Tuning TCR Immunotherapy Targeting Prostatic Acid Phosphatase via Catchbond Modifications for Advanced Prostate Cancer

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Late-stage prostate cancer is an incurable disease with no effective therapy currently available. 20-30% of patients receiving local therapy will experience disease relapse. The rise in serum prostate-specific antigen (PSA) level in these patients is often described as biochemical recurrence. This stage of prostate cancer, when micro-metastasis has occurred and overall tumor burden is low, can be a critical time window for cell-mediated immunotherapy. We aim to develop T cell receptor (TCR) immunotherapy targeting prostatic acid phosphatase (PAP) to treat patients with chemically recurrent prostate cancer. Elevated expression of PAP is commonly observed in early and late stages of prostate cancer. PAP was previously used to develop the first FDA-approved cancer vaccine, Provenge, but the specific epitopes and cognate TCRs were not clearly defined. Our group has profiled the immunopeptidome of PAP on HLA-A*02:01 using a secreted MHC-based platform (ARTEMIS), and successfully isolated multiple TCRs reactive with PAP. Recent results have also demonstrated that further engineering with "catch bonds" on these candidate TCRs lead to dramatically improved cytotoxicity both in vitro and in vivo. This work demonstrated the feasibility of developing and enhancing TCRs targeting PAP for potential therapeutic usage.

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