CD3-bispecific T cell engager (TCE) therapies have exhibited clinical utility against hematological malignancies, but successes in solid tumor indications have been limited. Compared to hematological malignancies, treatment of solid tumors is hindered by immunosuppressed microenvironments that can be refractory to traditional CD3 bispecific TCEs. Immunosuppression in the tumor microenvironment limits access to tumor cells and inhibits the function of T cells.

In this study, we evaluated the activity of tri-specific TCEs (TriTEC) with different valencies for PD-L1-dependent T cell responses. The TriTCE CPI formats were evaluated for their ability to modulate T cell activation in the presence of PD-L1 expressing DCs in co-culture assays.

**TriTCE CPIs Induce TAA-dependent T Cell Cytotoxicity and PD-1/PD-L1 Checkpoint Blockade**

**Lead TriTCE CPI Formats were Identified by TAA-dependent Cytotoxicity and PD-1/PD-L1 Checkpoint Blockade Activity**

**TriTCE CPIs Contain a PD-1 Domain Engineered to have Increased Affinity for PD-1 Relative to Wild Type PD-1**

**Different TriTCE CPI Geometries Were Screened to Identify Formats Where Addition of Affinity-engineered PD-1 Domain Potentiated Increased T cell-dependent Cytotoxicity**

**Conclusions**

We have generated multiple TriTCE CPI antibodies that combine tumor-dependent T cell cytotoxicity with checkpoint blockade, which may translate to improved T cell responses in immunosuppressed solid tumors. Zymeworks’ Asymmetric™ technology serves as a versatile platform to generate multispecific TCEs with different molecular architectures to identify antibody formats with enhanced avidity-driven tumor cell binding, TAA-dependent anti-tumor activity, and PD-1/PD-L1 checkpoint blockade. These novel molecular design characteristics may widen the TCE therapeutic index and lead to improved clinical outcomes.

**References**

2. This study was sponsored by Zymeworks Inc.