

Presentation at Neoantigen Summit 2016 in Boston (USA) on 16 November:

Targeting neoantigens by TCR therapy: Are we limited to treatment of tumors with high-mutational loads and patients with pre-existing neoantigen-specific T cells?

Dolores J. Schendel, CEO and CSO Medigene AG, Munich Germany

Several facts currently shape our considerations regarding the use of neoantigens as highly specific target antigens for immunotherapy of cancer. First, adoptive T cell therapy using tumor-infiltrating lymphocytes (TILs) seems to be most successful if the TILs that are expanded ex vivo and reinfused into patients include T cells specific for individual tumor mutations.

Second, the success of checkpoint inhibitors is correlated with the mutational load of tumors leading to the interpretation that, in line with adoptive TIL therapy, responding tumors carry TILs specific for mutated epitopes displayed by the tumor cells. "Hot" tumors that contain many TILs indeed seem to respond better to checkpoint inhibition than "cold" tumors lacking TILs. Missing tools which allow an easy assessment of neoantigen-specific T cells among TILs unfortunately limit a broad proof of these contentions. However, animal models have demonstrated that T cells with specificity for a single mutation can eradicate large tumor burdens, experimentally providing proof of concept for the power of neoantigens as tumor targets. Still, not all tumor mutations seem to be equal; i.e. despite being processed and presented by MHC molecules some mutations are visible to efficacious T cells whereas others are not (see e.g. Leisegang et al. J.Clin.Invest. 2016).

Therefore, targeting neoantigens as true patient-individualized epitopes encompasses a number of hurdles: identification of potential neoantigens must be made for patients contingent upon differing HLA allotypes and varying T cell visibility. Assessment of safety becomes paramount given that neoepitopes may differ by only one residue from the normal cellular protein. In addition, a plethora of mutations as potential targets presents the necessity to have in place robust processes for rational, rapid selection and validation of neoantigens as T cell targets. Last but not least, the regulatory pathway that would allow marketing of neoantigen-specific immunotherapies that are individualized for each patient remains to be elucidated.

The current central challenge is to understand whether neoantigens are accessible as targets only for tumors of high mutational burden and/or limited to patients with pre-existing neoantigen-specific T cells. Medigene uses its immunotherapy platform technologies to investigate neoantigens as future targets for vaccines and adoptive T cell therapies and various concepts and approaches will be presented and discussed.