SQ3370 enhances the safety of chemotherapeutics via local activation therapy

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Impact and Approach

With systemic chemotherapy, only 1-2% of the administered dose actually reaches a localized tumor, while the remaining leads to adverse off-target toxicities, including immunosuppression. Hence, there is a critical need to locally deliver cytotoxics directly to the tumor. Our patented approach (SQ3370) consists of:

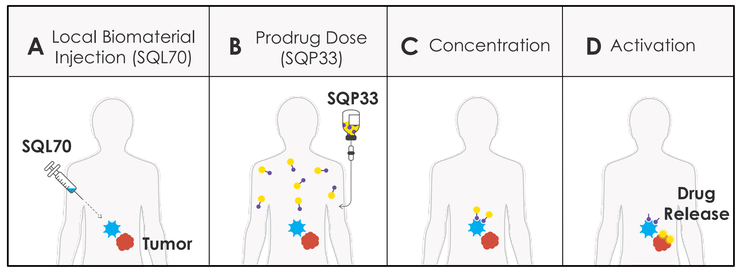
(1) SQL70 - a drug-activating biomaterial carrying no payload

(2) SQP33 - a chemically-modified prodrug of doxorubicin (Dox) with attenuated activity.

SQL70 (biomaterial) is injected at the tumor site followed by SQP33 (prodrug) administered systemically. SQP33 first concentrates to SQL70 at the tumor site due to their complementary chemical reactivities. The active drug is then spontaneously released over multiple days, providing sustained local delivery directly to the tumor region while reducing systemic side effects.

We have previously reported that this approach leads to higher efficacy with no adverse effects in an HT-1080 fibrosarcoma mouse model.[1] Here, we describe further investigation of the tolerability and pharmacokinetics of SQ3370, as well as efficacy in a syngeneic mouse tumor model.

Collectively, our results demonstrate that SQ3370 enables delivery of cytotoxic drugs to a target site while limiting exposure in off-target tissues in preclinical models, leading to improvements in both safety and efficacy.



SQ3370 allows greater amounts of treatment to be given safely

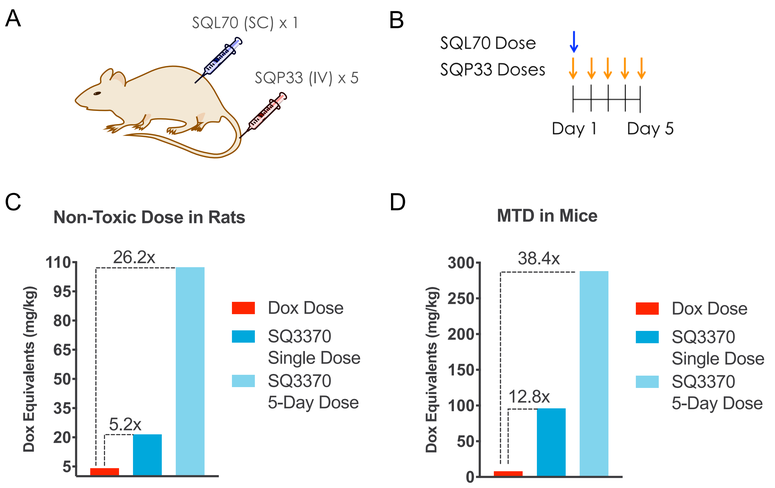


Figure 1. (A, B) SQ3370 was administered in rodents as a single local injection of biomaterial SQL70 (SC flank), followed by prodrug SQP33 (IV tail vein) QD x5 days, beginning 1 h after SQL70. (C) Sprague Dawley rats (n=10) were treated with standard Dox (4.05 mg/kg IV, single dose) or SQ3370: 1 mL SQL70, followed by SQP33 at 21.46 mg/kg Dox equivalents QD x5 days. (D) MTD of a prototype of SQ3370 was determined in NSG mice. Mice (n=5) received 100 µL biomaterial, followed by either a single dose of prodrug at 96.1 mg/kg Dox equivalents, or 57.6 mg/kg Dox equivalents QD x5 days. MTD of a single dose of Dox (7.5 mg/kg) was determined without biomaterial. MTD was determined by a 10% drop in body weight and clinical observation.

Improved tumor response and survival in a syngeneic tumor model

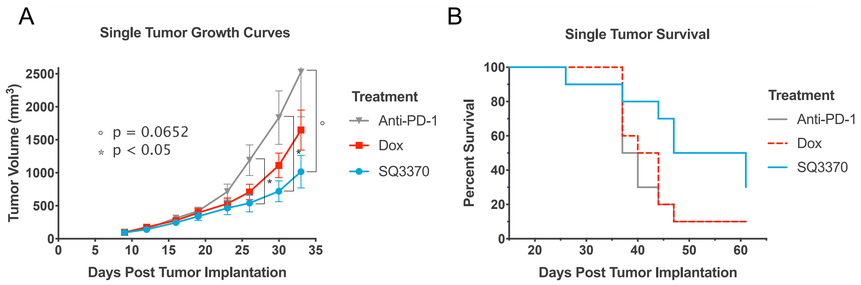


Figure 2. C57BL/6 mice were inoculated with 5x10^5 MC-38 tumor cells (SC flank). 9 days post-implantation, mice (n=10/group) were treated with either Dox (8.1 mg/kg IV, Q4D x3), anti-PD-1 (10 mg/kg IP, Q4D x2), or SQ3370: 100 µL SQL70 peritumoral injection followed by SQP33 (10 doses of 43 mg/kg Dox equivalents IV, QD x5 days twice, 2-day break between cycles). (A) Tumor growth curves following treatment. Mean ± SEM. One-way ANOVA with Tukey's multiple comparisons test. (B) Percent survival following treatment.

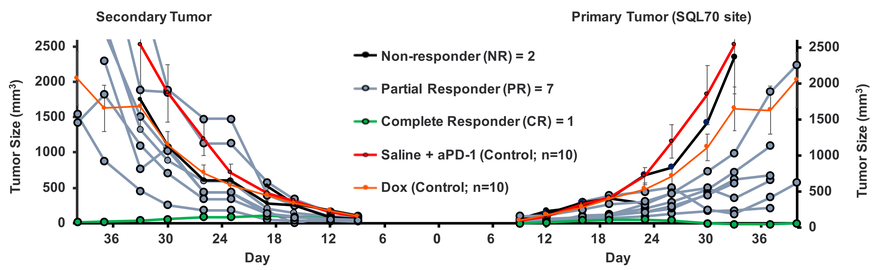
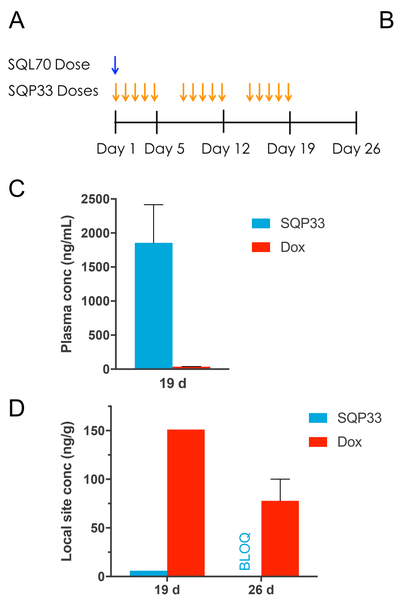


Figure 3. C57BL/6 mice were inoculated with 5x10^5 MC-38 cells (SC flank, primary tumor) and 1x10^5 MC-38 cells (SC opposite flank, secondary tumor). 9 days post-implantation, mice (n=10/group) were treated with either Dox (8.1 mg/kg IV, Q4D x3), anti-PD-1 (10 mg/kg IP, Q4D x2), or SQ3370: 100 µL SQL70 injection followed by SQP33 (10 doses of 43 mg/kg Dox equivalents IV, QD x5 days twice, 2-day break between cycles). SQL70 was administered peritumorally to the primary tumor only. Average tumor growth curves (mean ± SEM) are shown for anti-PD-1 and Dox groups. Individual tumor growth curves shown for SQ3370 group.

Sustained cytotoxic delivery to local site



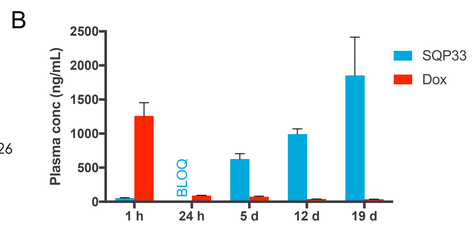
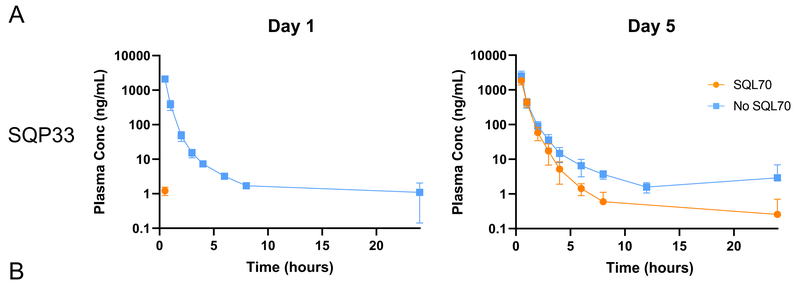


Figure 4. (A) C57BL/6 mice (n=5) received a single dose of SQL70 (SC flank) followed by SQP33 (15 doses of 43 mg/kg Dox equivalents IV, QD x5 days three times, 2-day break between cycles). (B) Bioanalysis of plasma collected following first SQP33 injection at timepoints of 1 h (n=3), 24 h (n=2), and on days 5, 12, and 19 (n=5 each). Mean ± SEM. (C) Plasma concentration of day 19 only. Mean ± SEM. (D) Bioanalysis of SQL70 site tissue collected from mice euthanized on days 19 (n=1) or 26 (n=4). Mean ± SEM. All bioanalysis performed by LC-MS/MS to quantify prodrug and Dox.

Pharmacokinetics of drug activation in rats



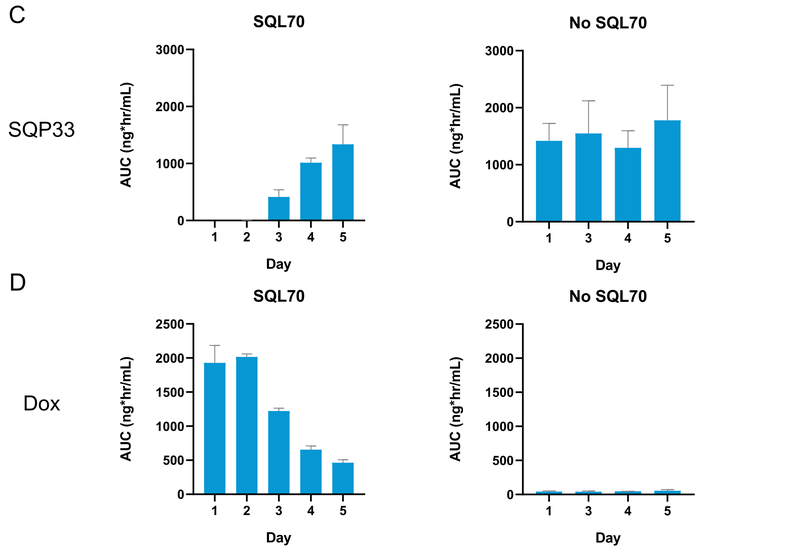


Figure 5. Sprague Dawley rats were treated with SQ3370: 1 mL SQL70 (SC flank), followed by SQP33 at 21.46 mg/kg Dox equivalents QD x5 days (IV tail vein). Control group received SQP33 only (no SQL70). Plasma was collected over 5 d for bioanalysis of SQP33 and Dox. Shown are PK curves of (A) SQP33 on days 1 and 5, and (B) active Dox on days 1 and 5. Area-under-the-curve (AUC) of (C) SQP33 and (D) Dox was determined for the SQL70 and no SQL70 group. All values are represented in Dox equivalents. Mean ± SD (n=3). Plasma was not collected for No SQL70 group on day 2.

Conclusions

Through a local drug activation approach, SQ3370 enhances the tolerability of cytotoxic therapy, allowing significantly greater doses to be given safely compared to conventional treatment. As a result, in a mouse syngeneic tumor model, SQ3370 showed improved tumor response and survival compared to standard chemotherapy or anti-PD-1 treatment. In mice bearing dual tumors, with only one tumor site receiving a local biomaterial injection, we observed that SQ3370 can induce a response in both primary and secondary tumors, potentially expanding indications beyond strictly local disease. Biodistribution data indicate sustained delivery of active cytotoxic at the local site for up to seven days after completion of the prodrug treatment regimen. Pharmacokinetics results show that the prodrug is rapidly removed from detection in circulation within one hour of initial dose, highlighting the efficiency of the biomaterial in the prodrug concentration step. The drug activating capability is retained over multiple days of high-dose therapy.

References: 1) Mejia Oneto et al. ACS Cent. Sci. **2016**, 2, 476-482.