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TREATMENT WITH SQ3370, A DOXORUBICIN-BASED THERAPEUTIC, CORRESPONDS WITH IMMUNOMODULATION OF THE TUMOR MICROENVIRONMENT

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Background The CAPAC platform uses click chemistry to activate potent anti-cancer drugs specifically at the tumor while minimizing systemic toxicity. SQ3370, the lead investigational asset, consists of 1) tetrazine-modified biopolymer injected into the tumor protodrug; 2) intravenously administered protodrug of doxorubicin (Dox). Active Dox is released in the tumor through an efficient chemical reaction between the biopolymer and protodrug. SQ3370 enables a 19-fold increase over the conventional Dox dose in mice with minimal systemic toxicity.¹ Moreover, SQ3370-treated tumor-bearing mice show improved survival, T-cell infiltration, and a robust anti-tumor response against both biopolymer-injected and non-injected lesions,² suggesting SQ3370 promotes anti-tumor immune activation.

SQ3370 is currently in a Phase I clinical trial in patients with advanced solid tumors (NCT04106492). The on-going dose escalation phase has shown no dose limiting toxicity thus far. No acute cardiotoxicity has been observed with Dox levels >12-times the molar equivalent dose of conventional Dox treatment.

We performed in-depth evaluation of tumor immune infiltration after SQ3370 treatment using syngeneic tumor models and correlated findings with data obtained from clinical samples from patients treated with SQ3370. Based on these data, we present a mechanism-of-action for SQ3370 and propose rationale for combination therapies of SQ3370 with immunotherapies.

Methods SQ3370 treatment is described in figure 1. Immuno-competent mice were inoculated with B16-F10 or MC38 tumor cells. SQL70 was given intratumorally; SQP33 was given intravenously as five daily doses. Tumors used for immune analysis were harvested 2 weeks after the last SQP33 dose and were assessed by flow cytometry and multiplex immunofluorescent analysis. Patient samples were assessed by multiplex immunohistochemistry (tumor biopsies) and CyTOF analyses (blood cells).

Results SQ3370 treatment induced immune activation in patient tumor biopsies despite assessment of a diverse, heavily pre-treated population. Similarly, SQ3370 promoted immune activation in preclinical models. The data are consistent with immunogenic cell death and characterized by activation of T-cell responses.

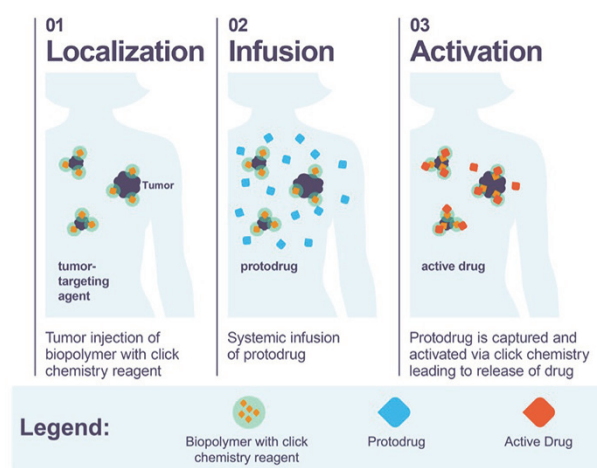
Conclusions SQ3370, CAPAC's lead candidate, improves safety and efficacy as compared to conventional Dox. It also activates an anti-tumor immune response through induction of immunogenic cell death and modulates adaptive and innate immune cell populations. Consistency between immune responses observed in clinical samples and mouse syngeneic tumor models underlines the translatability of the SQ3370 preclinical data and suggests a window of opportunity for combination strategies with immunotherapies.

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REFERENCES

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Ethics Approval Animal studies were approved by the Institutional Animal Care and Use Committee (IACUC) of respective vendors. Study protocol number SP17-010-139B was carried out at Explora BioLabs operating several Office for Laboratory Animal Welfare (OLAW) Animal Welfare Assurance Statements #D16-00743) with Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) accreditation and United States Department of Agriculture (USDA) license #93-R-0512. Study protocol number CA-SHAS-1 was carried out at Washington Biotechnology Inc. Operating under OLAW Assurance Statement #D16-00616. The clinical trial was approved by the US Federal Food and Drug Administration (FDA), IND #137024.



Abstract 953 Figure 1 The CAPACTM platform (1) SQL70 biopolymer is locally injected at the tumor area and (2) SQP33 protodrug is infused systemically. (3) SQP33 protodrug is activated by SQL70 biopolymer at the tumor site through a rapid covalent reaction between tetrazine and trans-cyclooctene moieties, followed by chemical rearrangement to release active Dox

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