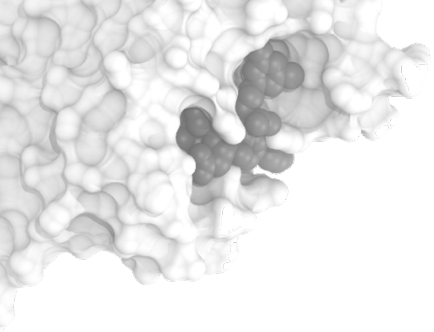

ProteinQure

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).