SESS-2069

Pre-Clinical Data and Phase I Design for PQ203: A Novel Peptide-Drug Conjugate (PDC) Targeting the SORT1 Receptor in Hormone Receptor Triple Negative Breast Cancer (TNBC)

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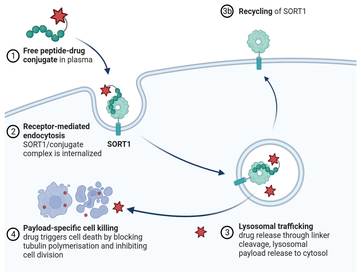
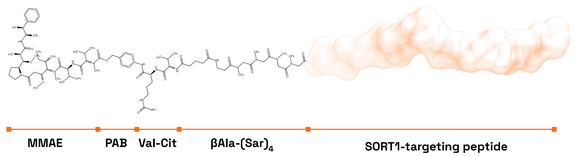
Introduction

- Sortilin (SORT1) is a member of the vacuolar protein sorting 10 protein (VPS10p) receptor family.
- SORT1 functions as a scavenging receptor facilitating efficient endocytosis of extracellular peptides and proteins[1].
- Enriched SORT1 expression has been reported in numerous cancer subtypes including melanoma, ovarian, hormone-receptor positive breast cancer and triple negative breast cancer (TNBC)[2,3].
- We seek to exploit SORT1-mediated peptide internalization for rapid and specific chemotherapy delivery into TNBC cells.
- A peptide drug conjugate (PDC) PQ203 was generated via a linkage strategy that combines a computationally designed high-affinity SORT1 targeting peptide to the chemotherapeutic payload Monomethyl Auristatin E (MMAE).
- In contrast to established antibody drug conjugate (ADC) pharmacokinetics, PQ203 exhibits rapid plasma clearance with sustained tumour delivery of MMAE accompanied by potent anti-tumour activity across a range of *in vivo* xenograft models.



Design of PQ203: a SORT1-targeting PDC



Methods

SORT1 Binding Affinity: Binding affinity studies were conducted using surface plasmon resonance (SPR) by immobilizing the extracellular domains of SORT1 (human, mouse, rat, canine), SORCS1, SORCS2, SORCS3, or SORLA followed by sequential injections of 3-fold serial dilutions of PQ203.

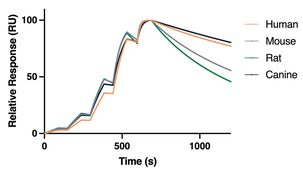
Internalization: MDA-MB-231 triple negative breast cancer cells were dosed with 1 µM AF488-labeled SORT1 targeting peptide or a scrambled non-targeting control peptide for the indicated time points at 4°C or 37°C. Following incubation, cells were washed and acid-treated to remove peptide bound to the cell surface. Cells were resuspended in FACS buffer and analyzed on a flow cytometer. The internalized mean fluorescence intensity (MFI) was determined by subtraction of the 37°C and 4°C sample MFIs. Data represent means ± SD (n=3)

Pharmacokinetics: MDA-MB-231 tumour-bearing Balb/c nude mice were given a single intravenous dose of 3 mg/kg PQ203. Plasma and tumour samples were collected at the indicated time points following dosing and detection of intact PQ203 and/or free MMAE was performed by LC-MS/MS using qualified bioanalytical methods. Data represent means ± SEM (n=3).

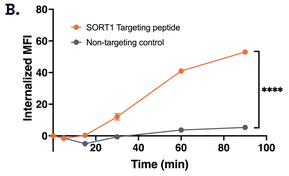
***in vivo* efficacy:** Balb/c nude mice were inoculated with MDA-MB-231 cells or BR5017 patient-derived TNBC cells and dosed intravenously via tail vein with the indicated test articles. Vehicle, PQ203, non-targeting control PDC, or free MMAE were dosed QW x 4 whereas Sacituzumab Govitecan (SG) was dosed biw x 4. Tumor volumes and body weights were measured twice weekly with daily clinical observations. Data represent means ± SEM (n=8)

Results

1 PQ203 binds SORT1 with high affinity and internalizes into TNBC cells



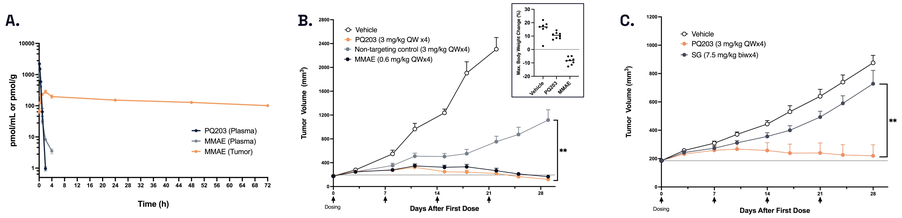
PQ203 SORT1 affinity and species cross-reactivity (K_D, nM)	
Human	0.14
Mouse	0.38
Rat	0.37
Dog	0.20



A. PQ203 binds to human SORT1 with high affinity (K_D=0.14 nM) and is cross-reactive with mouse, rat, and dog orthologs as determined by SPR

B. An Alexa Fluor 488 (AF488) labeled SORT1-targeting peptide is rapidly internalized into MDA-MB-231 TNBC cells in a SORT1-dependent manner as measured by flow cytometry. Minimal internalization is observed with an AF488-labeled non-targeting control peptide. **** p < 0.0001, Two-way ANOVA

2 PQ203 efficiently delivers MMAE to tumors and has high antitumor activity *in vivo*



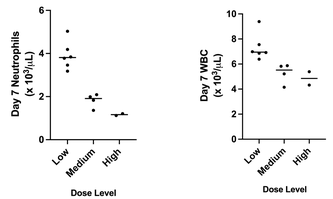
A. 3 mg/kg PQ203 intravenous dose in MDA-MB-231 tumor-bearing mice results in transient intact PQ203 and MMAE levels in plasma with sustained MMAE levels in tumor samples beyond 72 hours.

B. QWx4 dosing of PQ203 in a TNBC CDX model (MDA-MB-231) results in potent tumor regression relative to non-targeting control PDC treatment. **Inset:** PQ203 is well-tolerated in mice with minimal body weight impact relative to the molar equivalent of MMAE. ** p < 0.01, Two-way ANOVA

C. QWx4 dosing of PQ203 in a TNBC PDX model (BR5017) results in potent tumor regression relative to Sacituzumab Govitecan (SG, biwx4) treatment. ** p < 0.01, Two-way ANOVA

3 Safety of PQ203 in a dose range finding study in Beagle dogs

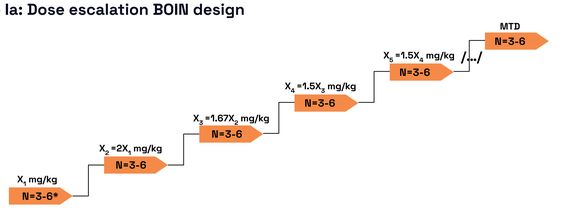
- Reversible, dose-dependent reductions in neutrophils, white blood cells, lymphocytes, platelets and red blood cells were observed in dose-range finding studies in Beagle dogs.
- Reduced cellularity in hematopoietic and lymphoid organs, as well as mucosal degeneration and necrosis in the gastrointestinal tract were also observed.
- Overall, toxicology findings were consistent with the expected toxicity profile of the released payload, MMAE.
- All findings are monitorable in the clinic.
- **Right panel:** Dose dependent decreases in neutrophil and white blood cell counts are observed on day 7 following intravenous infusion of PQ203 at high, medium, and low dose levels.



Results

4 Preliminary PQ203 Phase I Outline

Phase Ia: Dose escalation BOIN design



**Additional patients may be backfilled into dose cohorts of interest*

Phase Ib: Dose Optimization
Optimization of dosing regimen to determine recommended Phase 2 dose

Eligibility criteria
- Metastatically or locally advanced solid tumors progressing through or otherwise ineligible to receive approved standard-of-care therapies
- ECOG Performance Status 0-1
- Adequate organ function
- RECIST measurable disease
- Emphasis on enrolment of histologic tumor types known to overexpress SORT1 (breast, melanoma, ovarian, colorectal, gastric)

Primary Objectives
- Determine the RP2D for expansion
- Evaluate safety of PQ203 in subjects with advanced solid tumors

Secondary Objectives
- Evaluate preliminary signals of anti-cancer activity
- Characterize the pharmacokinetics of PQ203
- Evaluate drug exposure and correlate safety endpoints

BOIN = Bayesian Optimal Interval; ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumors; MTD = Maximum Tolerated Dose; RP2D = Recommended Phase 2 Dose

Conclusions

- PQ203 demonstrates high affinity binding to SORT1 and internalizes via a SORT1-dependent mechanism.
- PQ203 displays rapid in vivo pharmacokinetics, with rapid PQ203 and MMAE plasma clearance coinciding with sustained MMAE delivery to tumors.
- PQ203 shows potent anti-tumor efficacy across a range of *in vivo* models, including a PDX model resistant to Sacituzumab Govitecan treatment.
- Adverse findings were consistent with the payload MMAE and found to be reversible.
- A well-tolerated dose was identified in beagle dogs and IND-enabling GLP-toxicology is currently underway.
- ProteinQure is currently targeting enrolment for a Phase 1a/b first-in-human trial in the second half of 2025.

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