438 IN VIVO ENGINEERED CAR-T CELLS FOR ONCOLOGY USING A SURFACE-ENGINEERED LENTIVIRUS PLATFORM: NONCLINICAL SAFETY AND BIODISTRIBUTION

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Background Chimeric antigen receptor (CAR) T cell therapy has demonstrated transformative outcomes in hematologic malignancies; however, many challenges remain, such as manufacturing complexity, high cost, requirements for lymphodepletion, and poor product persistence. To overcome these challenges, Umoja has developed VivoVec, a scalable, off-the-shelf lentiviral vector platform designed to drive efficient and targeted in vivo T cell transduction following direct administration to patients. VivoVec particles are surface-engineered with the cocal fusion glycoprotein and incorporate an anti-CD3 single chain variable fragment (scFv) and T cell costimulatory ligands on the particle surface to promote T cell binding, activation, and transduction. Here, we present preclinical studies demonstrating the biodistribution and preliminary safety of the VivoVec platform when delivered via either intranodal (IN) or intravenous (IV) routes of administration (ROAs).

Methods VivoVec particle selectivity for T cell binding and transduction was assessed in vitro using PBMCs. Toxicology and biodistribution studies were conducted in canines and humanized mice. A surrogate ROA was used (intraperitoneal) in mice as IN is not feasible.

Results VivoVec particles cultured with unprimed human PBMCs in vitro selectively bind, activate, and transduce CD3+ T cells with no detectable transduction of other immune cell subtypes. VivoVec particles displayed high selectivity and avidity for T cell binding within 5 minutes of incubation. In vivo toxicology studies demonstrate a favorable safety and biodistribution profile. VivoVec administered to canines was well tolerated and resulted in transduction that was largely restricted to the injected lymph nodes when delivered IN Evaluation of VivoVec safety and biodistribution in the presence of human CD3+ T cells was performed in CD34-humanized NSG mice. IP or IV administration of up to 4 $\times 10^7$ VivoVec transducing units was well tolerated; efficacy in humanized mouse models (B cell aplasia and tumor clearance) is observed at these doses. Comprehensive tissue analysis via qPCR at 1–13 weeks post treatment primarily detected vector copies in the liver, spleen and injection site, and RNA in situ hybridization analysis demonstrated that the predominant cell types expressing the viral payload were human T cells and murine macrophages.

Conclusions Nonclinical studies in two species demonstrate a favorable VivoVec safety and biodistribution profile following multiple ROAs. These findings support the potential of the VivoVec platform to generate safe and effective CAR T cells in vivo, which could expand patient access to CAR T technology in both hematologic and solid tumors without the need for ex vivo cell therapy manufacturing or lymphodepletion.

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