

A Novel CD3xPSMA Bispecific Antibody for Efficient T Cell Mediated Killing of Prostate Tumor Cells with Minimal Cytokine Release

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Background

Castration resistant prostate cancer remains an incurable disease, and new therapeutics are urgently needed. Prostate specific membrane antigen (PSMA) is highly expressed on the surface of prostate cancer cells and expression increases with disease progression. Therapies directed against PSMA, such as radiolabeled antibodies, have shown promising results in clinical trials, validating this molecule as a target for the treatment of CRPC. T-cell recruiting bispecific antibodies (T-BsAbs) have demonstrated potent tumor killing activity, however cytokine release-related toxicities present significant limitations in the clinic. Novel anti-CD3 engaging domains with more favorable properties may be required to create T-BsAbs with a broader therapeutic window. Using our unique antibody discovery platform, we developed fully human CD3xPSMA bispecific antibodies that efficiently eliminate prostate tumor cells with minimal cytokine release.

Methods

Antibodies targeting CD3 and PSMA were generated through immunization of transgenic rats engineered to produce human antibodies (UniRat™, OmniFlic™). Monoclonal antibodies were then isolated by repertoire deep sequencing of lymph nodes isolated from immunized animals, followed by high-throughput gene assembly and recombinant expression. Bispecific antibodies targeting CD3 and PSMA were assembled and evaluated for their ability to activate primary human T cells and to selectively eliminate PSMA+ tumor cells *in vitro*. T cell activation surface markers, cytokine production and tumor cell cytotoxicity were measured.

Results

Primary human T cells were activated only in the presence of both bispecific CD3xPSMA antibodies and PSMA (either plate-bound or on the surface of tumor cells). Potent and selective cytotoxicity against PSMA+ prostate tumor cells was observed in co-cultures of primary human T cells and tumor cells treated with CD3xPSMA bispecific antibodies. Strikingly, CD3xPSMA bispecifics containing a novel low affinity anti-CD3 domain produced similar levels of tumor cell cytotoxicity compared to CD3xPSMA bispecifics containing a traditional high affinity anti-CD3 domain, but with reduced cytokine production.

Conclusions

We have created novel CD3xPSMA bispecific antibodies that mediate T-cell killing of PSMA+ tumor cells with minimal production of cytokines. Such T-BsAbs may improve safety, efficacy, and opportunities for combination therapy to treat CRPC.

Conflict of Interest: All authors are employees of Teneobio Inc, with equity interests.

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