SQ2270, A NOVEL MMAE-BASED THERAPEUTIC, PROMOTES TUMOR GROWTH INHIBITION AND EXTENSIVE IMMUNE CELL INFILTRATION IN THE RENCA CANCER MODEL

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Background The CAPAC™ platform aims to help patients beat cancer by activating powerful therapies at the tumor site while minimizing systemic exposure. The click chemistry-based technology is highly modular and can be applied to a broad range of cancer drugs whose use is limited by toxicity.

The platform consists of an intratumorally injected biopolymer and an intravenously administered protodrug. Efficient reaction between the biopolymer and prodrug releases the active drug in situ. SQ3370, the lead asset, uses a Doxorubicin protodrug and is being evaluated in a Phase 1 clinical trial in solid tumors (NCT04106492).

We’ve developed a new protodrug of monomethyl auristatin E (MMAE) and demonstrated its antitumor efficacy when combined with the biopolymer in two tumor models. Here, we performed analyses of immune infiltration into syngeneic tumors that were treated with this novel therapeutic, SQ2270.

Methods SQ2270 treatment is described in figure 1. Immunocompetent mice were inoculated with RENCA tumor cells. The biopolymer was given intratumorally and MMAE protodrug was given intravenously. Control groups—vehicle and MMAE (1 mg/kg), were treated intravenously. After 2 weeks, tumors were harvested, and immune infiltration was assessed by flow cytometry and immunofluorescent (IF) analyses. Tumor histology was evaluated by H&E staining.

Results SQ2270 and MMAE control significantly inhibited growth of RENCA tumors compared to vehicle (p<0.0001). Histological analysis indicated increased stromal cell infiltration, extracellular matrix deposition, and presence of large phagocytic cells in SQ2270- and MMAE-treated tumors. Flow cytometry indicated >110-fold increase in CD45+ cells fraction of SQ2270-treated tumors compared to vehicle (41% vs 0.4%, p=0.01). MMAE, on the other hand, expanded the CD45+ fraction in tumors by 27-fold (10% vs 0.4%, p=0.0004). SQ2270-treated tumors showed significant increases in several immune populations compared to vehicle, including CD3+, CD8+ (including activated and PD-1+) and CD4+ T-cells, NKT-cells, and activated NK cells. MMAE-treated tumors exhibited less pronounced increases. IF analysis supported these findings, showing increased frequencies of total and Granzyme B-positive CD8+ T-cells in SQ2270-treated tumors compared to controls.

Conclusions SQ2270, CAPAC’s novel MMAE-based candidate, is a potent anticancer therapeutic. Here, we show that it also activates an anti-tumor immune response through an extensive immune cell infiltration. Several immune cell types infiltrate the SQ2270-treated tumors where they become activated, including cytotoxic CD8+ T-cells.

Ethics Approval These studies, project numbers SQONCO22-001 and SQONCO22-002, were approved by the Institutional Animal Care and Use Committee (IACUC) of the vendor, following the guidance of Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), accreditation number 001738.

Abstract Figure 1 The CAPAC Platform
(1) Biopolymer click reagent (e.g., SQL70 biopolymer) is locally injected at the tumor area. (2) Protodrug, an attenuated therapy activated by click chemistry, is infused systemically. (3) Protodrug is captured by its click chemistry partner through a rapid covalent reaction between tetrazene and TCO moieties, followed by localized release of the active drug.