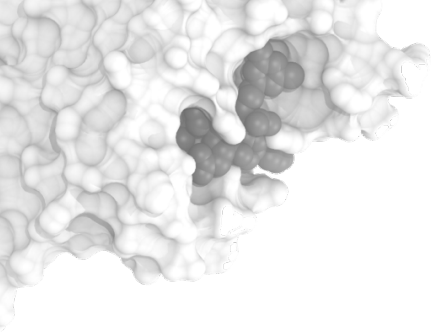


ProteinQure

Sortilin Platform

Target

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 where the cargo is released into the cytosolic compartment (Hu et al., 2010)

Platform

We sought to exploit SORT1-dependent internalization of peptides as a platform for cargo delivery into SORT1 expressing cells. Using ProteinStudio, our proprietary computation-enabled design capabilities, we generated 1st generation high affinity SORT1 targeting peptides (Table 1) that are efficiently internalized and shuttled to the lysosome via a SORT1 dependent mechanism. Full characterization of the DMPK properties of the designed peptides is currently underway. These peptides are highly soluble in aqueous buffer, exhibit reasonable serum stability, and have intrinsic sequence and charge motifs indicative of peripheral distribution when delivered via intravenous injection. We are now developing this platform for various therapeutic applications including the delivery of cytotoxic agents, radioisotopes, and oligonucleotides. By scrambling the sequence of one our hits, we've also created a non-targeting peptide control (NT Control).

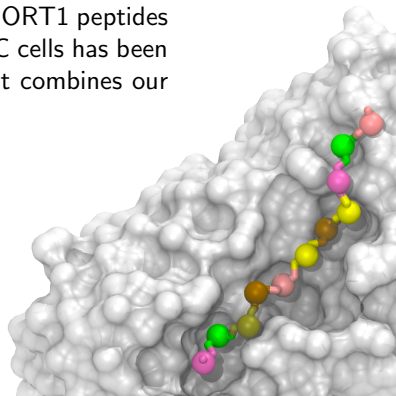
Peptide	SORT1 Affinity (nM)
ARB-1-6	20
ARB-2-3	40.4
ARB-3-5	36.45
NT Control	Not detected

Table 1: Affinity of 1st generation SORT1 targeting peptides

Oncology Therapeutics

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). 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 (Roselli et al., 2015).

Exploiting high level SORT1 expression on TNBC cells allows cytotoxic agents to be preferentially delivered and internalized into TNBC tumors, leaving healthy cells unharmed and avoiding deleterious chemotherapy-induced side effects. Based on this scientific premise, conjugation of the SORT1 peptides as a platform for rapid and specific chemotherapy delivery into SORT1 expressing TNBC cells has been developed. Peptide drug conjugates (PDCs) were generated via a linkage strategy that combines our designed peptides to the antimitotic agent monomethyl auristatin E (MMAE).



Our **designed PDC molecules** exhibited *potent tumor regression* of MDA-231 TNBC xenograft tumors at a dose of 3 mg/kg (7 day dosing interval) and *negligible body weight* changes (Figure 1A). In contrast, unconjugated MMAE at a molar equivalency to the PDCs exhibited toxicity as evident by fluctuations in body weights (Figure 1B). These results highlight the potential of SORT1-engaging PDCs as an efficacious targeted chemotherapeutic delivery strategy. We are now continuing the evaluation of our PDC molecules in additional TNBC patient derived xenografts (PDX models) as well as initiating the evaluation of our platform derived molecules in additional oncology indications.

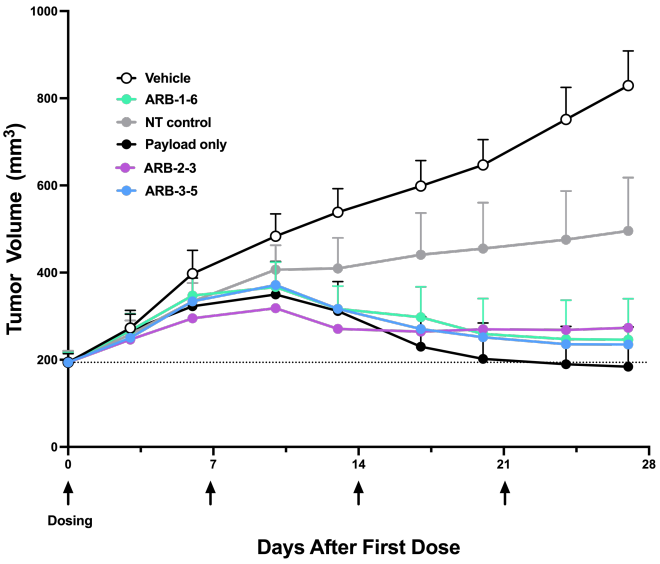


Figure 1A: Tumor volume at 3mg/kg dosage

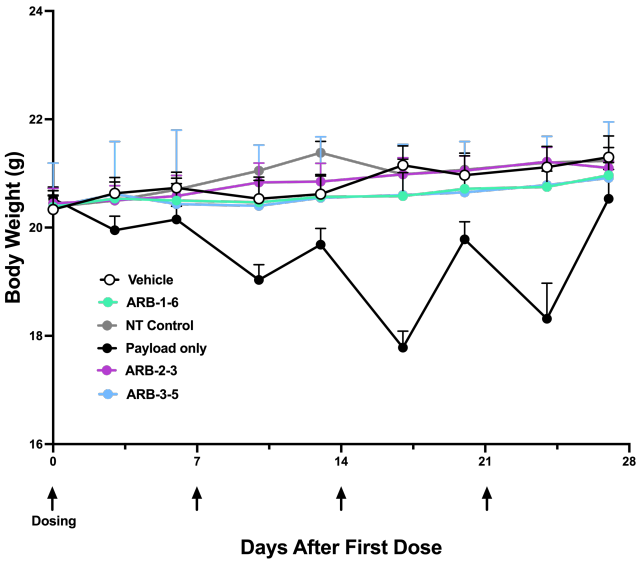


Figure 1B: Body weight at 3mg/kg dosage

Oncology Diagnostics

In addition to the therapeutic application of the SORT1 PDC delivery platform described above, we have also developed radioisotope labeled SORT1 peptides for in vivo diagnostic imaging of tumors that have enriched SORT1 expression (Ghaemimanesh et al., 2021).

CNS Therapies

SORT1 also exhibits enrichment on the surface of neurons in the central nervous system (Petersen et al., 1997). This expression pattern provides an opportunity for targeted neuronal delivery of oligonucleotide therapies that are otherwise unable to efficiently cross the neuronal membrane. Our current focus is the development of SORT1 targeting peptides coupled to siRNA cargo to downregulate transcription of disease-associated genes in order to address the underlying genetic causes of neurodegenerative disease. Maturation of this technology will allow us to build a portfolio of CNS therapeutics to address unmet medical needs in neurodegenerative disorders.

If you're interested, please e-mail me at `lucas@proteinqure.com`.