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Published in:
Human Gene Therapy

DOI:
[10.1089/hum.2014.2536.abstracts](https://doi.org/10.1089/hum.2014.2536.abstracts)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Van De Wall, S., Ljungberg, K., Peng IP, P., Boerma, A., Nijman, H. W., Liljeström, P., & Daemen, T. (2014). Development of a next generation Semliki Forest virus-based DNA vaccine against cervical cancer. *Human Gene Therapy*, 25(11), A30. [OR018]. <https://doi.org/10.1089/hum.2014.2536.abstracts>

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Research (CDR) and Division of Pharmaceutical Bioscience, Faculty of Pharmacy University of Helsinki 3: Division of Pharmaceutical Bioscience, Faculty of Pharmacy University of Helsinki

Cancer is a lethal disease still in need of novel therapies. Oncolytic adenoviruses have been particularly successful in the last decade in different tumour types. Several groups, including ours, have highlighted that oncolytic adenoviruses are capable to trigger some degree of tumour-specific immunity as “side-effect” of the anti-viral immunity. To exploit this natural characteristic we have developed a strategy to generate immune privileged oncolytic adenoviruses that converts the anti-capsid immune response into anti-tumour immune response; we have called our system PeptiCrad. We first have developed and evaluated a system to conjugate peptides on viral capsid based on electrostatic interaction. By dynamic light scattering (DLS) and Surface Plasma Resonance (SPR) we have assessed the efficacy of our strategy and quantified the amount of peptides loaded on every single particle. Following we studied the mechanism of cross-presentation by antigen-presenting cells pulsed with PeptiCrad vs peptide alone or the combination of peptides and virus. Then we assessed the biological function of PeptiCrad with regard of cell entry (CAR positive and CAR negative cells), and infectivity in presence of neutralizing antibodies as well as the oncolytic activity. More importantly, using the murine melanoma model over-expressing chicken ovalbumin (B16-OVA) we have demonstrated that SIINFEKL-PeptiCrad (oncolytic virus loaded with OVA derived peptide) was able to completely eradicate tumors from B16-OVA bearing mice producing one log higher OVA specific immunity compared with mice treated with the same virus in combination with the same amount of OVA peptides but not loaded on the capsid. In conclusion we have developed a novel and rapid system to produce tumor-specific immune-privileged oncolytic viruses. The system is versatile, efficient and easy to adapt to different other strategies than only cancer oncolytic vaccines.

OR017

Lentiviral-based anti-HIV therapeutic vaccine: design, preclinical studies and phase I/II clinical trial preliminary results

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THERAVECTYS, a spin off the Pasteur Institute, develops a new generation of therapeutic vaccines using optimized lentiviral vectors. Its most advanced product, a therapeutic anti-HIV vaccine treatment, has entered clinical Phase I/II end of 2012. This vaccination should allow seropositive patients to gain an immunological status identical to the so-called “Sustainable Cured” patients who develop an efficient immunological response capable of controlling the infection without therapy. Vaccine candidates are integrative and self-inactivated live-recombinant lentiviral vectors. They have been classified as “Live recombinant vectored vaccines” (EMA, 2011). Preclinical studies demonstrated i) the generation of a strong, specific and very long lasting T-cell immune response (up to 2 years in

murine animal models), ii) the restricted diffusion of the vaccine candidates after injection and iii) their fast disappearance within few weeks, correlated with an absence of macroscopic and microscopic toxicity. These data allowed the settlement of the anti-HIV therapeutic Phase I/II clinical trial that is held in France and Belgium and that has ended the enrollment of the 36 HIV-1 infected patients. THERAVECTYS’ anti-HIV vaccine treatment is assessed at three doses and safety, tolerability and immunogenicity compared to a placebo group. Furthermore, vaccine efficiency is being evaluated by the interruption of the HAART treatment in all patients, including placebo. Final results are expected by 2014 and intermediary results will be presented.

OR018

Development of a next generation Semliki Forest virus-based DNA vaccine against cervical cancer

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Cervical cancer is the second most prevalent cancer among women worldwide. The disease develops as a result of infection with high-risk human papillomavirus (HPV) through persistent expression of early proteins E6 and E7 with transforming capacities in cervical epithelial cells. Our group pioneered the application of a replication-defective recombinant viral vector system based on Semliki Forest virus (SFV) for vaccination against cervical cancer. In preclinical studies, we demonstrated that recombinant SFV (rSFV) encoding HPV E6 and E7 (rSFVeE6,7), induces robust HPV-specific cellular immune and memory responses upon intramuscular (i.m.) administration in mice resulting in excellent therapeutic anti-tumour efficacy. Despite the clear potency of the SFV vector system, there are a number of inherent challenges. These include manufacturing costs, shelf-life and anti-vector responses. DNA vaccination is an alternative method with the potential to be inexpensive and safe. In this project, the drawbacks associated with both SFV-based vaccines and DNA vaccines are circumvented with the development of a DNA vaccine based on the SFV replicase (DREP). This next generation vaccine will exploit the advantages of both strategies for the development of an immunotherapeutic response against cervical neoplasia by encoding the fusion protein eE6,7 (DREPeE6,7). Our initial results show that upon intradermal delivery via electroporation of mice with DREP-eE6,7, similar E7-specific responses were elicited as compared to i.m. administration of rSFVeE6,7. These results will be further confirmed for assessment of therapeutic efficacy using a TC-1 tumor model.

OR019

ORCA-010, a novel potency enhanced oncolytic adenovirus, exerts strong antitumor activity in preclinical models

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