Development of a next generation dendritic cell-based immunotherapy for patients with castration-resistant prostate cancer

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Prostate cancer is the second leading cause of cancer death in men. Anti-androgen therapy is the treatment of choice for patients diagnosed with metastatic disease. However, cancer growth progresses despite hormone ablation therapy in almost all patients after 2-3 years, resulting in castration-resistant prostate cancer (CRPC). CRPC patients have a poor prognosis and current treatment options can prolong overall survival for only a few months. Therefore, novel efficient therapeutic approaches are urgently needed.

Active immunotherapy using *ex vivo* generated dendritic cells (DCs) represents a promising treatment option - and the capacity of DC-based vaccines for activation of tumor-specific T cell responses has been demonstrated in numerous clinical trials. However, the clinical benefit is still not satisfactory. We have developed a new generation of DCs with improved immunogenicity and optimized for the use in cell-based immunotherapy of cancer. Currently this new generation of DCs is analyzed in a clinical trial phase I/IIa for the treatment of patients with acute myeloid leukemia using leukemia-associated antigens. In order to develop a DC vaccine formulation for the treatment of CRPC as a solid tumor indication, we performed an extensive preclinical evaluation of DCs expressing tumor antigens (TAs) associated with prostate cancer.

Monocyte-derived mature DCs were generated from healthy donors within three days by using a maturation cocktail containing a synthetic TLR7/8-agonist. DCs were loaded with mRNA encoding for different TAs and cryopreserved. After thawing DCs were analyzed regarding antigen expression, phenotype and function. Expression of TAs was high and not altered by cryopreservation. Additionally, DCs expressed high levels of CD83 and were negative for CD14, demonstrating a mature phenotype. Moreover, the expression of costimulatory molecules CD80, CD86 and CD40 was high compared to expression of inhibitory molecules CD274 and CD273. DCs secreted high levels of bioactive IL-12p70 and only low levels of IL-10, highlighting their capacity to polarize immune responses towards the Th1/Tc1 phenotype. Furthermore, TA-expressing DCs also had the capacity to induce antigen-specific T cell responses *de novo*.

These studies demonstrated the high potential of our vaccine cells for the activation of anti-tumor immune responses in prostate cancer. The three best candidate antigens will be selected for the final vaccine formulation.