

Editorial

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Recent Advances in Adenovirus-Vectored Vaccines Development

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Recombinant adenovirus-vectored vaccines based on human adenovirus serotype 5 (HAdV-5) have been extensively studied both pre-clinically and in clinical trials for the past 25 years. Initially, they were considered as the most promising platform for human immunodeficiency virus (HIV) vaccine development. However, HAdV-5-based vaccine did not meet expectations in a large-scale clinical trial called STEP trial.¹ In that trial, the vaccine not only showed lack of efficacy, but also suggested an increased trend for HIV acquisition in individuals with pre-existing HAdV-5 neutralizing antibodies.

Researches have developed vectors based on alternative serotypes of human and non-human adenoviruses in order to overcome challenges with HAdV-5-based vectors. To date, HAdV-35, HAdV-26 and simian adenoviruses ChAd3, ChAd63 and ChAdOx1 have been tested in several phase 1 clinical trials as candidate vaccine component against *Mycobacterium tuberculosis*, *Plasmodium falciparum*, HIV, Ebola, HCV and influenza virus. These vectors were chosen because most people have little or no immunity to them, and their biological characteristics, such as utilization of primary cellular receptor and elicitation of innate cytokine responses, differ from HAdV-5.

Vaccine Ad35-TBS (or AERAS-402) consists of recombinant replication-defective HAdV-35 vector expressing *M.tb* antigens Ag85A, Ag85B and TB10.4 as a single fusion protein.² A phase 1 trial in healthy Bacillus Calmette-Guerin (BCG)-vaccinated adults in South Africa demonstrated that the vaccine is safe and immunogenic.³ In addition, the vaccine safety and immunogenicity has been reported in healthy adults living in the US.⁴ In the study, volunteers were primed with BCG three or six months prior to AERAS-402 boosting. Also, AERAS-402 was safe and immunogenic in healthy infants previously vaccinated with BCG at birth.⁵

Vaccine Ad35.CS.01 is a pre-erythrocytic malaria candidate vaccine. To make the vaccine, the codon optimized nucleotide sequence of *P. Falciparum* circumsporozoite (CS) surface antigen was inserted in the E1 region of a replication deficient HAdV-35 vector. Phase 1 trial demonstrated that the vaccine was well-tolerated and modestly immunogenic in healthy adults living in the US or Sub-Saharan Africa.^{6,7}

The development of a vaccine to prevent HIV infection remains a global health priority. Therefore, recombinant HAdV-26 and HAdV-35 with HIV clade A envelope gene inserts were constructed. In a randomized, double-blind, placebo-controlled, multicenter, international clinical trial in the US, Kenya, Rwanda and South Africa both vaccines elicited significant immune responses in all populations. Baseline vector immunity did not have a significant impact on immune responses, and second vaccinations in all regimens significantly boosted EnvA immunity.⁸

Another approach was developed based on designing mosaic antigen using genes from different HIV subtypes responsible for HIV-1 infections worldwide. The antigen was expressed in recombinant replication-defective HAdV-26 vector adenovirus serotype 26-Mosaic-human immunodeficiency virus (Ad26.Mos.HIV). A phase 1/2a study (named APPROACH) in 393 healthy HIV-uninfected adults has been conducted in the US, Rwanda, Uganda, South

Africa and Thailand. Vaccine regimens contained two prime doses of vector Ad26.Mos.HIV and two boosts of either Ad26.Mos.HIV, MVA-Mosaic and/or different doses of the soluble protein Clade C gp140 adjuvanted with aluminum phosphate. As presented at the 9th IAS Conference on HIV Science (IAS 2017), the results indicated that the “mosaic”-based vaccine regimen appeared to be well-tolerated and elicited HIV-1 antibody responses in 100% participants.

Chimpanzee-origin vectors tested in humans were derived from serotype 63 (ChAd63), and were used to express the pre-erythrocytic malarial antigen ME-TRAP.29.⁹ Hundreds of individuals had been immunised in Africa and UK with ChAd63-vectored malaria vaccine.^{10,11} Similarly, serotype 3 (ChAd3) vector expressing non-structural proteins from hepatitis C virus (HCV) genotype 1b successfully induced a T-cell response against HCV in healthy volunteers.^{12,13} In addition, simian adenovirus vector ChAdOx1 expressing the conserved influenza antigens, nucleoprotein (NP) and matrix protein 1 (M1), was constructed and shown to be safe and immunogenic in adult humans.¹⁴

As a rapid response to the 2014 Ebola epidemic, adenovirus-vectored vaccines were developed and subsequently tested in phase 1 clinical trials. Those were a replication defective recombinant chimpanzee adenovirus ChAd3-vectored vaccine (cAd3-EBO), encoding the glycoprotein (GP) from Zaire and Sudan species and a replication-defective HAdV-26-vectored vaccine expressing GP from the Zaire Ebola virus (Ad26.ZEBOV). Ad26.ZEBOV was used in a combination with MVA-BN-Filo in a heterologous prime boost vaccination strategy with MVA-BN-Filo as a booster vaccine. Both these vaccines were well tolerated and immunogenic in healthy adults.^{15,16}

CONCLUSION

In conclusion, although adenovirus-based vectors have seen their share of setbacks in recent years, they remain to be a valuable tool for vaccination against infectious diseases. Development of novel vectors based on alternative human and non-human serotypes helps to overcome challenges observed with HAdV-5-based constructs.

COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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