Title:
SQ3370: Biomaterial-dependent local drug activation of systemic cytotoxic prodrugs enhances safety and efficacy.

Authors:
S Srinivasan, NA Yee, M Royzen, JM Mejia Oneto

Abstract:
Background: In treating localized tumors with systemic chemotherapy, only 1-2% of the administered dose actually reaches the tumor site, while the remaining causes adverse off-target toxicities, including immunosuppression. To address the critical need of locally delivering cytotoxics to tumors, we present our patented combinatorial approach (SQ3370) consisting of two components:

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

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

Methods: SQL70 is first injected at the local tumor and SQP33 is then given intravenously. The inactive prodrug concentrates to the biomaterial at the tumor site due to their complementary chemical reactivities. The activated drug is then spontaneously released over multiple days, providing sustained local delivery directly to the tumor region while reducing systemic side effects.

Results: Previously, we have shown that SQP33 can be given at over 38 times the dose of standard Dox in SQL70-injected mice due to its attenuated toxicity. Pharmacokinetic and biodistribution studies in SQ3370-treated rodents and dogs show that SQP33 disappears from plasma within the first hour of administration, likely due to the rapid concentration at the SQL70 site. Without SQL70, SQP33 shows minimal off-site conversion to Dox. These studies also indicate that a single injection of SQL70 can activate multiple doses of SQP33, maximizing the local therapeutic index.

SQ3370 treatment enhances therapeutic response and survival in tumor-bearing mice. In a syngeneic MC38 cancer model, SQ3370 reduced tumor progression in 8/10 mice and an improved tumor response compared to standard Dox or anti-PD-1 therapy. SQ3370 also prolonged overall survival compared to either control.

In mice bearing dual tumors, with one tumor site injected locally with SQL70, SQP33 induces a response in both primary and secondary tumors suggesting an anti-tumor immune activation effect. Furthermore, SQ3370 appears to synergize with anti-PD-1. This expands potential treatment options in the clinic and highlights the advantages of immune-sparing cytotoxic therapy.

Conclusions: SQ3370 allows the delivery of cytotoxic drugs to a target site while limiting exposure in off-target tissues in small and large animals, leading to improved safety and efficacy.