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CURRENT CATEGORY: Basic Science

TITLE: SQ3370, A NOVEL APPROACH TO LOCALLY CAPTURE AND ACTIVATE CYTOTOXIC DRUGS, PRODUCES SUSTAINED RESPONSES IN INJECTED AND NON-INJECTED LESIONS VIA IMMUNE ACTIVATION IN PRECLINICAL MODELS.

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ABSTRACT BODY:

Objective: Conventional chemotherapy is the gold standard for treating a variety of solid tumors, but it's effectiveness is limited by systemic off-target toxicity. Here, we present SQ3370, a modular chemistry-based approach that allows the capture and activation of therapeutics at a tumor site. In contrast to mAbs, ADCs, and other targeted/precision medicine approaches, SQ3370 is independent of biomarkers, enzymatic activity, pH or oxygen levels. SQ3370 consists of a local intratumoral injection of a prodrug-capturing biomaterial (SQL70) followed by 5 daily systemic infusions of SQP33, an attenuated prodrug of doxorubicin (Dox). Complementary chemical groups in the 2 components allow the local capture of the prodrug and trigger release of active Dox at the tumor site. Through this local activation approach, SQ3370 allows higher doses to be given systemically with reduced side effects, overcoming the toxicity limitations of conventional Dox. Our team first introduced the concept1 and showed enhanced safety and efficacy in a mouse fibrosarcoma model2. Here, we show that SQ3370 produces a sustained anti-tumor response against both injected and noninjected lesions. In addition, we show the pharmacokinetic (PK) profile and tolerability of SQ3370 given at high doses in different species.

SQ3370 is being tested in a Phase I open-label dose escalation first-in-human clinical trial in patients with advanced solid tumors. (A separate trial-in-progress abstract has been submitted.)

References: 1. JM Mejia Oneto, et al., Acta Biomaterialia, 2014. 2. JM Mejia Oneto, et al., ACS Central Science, 2016.

Methods: The pharmacokinetic profile of SQ3370 was evaluated in rats and the safety profile of SQ3370 was evaluated in dogs, the most relevant species for Dox. In mice, two subcutaneous flanks were inoculated with MC38 tumor cells. One tumor was injected with SQL70 biomaterial, while the other remained non-injected. SQP33 was then given in 5 daily intravenous doses. Tumors were harvested from a subset of mice at 2 weeks and were assessed for infiltrating immune biomarkers.

Results: The greater safety of SQ3370 allows significantly higher doses to be administered compared to conventional Dox. The PK profiles in rats demonstrated that SQL70 biomaterial efficiently captures and activates the prodrug. Safety evaluation in dogs showed that SQ3370 allowed up to 8.95-fold increase in Dox dosing with minimal systemic adverse events including cardiotoxicity. Further, in mice bearing two flank tumors, SQ3370 significantly increased median overall survival and sustained tumor regression of injected and non-injected tumors. Tumor biomarker analyses indicate immune activation with increased total infiltrating T cells in both lesions, increased CD8+ T cells in the injected lesions and decreased regulatory T cells in the non-injected lesions. Together, the data suggest that the anti-tumor response is mediated by immune activation via immunogenic cell death (ICD).

Conclusion: SQ3370 is a novel therapeutic modality to treat solid tumors by using a known effective cytotoxic, Dox, and unlocking its dosing capabilities while minimizing its off-target toxicity. SQ3370's systemic anti-tumor effect could greatly benefit patients with undetectable micro-metastatic or widely disseminated lesions. SQ3370 is the first proof-of-concept of the local capture and activation technology. In the future, this platform could be applied to a variety of cytotoxics and other anti-cancer drugs improving their efficacy and minimizing their systemic toxicity.

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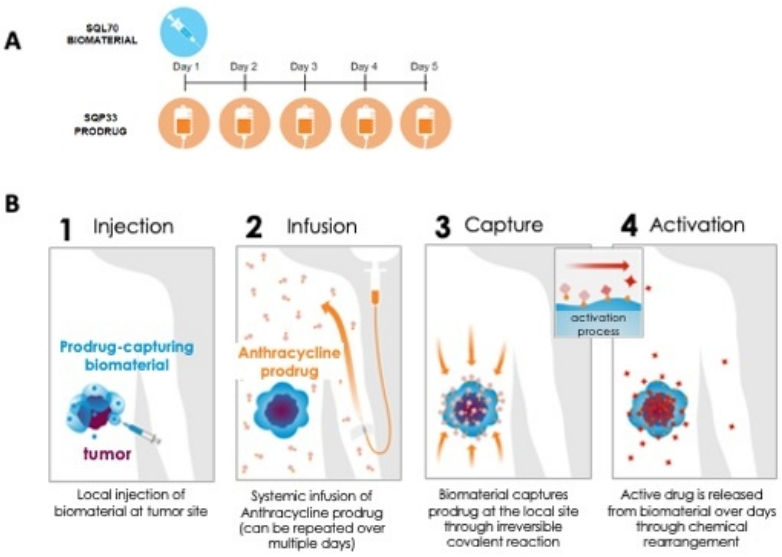
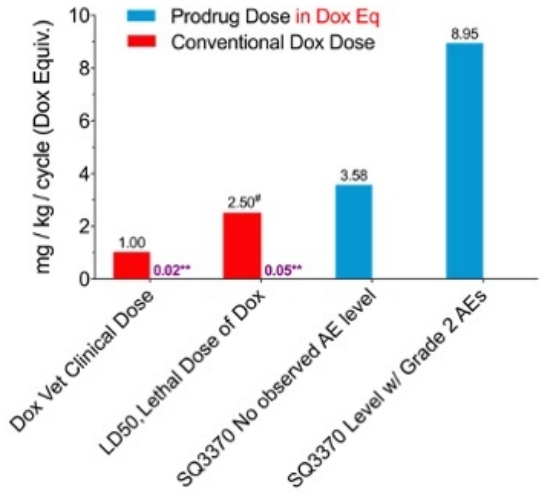


Figure 1. SQ3370 Investigational Product. (A) Treatment cycle and (B) Mechanism of Local Capture and Activation.



* Doxorubicin exposure to tumor,
# C. Bertazzoli et. al. Toxicol. Appl. Pharmacol, 1985; 79:412-422.
** C. Li et. al. J. Nuc. Med. 1997, 38, 1042 - 1047
ζ Grade 2 AE level corresponds to highest non-severely toxic dose (HNSTD)
Dox Eq = Doxorubicin equivalents

Figure 2. Dose Comparison of SQ3370 with Conventional Doxorubicin in Dogs (GLP Toxicology)

Abstract ID - 3465109

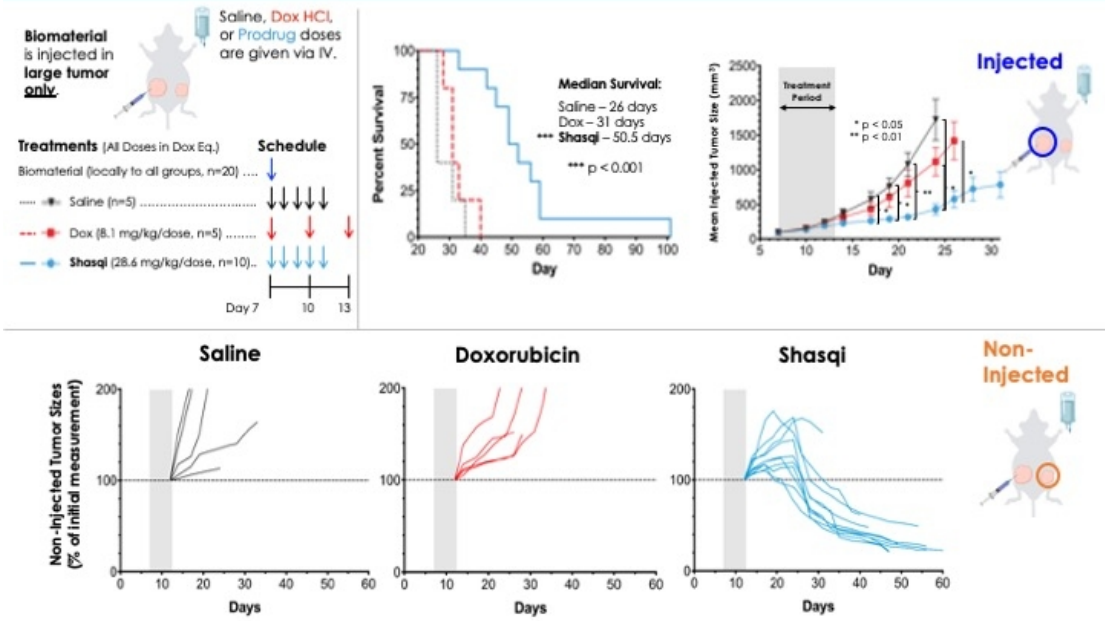


Figure 3. SQ3370 induced systemic anti-tumor response Injected and Non-Injected syngeneic mouse tumors