated in chapter 3 if receptor usage may play a role in the immunogenicity of a particular vaccine. Therefore, and Ad35k5 vector was constructed which was able to use the Ad5 cellular receptor CAR. We indeed showed that the immunogenicity of the Ad35k5 was improved in both mice and non-human primates compared to the parental Ad35-based vaccine. These data suggest that the cellular receptor used by the vaccine vector plays a role in immunogenicity.

In the presence of anti-Ad5 immunity, Ad35-based vaccines are far more immunogenic compared to Ad5-based vaccines. Utilizing prime-boost studies it was demonstrated that, as for Ad5, heterologous prime-boost regimens were superior to homologous prime-boost regimens. However, any prime-boost regimen comprising an Ad5-based vaccine was abrogated by anti-Ad5 immunity. In chapter 4 we investigated an Ad35-Ad11 prime-boost regimen. Even though this Ad35-Ad11 prime-boost regimen was superior in mice with Ad5 pre-existing immunity, any regimen containing Ad5 proved better in naïve settings. Further investigation revealed the presence of both Ad35-Ad11 cross-reactive NAb and CD8+ T
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lymphocytes. It was therefore hypothesized that for an effective adenoviral-based prime-boost regimen, both vectors should not only be able to evade anti-Ad5 immunity but should also be immunologically distinct. Therefore we developed an Ad49-based vector system in chapter 5. Since Ad49 is derived from adenovirus subgroup D instead of subgroup B, it should provide a better boosting vector. In chapter 6 we investigated potential of an Ad35-Ad49 prime-boost regimen and showed that this regimen was indeed superior to the Ad35-Ad11 prime-boost regimen. As expected, we also could not detect any functional immunologic cross-reactivity between Ad35 and Ad49. Importantly, the Ad35-Ad49 prime-boost regimen also retained its immunogenic potential in anti-Ad5 immunity settings. The work described in chapter 6 confirmed our earlier hypothesis that for effective prime-boost regimens both vectors should be immunologically distinct.

In chapter 7 the immunogenic potential of seven different rAd-based vaccines, derived from Ad5, Ad11, Ad35, Ad50, Ad26, Ad48 and Ad49, was determined in a head-to-head comparison. All vaccine-vectors elicited potent transgen-specific CD8+ T lymphocytes and importantly all rare-serotype vaccine vectors were not hampered by anti-Ad5 immunity. In this study, the Ad26-based vaccine proved most immunogenic among the rare adenovirus serotypes-based vaccines in both mice and non-human primates. Therefore, the Ad26-based vaccine is a promising addition to the list of potent adenovirus-based vaccine vectors for HIV.

The research described in this thesis has resulted in several potent adenovirus-based vectors, in addition to the Ad5 and Ad35-based vaccines, that warrant great promise as an HIV-vaccine. Both the Ad26-based and Ad5HVR48-based HIV vaccine vectors have received the prestigious Integrated Preclinical/ Clinical AIDS Vaccine Development Program (IPCAVD) grant of the NIH and for both a phase I clinical trial will be initiated in the near future.