



Editorial

## Tailoring Adeno-Associated Virus Vectors for Cancer Immunotherapy

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Cancer is a one of the leading cause of the death word-wise. Surgery, radiation and chemotherapy are widely used to treat cancer patients, tend to be largely successful, however they all have serious side effects and undermine the health of patients already weakened by cancer. Development of alternative strategies to increase selective cytotoxicity for tumor cells and effectively control tumor growth with limited adverse side effects is necessary.

Immunotherapy represents an attractive alternative to currently used anti-cancer treatments. Although a naturally occurring anti-tumor immune response is detectable in patients, this response fails to control tumor growth. On the other hand, monocyte-derived dendritic cells (moDCs), generated *ex vivo* in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 4 (IL-4), possess the capacity to stimulate antigen-specific T-cells after endogenous expression of antigens. For this reason, genetically-modified DCs have been extensively studied and numerous Phase I and II clinical trials evaluating the efficacy of DC-based therapy in patients with cancer have been initiated. *In vivo*, DCs take up and process antigen, migrate to T-cell rich tissues, present the antigen as peptides within major histocompatibility (MHC) molecules to T-cells with additional stimulatory signals to cause specific T-cell clone proliferation. In the case of using DCs for therapeutic applications, desired tumor specific antigen should be efficiently delivered to DCs. Although tremendous progress has been made in past decade particularly for immunotherapy for prostate cancer with first therapeutic vaccine approved by FDA in 2010, current methods for DC loading are inadequate in terms of cell viability, uncertainty regarding the longevity of antigen presentation, and the restriction by particular patient haplotypes.

The widely used approaches for achieving satisfactory antigen presentation by DCs includes loading DCs with antigen in the form of whole protein or peptide, otherwise naked or lipid encapsulated plasmid DNA, and naked RNA used for endogenous expression. The

possibility of manipulating viral genomes and the natural ability of viruses to efficiently infect various cell types has increased an interest in using a virus-based delivery system to express antigens in DCs in the anticipation of inducing a protective antitumor immune response in patients. Among different viral methods for gene delivery, vectors based on a human parvovirus, the adeno-associated virus (AAV), have attracted much attention mainly because of the non-pathogenic nature of this virus, lack of toxicity to infected cells, and its ability to mediate long-term, sustained therapeutic gene expression. AAV vectors as a safe and efficient delivery vehicle are currently in use in a number of clinical trials, such as hemophilia B, Parkinson's disease, muscular dystrophy, and ocular diseases. Successful transduction of different subsets of DCs by different commonly used serotypes of AAV vectors has been demonstrated and the potential advantage of an AAV-based antitumor vaccine discussed. However in our previous studies, it has become clear that naturally occurring serotypes of AAV vectors are not optimal for transduction of a number of cell types, including DCs, and their efficacy can be significantly enhanced by modifying the surface-exposed amino acids on their capsid, such as tyrosine, serine or threonine. These residues play important role in intracellular trafficking of AAV vectors, thus they can be phosphorylated by cellular kinases widely expressed in various cell types and tissues and provide signal for subsequent ubiquitination and proteasome-mediated degradation of the vectors. These studies have led to the generation of a number of vectors with increased transduction efficiency in monocyte-derived dendritic cells (moDCs) [1]. It is also important that one of the main obstacles, the induction of immuno-competition in cellular immune responses against vector-derived and transgene-derived epitopes, can be overcome with new AAV vectors by the fact that less capsid modified viral particles will be degraded by host proteasomes and thus, provide less material for presentation.

Taken together, these data suggest that high-efficiency transduction of moDCs by capsid-modified AAV vectors is indeed feasible, which supports the potential utility of these vectors for future human DC vaccine studies. However, further improvements in gene transfer by recombinant AAV vectors to DCs in terms of specificity and transduction efficiency are warranted to achieve a significant impact when used as an anti-tumor vaccine.

### Reference

1. Aslanidi GV, Rivers AE, Ortiz L, Govindasamy L, Ling C, et al. (2012) High-efficiency transduction of human monocyte-derived dendritic cells by capsid-modified recombinant AAV2 vectors. *Vaccine* 30: 3908-3917.

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