

and NK cells in a dose-dependent manner, and reduces growth of established tumors in vivo. This preclinical data, demonstrates conditional dual stimulation of 4-1BB and OX40 and supports further development of APVO603, a promising immuno-oncology therapeutic with potential for benefit in solid tumors.

Ethics Approval Treatment of study animals was in accordance with conditions specified in the Guide for the Care and Use of Laboratory Animals, and the study protocol (ACUP 20) was approved by the Institutional Animal Care and Use Committee (IACUC).

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PRODUCTION AND TESTING OF A NOVEL BISPECIFIC NANOBODY CONSTRUCT TARGETING NK CELLS AND EGFR EXPRESSING MALIGNANCIES

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Background The ability to kill tumor cells with an acceptable toxicity profile, makes Natural Killer (NK) cells promising assets for cancer therapy. However, strategies to enhance the preferential accumulation and activation of NK cells in the tumor microenvironment would likely increase the efficacy of NK cell-based therapies.

Methods In this study, we show a novel bispecific nanobody-based construct (biVHH) targeting both CD16A (low-affinity Fc receptor: FcRγIIIa) on NK cells and EGFR on tumors of epithelial origins.

Results Higher levels of NK cell activity and subsequent tumor cell lysis were found in vitro in the presence of the biVHH and were dependent on the expression of both CD16A and EGFR while they were independent of the KRAS mutational status of the tumor. Increased NK cell activity was found in NK cells derived from colorectal cancer (CRC) patients when co-cultured with the biVHH and EGFR expressing tumor cells. Finally, higher levels of cytotoxicity were found against patient-derived metastatic CRC cells in the presence of the biVHH and autologous peripheral blood mononuclear cells or allogeneic NK cells.

Conclusions Based on our results, the bispecific CD16A and EGFR targeting VHH construct could be a useful tool in combination with various NK cell-based therapies.

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A NOVEL SITE-DIRECTED CHEMICAL CONJUGATION TECHNOLOGY CONFERS ANTITUMOR ACTIVITY VIA NATIVE FC RECEPTOR TO PLASMA IMMUNOGLOBULIN BY ATTACHING TUMOR BINDERS

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Background We describe KPMW101, which was created by chemical conjugation of a CD38-specific binder to clinical

grade intravenous immunoglobulin (IvIg) pooled from healthy donors. Kleo's MATE™ technology enables efficient site-directed chemical conjugation to 'off-the-shelf' IvIg and allows the development of antitumor agents with rapidly introduced target specificity. Our platform allows for chemical engineering of existing IvIg in a cost-efficient manner. This technology relies on synthetic compounds that consists of antibody binder with react-and-release mechanism.

Methods Design of synthetic chemical reagents included antibody binding group capable of covalent bond formation with specific lysine, CD38 binding moiety proven to work in our clinical candidate KP1237, and tunable non-cleavable linker. Conjugation efficiency to polyclonal IvIg was evaluated using LC-MS analysis of IdeZ-digests. The binding of CD38, CD16a, and FcRn were determined by ELISA and BLI. For in vitro ADCC assays, PBMCs provided NK effector function. Daudi (CD38⁺) B lymphoblast cells were treated with KPMW101 or IvIg, PBMCs were introduced and incubated for 18h, and target cellular death was measured. For an in vivo IP macrophage lavage model of ADCP, SCID mice were implanted IP with CFSE-labeled Daudi cells. Mice were injected with IvIg or KPMW101 (0.21, 0.625, 1.875 mg/kg) SQ, and tumor cell counts were measured by flow cytometry. The pharmacokinetic profile of in vivo KPMW101 was determined from blood and analyzed utilizing a human Ig isotyping array.

Results Synthetic chemical reagents with multiple linker types have been conjugated to IvIg and evaluated in biochemical assays. KPMW101 showed the highest conjugation efficiency. Binding affinity of KPMW101 to CD38 was 27nM. ELISA results show KPMW101 binds to CD16a and FcRn, indicating that conjugation does not interfere with FcR binding. In vitro ADCC results demonstrate that KPMW101 elicited CD38⁺ target cell killing with an EC₅₀ of 0.91–2.09nM. In vivo studies showed that KPMW101 resulted in a 49.9–63.5% reduction of tumor cells. Pharmacokinetic profile showed stability of KPMW101 throughout the 144-hour study, whereby IgG1, IgG2, IgG3, and IgG4 isotypes were detectable.

Conclusions KPMW101 is created by chemical conjugation of CD38-specific binder to IvIg using our proprietary MATE™ technology, maintaining native binding to FcRs via the Fc domain. This ensures the stability of the molecule and retains immune-mediated mechanisms of action. KPMW101 induces IvIg to adopt Fc effector mechanisms like ADCC and ADCP. Our in vitro data and in vivo studies confirm KPMW101 ability to kill tumor cells, making IvIg into an active antitumor therapeutic agent.

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Immunotherapy toxicities

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IMMUNE-RELATED ADVERSE EVENTS (IRAE) MAY INDICATE A FAVORABLE PROGNOSIS IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS (ICI)

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Background Immune checkpoint inhibitors (ICI) have become an increasingly utilized treatment in metastatic renal