Tailoring immunotherapies for patients with different stages of prostate cancer

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Prostate cancer (CaP) has been historically regarded as a non-immunogenic cancer but several clinical trials using different vaccine strategies have induced anti-tumor immunity and clinical responses. In the past an investigator-initiated clinical phase I vaccine trial was performed using the allogeneic LNCaP cell line, gene modified to express recombinant IL-2 and IFN-gamma (*Brill, T.H., Kübler, H.R., Pohla, H., Buchner, A., Fend, F., Schuster, T., von Randenborgh, H., Paul, R., Kummer, T., Plank, C., Eisele, B., Breul, J., Hartung, R., Schendel, D.J. and B. Gansbacher. 2009. Therapeutic vaccination with an IL-2-IFNgamma-secreting allogeneic tumor vaccine in patients with progressive castration-resistant prostate cancer – a phase I/II trial. Hum. Gene Ther. 20(12): 1641-51*). HLA-A2-matched study patients (n=30) received up to six vaccine applications over a period of 270 days. Primary objectives were safety and toxicity and assessment of PSA doubling-time. The secondary objective was assessment of immune responses, whereby an extensive analysis was made by ELISpot assays of T cell responses to thirteen tumor-associated antigens (TAA) overexpressed by the vaccine cells and found to be commonly expressed by metastatic lesions of CaP patients. Increases in antigen-specific T cells were observed for several different HLA-A2-restricted T cell epitopes. Based on the frequency of T cell responses seen post-vaccination, seven TAAs were considered as lead candidates for further immunotherapy development.

In a first approach for immunotherapy of CaP, we utilized our established protocol for generating patient-individualized dendritic cell (DC) vaccines that use fast (3-day) mature DCs that are induced to secrete bioactive IL-12 through TLR7/8 activation (*Frankenberger B, Schendel DJ. Third generation dendritic cell vaccines for tumor immunotherapy. Eur J Cell Biol. 2012 Jan;91(1):53-8. Review*). The seven selected TAAs were introduced individually into mDCs using in vitro transcribed RNA (ivt-RNA) as the source of antigen. Recipient cells were then extensively characterized in vitro to determine which of the TAAs provided mDCs with desired antigen expression and function. From these studies, three TAAs have been chosen for a tailored DC vaccine formulation using defined antigens. This form of immunotherapy is best suited for use in high-risk patients who have undergone surgery or radiation therapy, or in combination with hormone ablation, to build complex immune responses that may limit or prolong time to relapse in patients with low tumor burdens, in order to allow time for effective immune responses to be generated in the absence of systemic immunosuppression caused by higher tumor burdens.

In a second immunotherapy approach for patients with more advanced disease, we immunized mice bearing a human TCR repertoire (*Li LP, Lampert JC, Chen X, Leitao C, Popović J, Müller W, Blankenstein T. Transgenic mice with a diverse human T cell antigen receptor repertoire. Nat Med. 2010 Sep;16(9):1029-34*), with a series of different HLA-A2-restricted peptide epitopes derived from our lead TAAs. Here we assessed the capacity of these peptides to induce T cell responses in the mice with the use of IFN-gamma capture or MHC-multimer binding assays. In those mice showing responses, the T cells were isolated and their TCRs further characterized. In this way, a library of lead TCR candidates is selected for further development of adoptive T cell therapy using TCR-engineered lymphocytes. This form of immunotherapy is foreseen for use in patients who have high tumor burdens which no longer respond to current therapy regimens.

Sequential ex vivo, in vitro and in vivo approaches have provided important insight into suitable antigens for targeting immunotherapies to CaP and allow DC vaccines and TCR gene therapies to be tailored for use according to antigen expression and stage of disease of the patient.

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