PQ203
Novel Chemotherapeutic

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ABSTRACT

Sortilin (SORT1) is a member of the vacuolar protein sorting 10 protein (Vps10p) family that functions as a receptor regulating peptide and protein trafficking between the plasma membrane, lysosomes, and trans-golgi network. As a cell surface receptor, SORT1 is able to mediate efficient endocytosis of extracellular ligands to the lysosomal compartment.

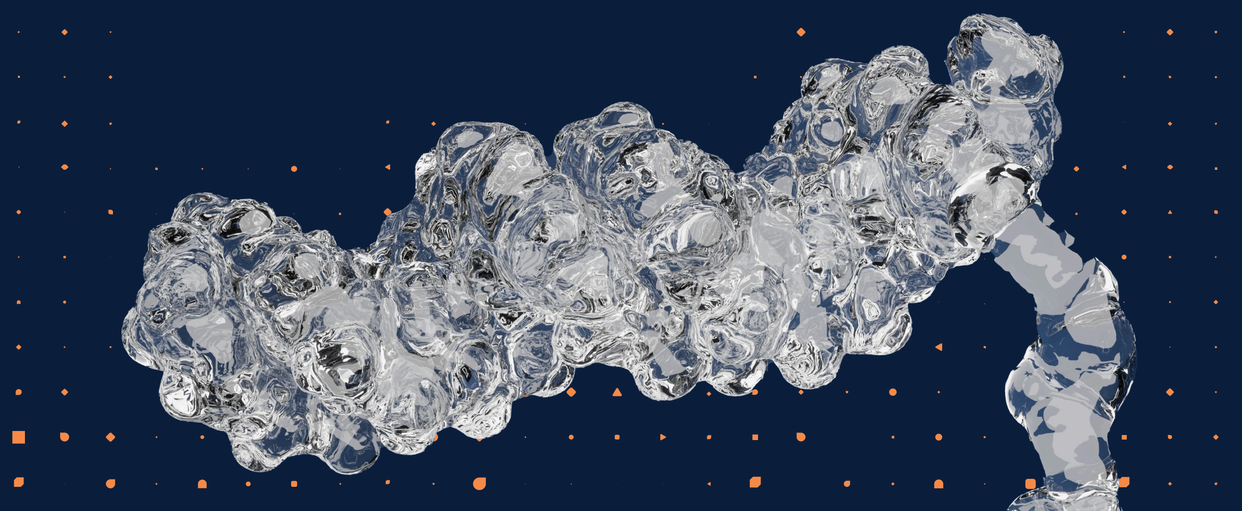
Numerous reports have identified enriched SORT1 expression in a variety of tumor types, including triple-negative breast cancer (TNBC), a subtype of breast cancer associated with aggressive clinical behavior and poor disease outcomes. We sought to exploit SORT1-dependent internalization of peptides as a platform for rapid and specific chemotherapy delivery into TNBC cells.

Using PQStudio™ (our proprietary computation-enabled design capabilities), we generated a high affinity SORT1 targeting peptide that exhibits efficient receptor dependent internalization and lysosomal localization.

A peptide drug conjugates (PDC) was generated via a linkage strategy that combines our designed peptide to the antimitotic agent monomethyl auristatin E (MMAE).

Our PDC molecule exhibits potent cell killing as well as tumor regression in a MDA-MB-231 TNBC cell derived xenograft model, thereby highlighting the potential of SORT1-engaging PDCs as an efficacious targeted chemotherapeutic delivery strategy.

Table Of Contents



SORT1: A Novel Target Antigen

Sortilin (SORT1) is a member of the vacuolar protein sorting 10 protein (Vps10p) family that functions as a receptor regulating peptide and protein trafficking between the plasma membrane, lysosomal compartment, and trans-golgi network (Ouyang et al. 2020, Talbot et al. 2019).

As a cell surface receptor, SORT1 is able to mediate efficient endocytosis of extracellular ligands to the lysosomal compartment followed by recycling to the cell surface (Charfi *et al.* 2021).

SORT1 mediated endocytosis is extremely rapid, endocytosis of the natural ligand progranulin occurs within minutes (Hu *et al.* 2010), and mutational studies of the SORT1 internalization motif results in the accumulation of SORT1 protein levels at the plasma membrane, indicating that a large number of receptors reach the cell surface but are rapidly internalized (Nielsen *et al.* 2001, Al-Akhrass *et al.* 2017).

The internalization properties of SORT1 have been utilized as a means to create a platform for delivery of therapeutic payloads (Figure 1).

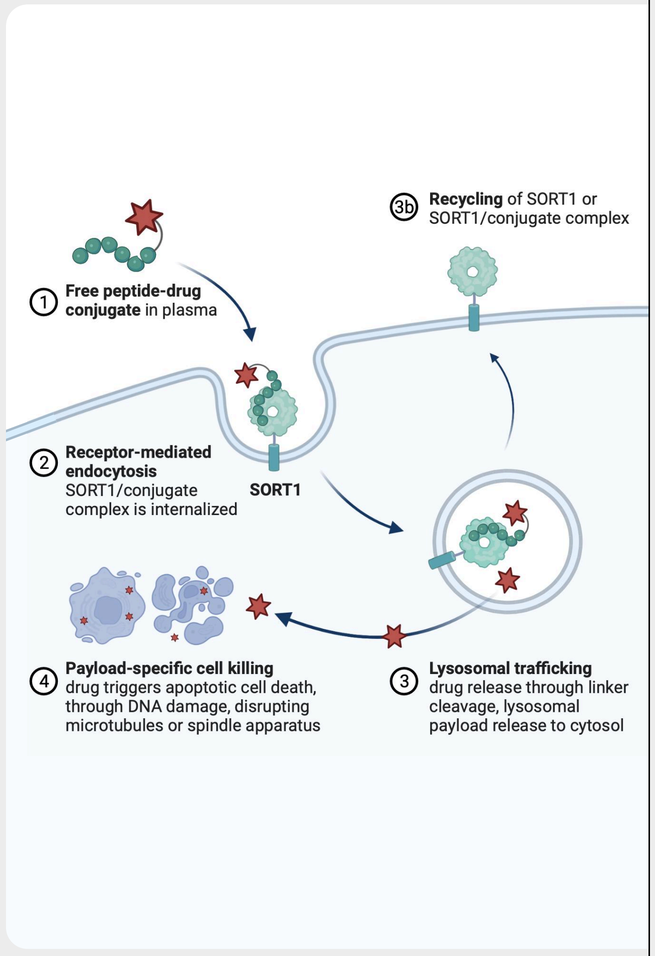


Figure 1: A Sortilin (SORT1) Mediated Intracellular Delivery Platform for Drug Delivery.

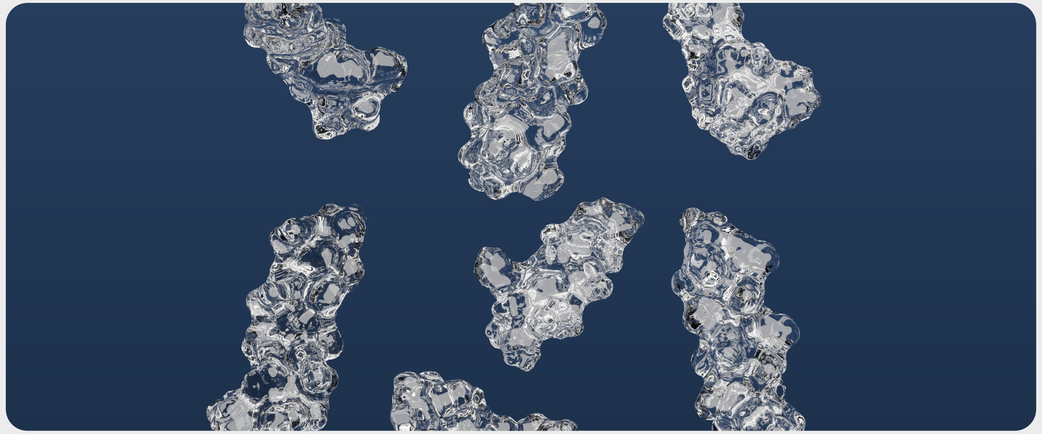
SORT1 And Oncology

Numerous reports have identified enriched SORT1 expression in a variety of tumor types including triple-negative breast cancer (TNBC) (Roselli et al. 2015), colorectal cancer (Akil et al. 2011), ovarian cancer (Ghaemimanesh et al. 2014), pancreatic (Gao et al. 2020) and neuroendocrine tumors (Kim et al. 2018).

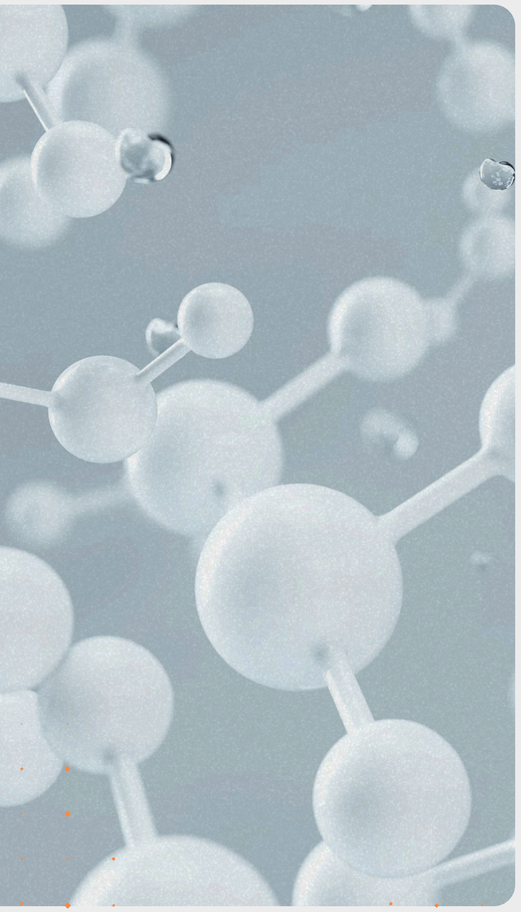
In the case of breast cancer, high SORT1 expression as determined by immunohistochemistry (IHC) is reported in 59% of TNBC tissues (n = 72) as well as 71% of estrogen receptor (ER)-positive breast cancers (n = 96) (Roselli et al. 2015). Cytotoxic agents used in traditional chemotherapy treatments cannot distinguish between healthy and cancerous cells, often leading to unwanted and life-threatening side effects.

For this reason, targeted chemotherapies that selectively kill cancer cells have risen to prominence in the oncology therapeutic landscape (Zhao et al., 2020). As described above, numerous reports have identified enriched SORT1 expression in a variety of tumor types, including TNBC, a subtype of breast cancer associated with aggressive clinical behavior and poor disease outcomes (Roselli et al., 2015). TNBC is clearly an area of unmet medical need with a large patient population (~16,000 patients/annum in the United States) in dire need of new therapeutic options.

Although the recent addition of the antibody drug conjugate Sacituzumab Govitecan (Trodelvy) (Goldenberg et. al, 2014)) to the existing armament of drugs for treating TNBC has been received with great hope, concerns of emerging resistance mechanisms (intrinsic or acquired) to either expression of the antigen or the payload will necessitate the development of new classes of drugs for treating TNBC.



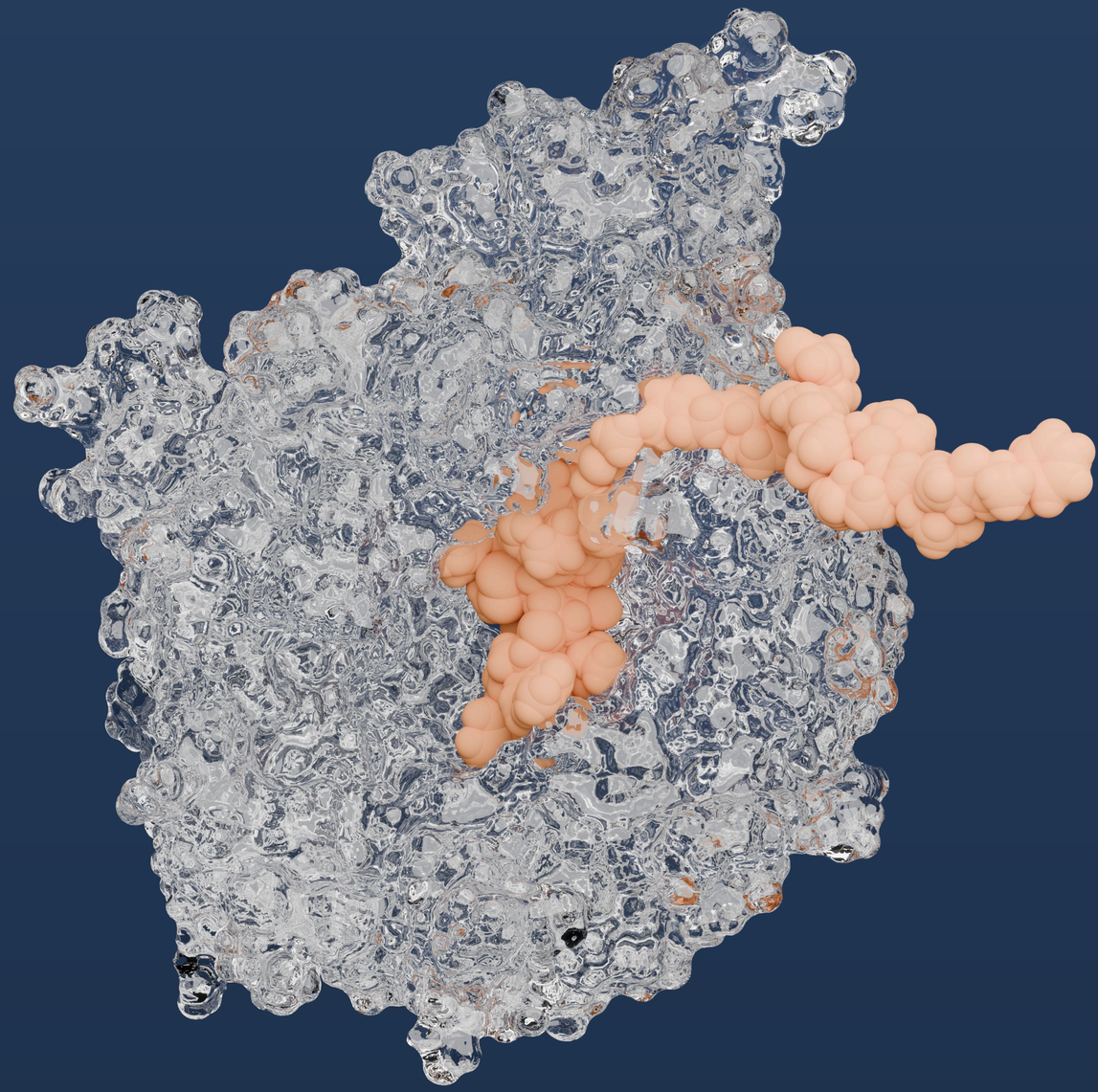
Platform



Using PQStudio™ (ProteinQure's proprietary computation-enabled design capabilities), a high affinity SORT1 targeting peptide was generated (Kd = 0.089 nM) through linear peptide design followed by insertion of non-canonical amino acids to enhance drug-like properties.

Structural modeling enabled epitope directed design of this ligand, paired with machine learning to predict solubility and solvent accessibility of sites for payload conjugation. It was found this ligand engages and undergoes SORT1 dependent internalization and subsequent lysosomal localization.

We subsequently conjugated this SORT1 engaging peptide to the antimitotic agent monomethyl auristatin E (MMAE) to create PQ203, a peptide drug conjugate (PDC). PQ203 is highly soluble in aqueous buffer, exhibits reasonable serum stability, and has intrinsic sequence and charge motifs indicative of peripheral distribution when delivered via intravenous injection.



Pre-Clinical Evaluation

We performed in-vivo preclinical tumor modeling studies to evaluate the efficacy of PQ203 as gauged by tumor regression in a MDA-MB-231 TNBC cell derived xenograft model. Specifically, this study involved 4 arms including vehicle, PQ203, a scrambled PDC control (affinity for human SORT1 (>25 uM), and free MMAE (dosed at a molar equivalent to PQ203).

> **“The study design was once weekly (QW) dosing at 3 mg/kg for 4 weeks.”**

As shown in **Figure 2A**, PQ203 exhibited potent tumor regression equivalent to unconjugated MMAE. Interestingly, the scrambled PDC control exhibited marginal efficacy on inhibition of tumor growth.

However, there is a clear statistically significant difference in tumor growth inhibition between PQ203 dosed mice and the scrambled control PDC, a result that is consistent with a SORT1 dependent mechanism.

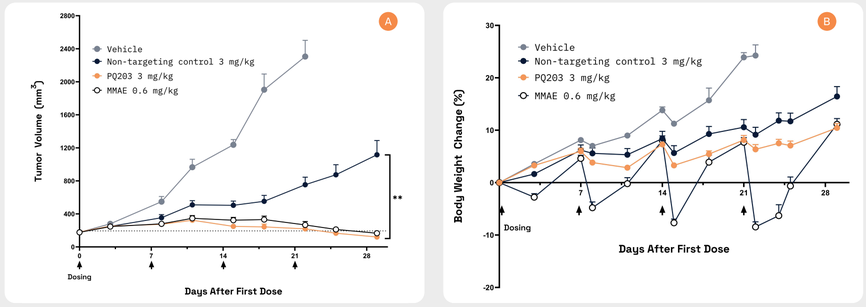


Figure 2. PQ203 Exhibits (A) Potent Efficacy and (B) Reduced Toxicity Relative to Unconjugated MMAE Payload in a Cell Derived Xenograft Study.

Additional studies to evaluate the efficacy of PQ203 were also performed in patient-derived xenograft (PDX) models. As in the CDX model, PQ203 was dosed QW for 4 weeks. As shown in **Figure 3**, we observed similar efficacy for PQ203 in the PDX as that observed in the CDX model. This work was presented at the American Association for Cancer Research (AACR 2024) (Elliott et al. 2024).

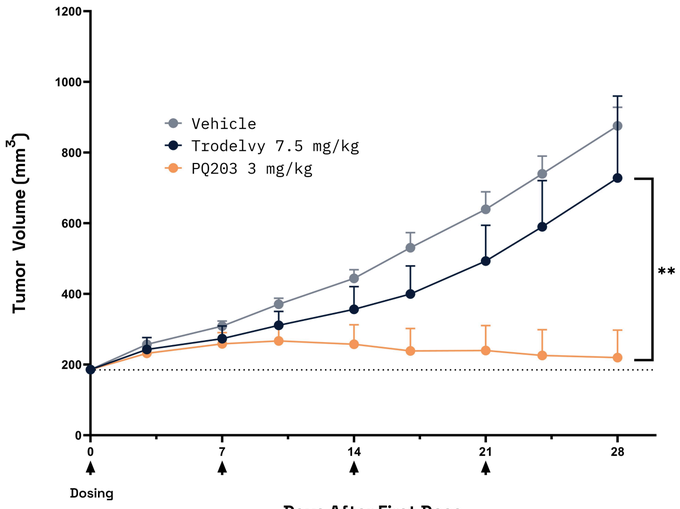


Figure 3. PQ203 Exhibits Greater Potency Relative to Trodelvy in a Human Derived Tumor Model

In this study we also evaluated Trodelvy, which is currently the only commercially approved therapy for TNBC. Our decision to evaluate PQ203 versus Trodelvy was driven by concern in the medical community that there is innate as well as acquired resistance to Todelvy in TNBC patients.

The Trodelvy dosing strategy was based on established efficacious dose in mouse models; BIW in 7 d at 7.5 mg/kg. In this model system, we observed that Trodelvy was less efficacious than PQ203. These results highlight the use of PQ203 as an highly efficacious and alternative to Trodelvy for TNBC tumors.

Clinical Development

We are currently advancing PQ203 through IND enabling studies that are projected to be completed in Q2 of 2025 with a projected first in human dose (FIH) dose in Q4 2025.

The aims of this first-in-human (FIH) study are to determine the recommended Phase 2 dose (RP2D) of PQ203 for continued development and to assess safety, pharmacokinetics and preliminary signals of anti-cancer efficacy of PQ203 delivered QW for 4 doses in 28-day cycles via 60 min intravenous infusion.

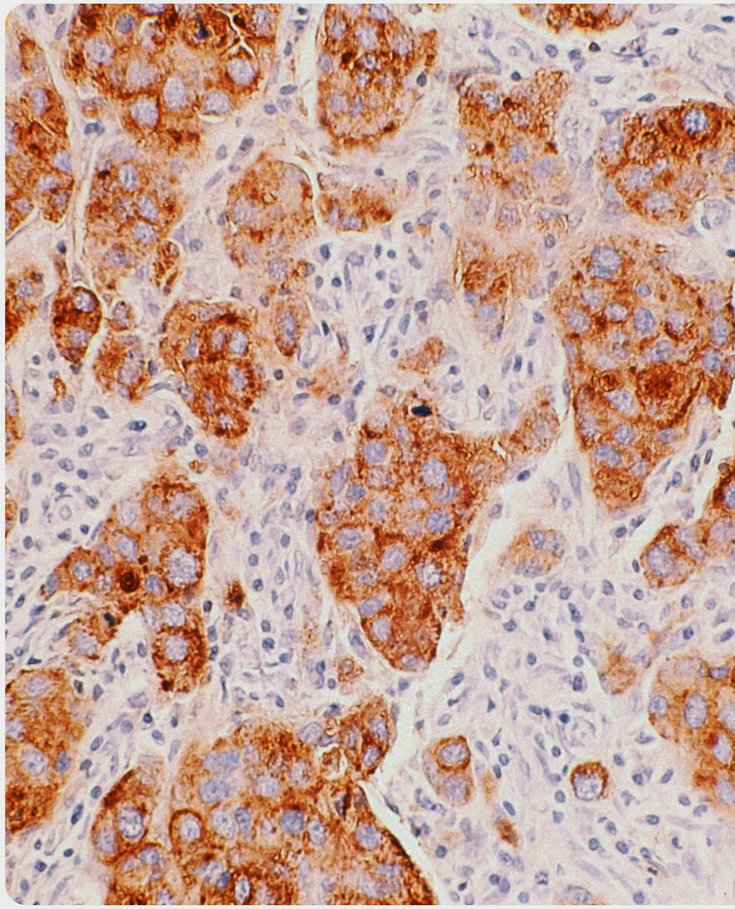
PQ203 will be evaluated in adults with advanced malignant solid tumors who have exhausted or are otherwise ineligible for approved standards of care. Tumor types for initial assessment will include those with historical precedence to overexpress SORT1 receptor including (although not necessarily limited to) melanoma, breast, ovarian, colorectal and gastric cancers.

Diagnostic Imaging

Our high affinity SORT1 engaging peptide also presents as an opportunity to develop both a diagnostic for SORT1 expressing solid tumors.

Effective diagnostic imaging is crucial for TNBC due to its aggressive nature and poor prognosis. Current diagnostic methods heavily rely on invasive pathological examinations. As such, standard treatment options such as chemotherapy and Trodelvy are often prescribed without any diagnostic imaging, despite a 60% inherent resistance rate, low response rates, and potential for severe side effects.

There is an urgent need for improved diagnostic approaches, particularly targeting the SORT1 receptor, which could benefit a substantial portion of TNBC patients. To address this, we are conducting pre-clinical R&D to optimize the labeling of our targeting peptide with a radioisotope to develop a diagnostic approach for imaging solid tumors.



Conclusion

SORT1 is a novel internalizing receptor found on the surface of numerous cancer cells, including TNBC. Enhanced by computational design, we have developed a therapeutic candidate for targeted delivery of cytotoxic agents to these cells called PQ203.

PQ203 has demonstrated pre-clinical activity and tolerability in cell line xenografts of breast cancer.

We further characterized antitumor activity of this compound in a collection of clinically and genomically annotated breast cancer patient-derived xenografts.

In the United States there are approximately 16,000 newly diagnosed TNBC patients/ year. Upon approval, we expect robust clinical use of PQ203 with peak sales of $1.3 billion per year. We also believe this SORT1 dependent platform will be applicable to other SORT1 positive tumor types.

We are targeting to evaluate these additional tumor types in a Phase I basket trial that will initiate in late 2025.

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