

Editorial

*Corresponding author

Alexander N. Zakhartchouk, PhD

Adjunct Professor

Department of Veterinary Microbiology
Western College of Veterinary Medicine
University of Saskatchewan

52 Campus Drive, Saskatoon
SK S7N 5B4, Canada

E-mail: alex.zak@usask.ca

Volume 2 : Issue 1

Article Ref. #: 1000VROJ1e004

Article History

Received: August 16th, 2017

Accepted: August 17th, 2017

Published: August 17th, 2017

Citation

Zakhartchouk AN. Recent advances in adenovirus-vectored vaccines development. *Vaccin Res Open J*. 2017; 2(1): e2-e4.

doi: [10.17140/VROJ-2-e004](https://doi.org/10.17140/VROJ-2-e004)

Copyright

©2017 Zakhartchouk AN. This is an open access article distributed under the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Recent Advances in Adenovirus-Vectored Vaccines Development

Alexander N. Zakhartchouk, PhD*

Department of Veterinary Microbiology, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK S7N 5B4, Canada

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.

REFERENCES

1. McElrath MJ, De Rosa SC, Moodie Z, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: A case-cohort analysis. *Lancet*. 2008; 372(9653): 1894-1905. doi: [10.1016/S0140-6736\(08\)61592-5](https://doi.org/10.1016/S0140-6736(08)61592-5)
2. Havenga M, Vogels R, Zuijdgeest D, et al. Novel replication-incompetent adenoviral B-group vectors: High vector stability and yield in PER.C6 cells. *J Gen Virol*. 2006; 87(Pt 8): 2135-2143. doi: [10.1099/vir.0.81956-0](https://doi.org/10.1099/vir.0.81956-0)
3. Abel B, Tameris M, Mansoor N, et al. The novel tuberculosis vaccine, AERAS-402, induces robust and polyfunctional CD4⁺ and CD8⁺ T cells in adults. *Am J Respir Crit Care Med*. 2010; 181(12): 1407-1417. doi: [10.1164/rccm.200910-1484OC](https://doi.org/10.1164/rccm.200910-1484OC)
4. Hoft DF, Blazevic A, Stanley J, et al. A recombinant adenovirus expressing immunodominant TB antigens can significantly enhance BCG-induced human immunity. *Vaccine*. 2012; 30(12): 2098-2108. doi: [10.1016/j.vaccine.2012.01.048](https://doi.org/10.1016/j.vaccine.2012.01.048)
5. Tameris M, Hokey DA, Nduba V, et al. A double-blind, randomised, placebo-controlled, dose-finding trial of the novel tuberculosis vaccine AERAS-402, an adenovirus-vectored fusion protein, in healthy, BCG-vaccinated infants. *Vaccine*. 2015; 33(25): 2944-2954. doi: [10.1016/j.vaccine.2015.03.070](https://doi.org/10.1016/j.vaccine.2015.03.070)
6. Creech CB, Dekker CL, Ho D, et al. Randomized, placebo-controlled trial to assess the safety and immunogenicity of an adenovirus type 35-based circumsporozoite malaria vaccine in healthy adults. *Hum Vaccin Immunother*. 2013; 9(12): 2548-2557. doi: [10.4161/hv.26038](https://doi.org/10.4161/hv.26038)
7. Ouedraogo A, Tiono AB, Kargougou D, et al. A phase 1b randomized, controlled, double-blinded dosage-escalation trial to evaluate the safety, reactogenicity and immunogenicity of an adenovirus type 35 based circumsporozoite malaria vaccine in Burkina Faso healthy adults 18 to 45 years of age. *PLoS One*. 2013; 8(11): e78679. doi: [10.1371/journal.pone.0078679](https://doi.org/10.1371/journal.pone.0078679)
8. Baden LR, Karita E, Mutua G, et al. Assessment of the safety and immunogenicity of 2 novel vaccine platforms for HIV-1 prevention: A randomized trial. *Ann Intern Med*. 2016; 164(5): 313-322. doi: [10.7326/M15-0880](https://doi.org/10.7326/M15-0880)

9. O'Hara GA, Duncan CJ, Ewer KJ, et al. Clinical assessment of a recombinant simian adenovirus ChAd63: A potent new vaccine vector. *J Infect Dis.* 2012; 205(5): 772-781. doi: [10.1093/infdis/jir850](https://doi.org/10.1093/infdis/jir850)
10. Sheehy SH, Duncan CJ, Elias SC, et al. ChAd63-MVA-vectored blood-stage malaria vaccines targeting MSP1 and AMA1: Assessment of efficacy against mosquito bite challenge in humans. *Mol Ther.* 2012; 20(12): 2355-2368. doi: [10.1038/mt.2012.223](https://doi.org/10.1038/mt.2012.223)
11. Ogwang C, Afolabi M, Kimani D, et al. Safety and immunogenicity of heterologous prime-boost immunisation with Plasmodium falciparum malaria candidate vaccines, ChAd63 ME-TRAP and MVA ME-TRAP, in healthy Gambian and Kenyan adults. *PLoS One.* 2013; 8(3): e57726. doi: [10.1371/journal.pone.0057726](https://doi.org/10.1371/journal.pone.0057726)
12. Barnes E, Folgori A, Capone S, et al. Novel adenovirus-based vaccines induce broad and sustained T cell responses to HCV in man. *Sci Transl Med.* 2012; 4(115): 115ra111. doi: [10.1126/scitranslmed.3003155](https://doi.org/10.1126/scitranslmed.3003155)
13. Swadling L, Capone S, Antrobus RD, et al. A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory. *Sci Transl Med.* 2014; 6(261): 261ra153. doi: [10.1126/scitranslmed.3009185](https://doi.org/10.1126/scitranslmed.3009185)
14. Antrobus RD, Coughlan L, Berthoud TK, et al. Clinical assessment of a novel recombinant simian adenovirus ChAdOx1 as a vectored vaccine expressing conserved Influenza A antigens. *Mol Ther.* 2014; 22(3): 668-674. doi: [10.1038/mt.2013.284](https://doi.org/10.1038/mt.2013.284)
15. Milligan ID, Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia ankara-vectored ebola vaccines: A randomized clinical trial. *JAMA.* 2016; 315(15): 1610-1623. doi: [10.1038/mt.2013.284](https://doi.org/10.1038/mt.2013.284)
16. De Santis O, Audran R, Pothin E, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: A randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. *Lancet Infect Dis.* 2016; 16(3): 311-320. doi: [10.1016/S1473-3099\(15\)00486-7](https://doi.org/10.1016/S1473-3099(15)00486-7)