AACR poster # 1079

Anti-cancer efficacy of TH1902, a docetaxel peptide-drug conjugate targeting SORT1, against ovarian and endometrial cancers xenografts alone or in combination with carboplatin

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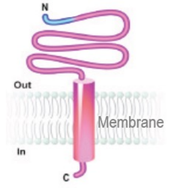
Introduction

SORTILIN (SORT1) RECEPTOR IN CANCER

- Sortilin receptors are preferentially expressed in many cancers compared to healthy tissues, which makes it an attractive target for cancer drug development.
- Transmembrane scavenger receptor involved in import-export of peptides into the cell via the endosomal/lysosomal pathway (cellular shuttle system).
- Ideal candidate for internalization of peptide-drug conjugates (PDCs).
- Sortilin expression increases as a function of tumor grade (I to IV) and is associated with poor prognosis and decreased survival in different cancers.
- Known sortilin expression in various tumor types:

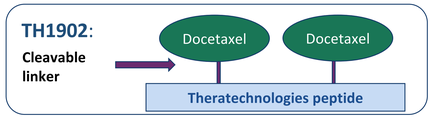
TNBC	59%
Invasive ductal breast	79%
Ovarian (OvCa)	>90%
Endometrial (EC)	>90%
Colorectal (CRC	30-40%
Pancreatic	30-50%
Melanoma	>90%



Sortilin structure

SORT1+ TECHNOLOGY™ PLATFORM

- **SORT1+ Technology™** is an innovative oncology platform consisting of novel peptides which target the SORT1 receptor.
- Targeting sortilin receptors with these peptide-drug conjugates (PDCs) leads to receptor-mediated internalization (endocytosis) of well-established anti-cancer agents (e.g., docetaxel, doxorubicin, curcumin) that are attached to the novel proprietary peptide.
- Once inside the cancer cells, active drug is released in the lysosomes from the peptide and exerts its cytotoxic effect directly on the cancer cell, sparing normal cells from toxicity.
- Versatile and flexible conjugation strategies achieve different ratios of drug to peptide.

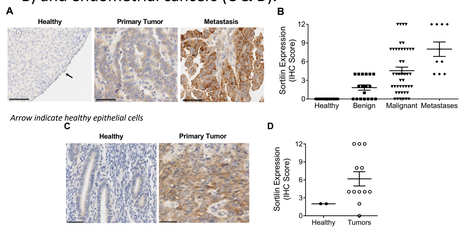


Results

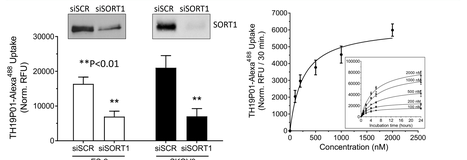
HIGH SORTILIN EXPRESSION IN HUMAN CANCERS

A. Tissue Microarray (IHC) and Sortilin Expression on Ovarian and Endometrial Cancers

- IHC shows high expression of sortilin in human ovarian (A & B) and endometrial cancers (C & D).

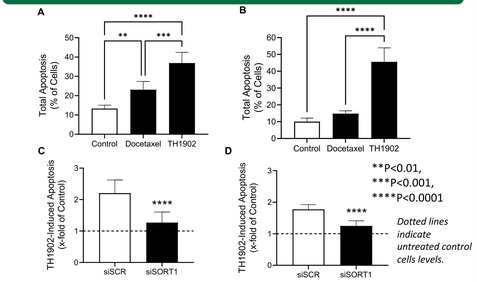


B. Sortilin-Dependent Internalization of TH19P01



- The internalization of fluorescently-labeled TH19P01 is inhibited by *SORT1* gene downregulation in ovarian cancer cell lines.
- This saturable internalization process suggests a receptor-mediated mechanism.

C. Strong TH1902 induction of Apoptosis

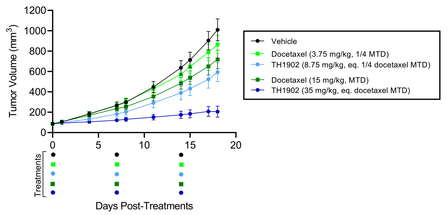


- More than 2-fold increase in apoptosis induction by TH1902 compared to docetaxel (at equivalent docetaxel content) in ES-2 (A) and SKOV3 (B) ovarian cancer cell lines.
- This effect is inhibited by *SORT1* gene downregulation in both SORT1-positive ovarian cancer cell lines (ES-2, C; SKOV3, D).

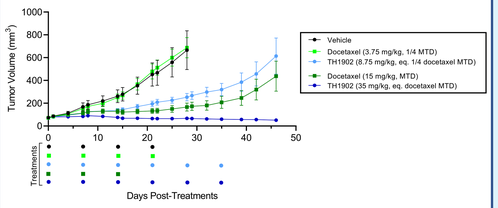
Results (cont'd)

TH1902 AGAINST OVARIAN TUMOR GROWTH

A. ES-2 S.C Xenografts (Ovarian Cancer)

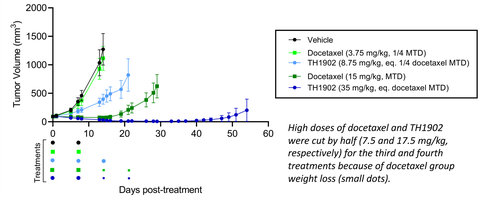


B. SKOV3 S.C Xenografts (Ovarian Cancer)



TH1902 AGAINST ENDOMETRIAL TUMOR GROWTH

A. AN3-CA S.C Xenografts (Endometrial Cancer)

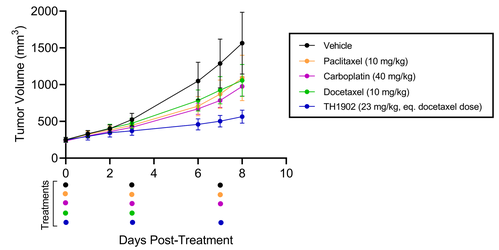


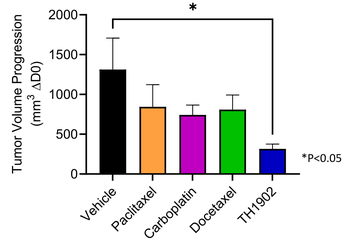
- **Better and sustained efficacy** with TH1902-treated mice at a dose equivalent to the MTD of docetaxel across tumor types.
- **Significant improvement of efficacy** with TH1902 even when administered at lower dose (1/4 of the equivalent MTD dose of docetaxel).
- **Higher cumulative injected dose** for TH1902 (2-fold; see SKOV3 study, B). Three weekly cycles of docetaxel at 15 mg/kg is considered the MTD.

Results (cont'd)

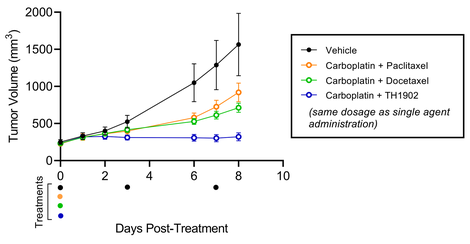
TH1902 PRODUCES STRONG INHIBITION OF OVARIAN TUMOR GROWTH AS SINGLE AGENT OR IN COMBINATION WITH CARBOPLATIN (A2780 S.C. Xenografts)

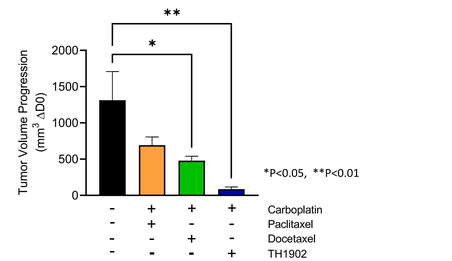
A. Single Agents





B. Combination with Carboplatin





- **Better efficacy** with TH1902-treated mice compared to carboplatin, paclitaxel or docetaxel (at equivalent docetaxel content of TH1902) as single agents in the ovarian tumor xenograft model (A2780).
- **Better efficacy** with TH1902 –carboplatin combination compared to both taxane-carboplatin standard of care combinations for ovarian cancers.
- These results suggest that TH1902-carboplatin combination could be beneficial for ovarian cancer patients.

Conclusions

- **SORT1+ Technology™** is an innovative, flexible platform consisting of novel peptides that target the sortilin receptor (SORT1).
- Tissue microarrays and IHC staining for SORT1 demonstrate strong expression across a variety of human cancers.
- The proprietary peptide, TH19P01, can be conjugated to well characterized anticancer agents, such as docetaxel (TH1902) and doxorubicin (TH1904).
- TH1902 peptide-drug conjugate is internalized via a sortilin-dependent endocytic mechanism.
- Once internalized, TH1902 induces apoptosis to a greater extent than docetaxel alone in ovarian cancer cells (ES-2 and SKOV3).
- TH1902 demonstrated better efficacy than docetaxel, paclitaxel or carboplatin in various ovarian and endometrial s.c. xenograft tumor models.
- Better efficacy with TH1902-carboplatin combination compared to both taxane-carboplatin standard of care combinations for ovarian cancers.
- This preclinical data demonstrates that **SORT1+ Technology™** is a novel approach for the delivery of established anticancer drugs directly inside the tumor cells, thereby optimizing efficacy, limiting toxicity and improving the therapeutic window of the cytotoxic overall that could also further improve combination therapies.

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