Improved DNA Vaccines: Shuffled Early Genes of the Human Papillomavirus Type 16 (P-974)

Key facts
- combination with adjuvant genes
- enhancing synergistically immune responses by DNA immunization
- genetic fusion can improve the immunogenicity of full-length and gene-shuffled DNA vaccines

Background
Cervical cancer is the second leading course of cancer-related death in women, causing approximately 250,000 deaths each year. Given the fact that infection with HPV viruses is evident in almost all cases and that vaccination against high-risk HPV viruses has been proven to be a valuable tool for cancer prevention, further improvement of vaccination is needed. The present invention offers a new method based on a "shuffled gene" technology using a combination with adjuvant genes to enhance synergistically immune responses by DNA immunization for the treatment of cervical cancer.

The Technology
To allow vaccination irrespective of HLA type, DNA vaccines encoding full-length antigens are required. However, here, we demonstrate that the immunogenicity of DNA vaccines encoding the full-length human papillomavirus (HPV) type 16 E7 and E6 proteins is highly reduced compared to vaccines encoding only the immunodominant epitope. Furthermore, the low remaining immunogenicity is essentially lost for both E7 and E6 when a nononcogenic "gene-shuffled" variant is utilized. To address these issues, we tested whether alterations in transgene design can restore the immunogenicity of full-length and gene-shuffled DNA vaccines. Remarkably, genetic fusion of E7 with tetanus toxin fragment C (TTFC) resulted in a dramatic increase in immunogenicity both for the full-length and the gene-shuffled version of E7. Moreover, the TTFC fusion vaccines were more immunogenic than a vaccine encoding a fusion of E7 and mycobacterial heat shock protein-70, which has recently been tested in a clinical trial. Interestingly, vaccination with these TTFC fusion vaccines also resulted in extremely persistent T-cell responses. The E7-specific CD8(+) T cells induced by TTFC fusion vaccines were functional in terms of IFN-γ production, formation of immunological memory, in vivo cytolytic activity and tumor eradication. Finally, we show that genetic fusion with TTFC also improves the immunogenicity of a gene-shuffled E6 DNA vaccine. These data demonstrate that genetic fusion with tetanus toxin fragment C can dramatically improve the immunogenicity of full-length and gene-shuffled DNA vaccines. The DNA fusion vaccines developed here will be evaluated for the treatment of HPV-positive carcinomas in future studies.

Development Stage
The technology is preclinical validated for further development of highly effective and safe DNA vaccines directed against HPV 16 E6 and E7.

Applications and Commercial Opportunity
The system can be used for manufacturing of a new cervical cancer vaccine using a combination with adjuvant genes to enhance synergistically immune responses by DNA immunization.

Inventors
References


Intellectual Property

The patent application “HPV derived polynucleic acids for therapy” EP 11009625.2 as well as the subsequent PCT application published as WO 2013/083287.

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Figure 1. Tumor regression by vaccination with the TTFC-E7SH fusion vaccine. C57BL/6 mice (n ¼ 5–7 per group) were injected with 1 × 105 TC-1 tumor cells on Day 0. Subsequently, mice were immunized by DNA tattoo vaccination on Day 3, 6 and 9 after tumor challenge with the indicated vaccines. Tumor sizes were determined by caliper measurements two to three times weekly. Peripheral blood was analyzed for antigen-specific CD8þ T cells by MHC tetramer staining. (a) Plot depicting the mean percentage 6 SD of H-2Db E749–57-specific CD8þ T cells for the indicated groups over time. (b) Plot depicting the mean tumor size 6 SD (mm3) for the indicated groups over time. (c) Plot depicting the percentage survival for the indicated groups over time.