AACR poster # 1313

TH1902, a docetaxel peptide-drug conjugate, shows pre-clinical efficacy in several sortilin-positive (SORT1+) cancers

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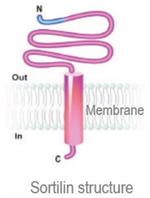
Introduction

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 (PDC's).
- 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

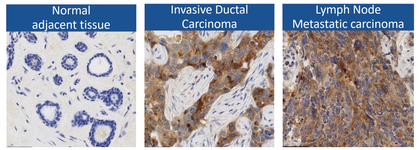
- **SORT1+ Technology™** is an innovative oncology platform consisting of novel peptides which target the SORT 1 receptor.
- Targeting sortilin receptors with these peptide-drug conjugates (PDC's) leads to receptor-mediated internalization (endocytosis) of well-established anti-cancer agents (e.g., docetaxel, doxorubicin, curcumin) that are attached to the novel proprietary peptide.
- Once inside the cancer cells, active drug is released 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.

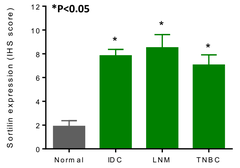
Results

HIGH SORTILIN EXPRESSION IN HUMAN CANCERS

A. Tissue Microarray (IHC) and Sortilin Expression in Breast Cancer

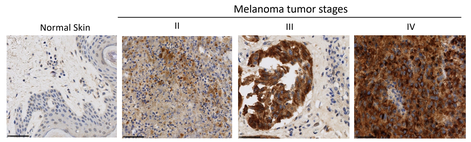
- IHC shows high expression of sortilin in human breast cancers.





IDC: invasive ductal carcinomas
LNM: lymph node metastases
TNBC: triple-negative breast cancers

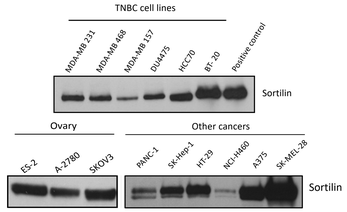
B. Tissue Microarray (IHC) and Sortilin Expression in Melanoma



- IHC shows strong expression of sortilin in human melanomas and is strongly correlated with increasing stage of disease.

C. Western blot

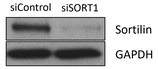
- Sortilin is highly expressed in different human cancer cell lines.

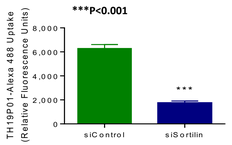


Results (cont'd)

SORTILIN-MEDIATED INTERNALIZATION AND APOPTOSIS

A. Peptide uptake (Sortilin gene silencing)

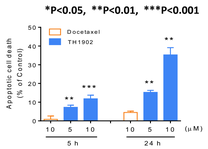


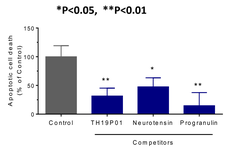


B. TH1902 induces apoptosis of MDA-MB-231 cells

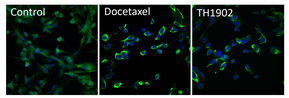
C. Reversal of TH1902 apoptosis by sortilin ligands

- Apoptosis induced by TH1902 was stronger than that of docetaxel and is reversed by sortilin ligands.





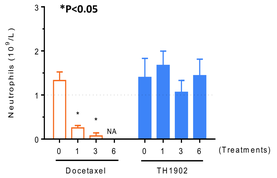
D. TH1902 alters microtubules polymerization



Immunostaining of α-tubulin (green)

TH1902 HAS BETTER TOXICITY PROFILE IN ATHYMIC MICE

A. Absence of neutropenia



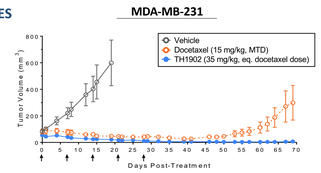
- **Absence of neutropenia** after 6 consecutive treatments of TH1902 at an equivalent dose of MTD docetaxel (15 mg/kg/week, 3 cycles) in athymic mice.
- In contrast, 1 treatment with docetaxel strongly reduced neutrophil counts.

Results (cont'd)

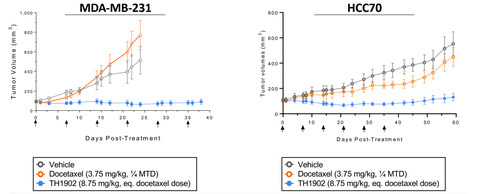
IN VIVO PROOF OF PRINCIPLE OF SORT1+ TECHNOLOGY™ PLATFORM (INCREASED EFFICACY ACROSS TUMOR MODELS)

A. TNBC s.c. xenograft tumor models

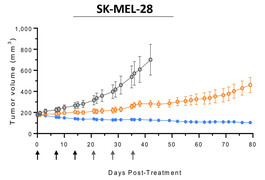
HIGH DOSES

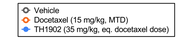


LOW DOSES



B. Melanoma (SK-MEL-28) s.c. xenograft tumor model



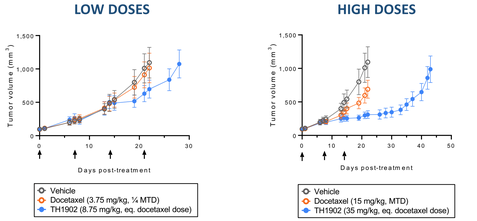


Study notes:
Black arrows: 3 cycles of Docetaxel or TH1902 treatment
Grey arrows: 3 additional cycles of TH1902 treatments at half the starting dose (17.5 mg/kg)

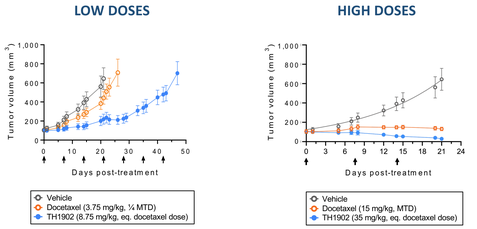
Results (cont'd)

TH1902 PRODUCES STRONG INHIBITION OF TUMOR GROWTH (HT-29 and PANC-1 S.C. Xenografts)

C. Colorectal (HT-29) s.c. xenograft tumor model



D. Pancreatic (PANC-1) s.c. xenograft tumor model



- **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 (up to 2-fold).

Conclusions

- SORT1+ Technology™ is an innovative, flexible platform consisting of novel peptides that target the sortilin receptor (SORT1). Sortilin is preferentially expressed in cancer cells.
- The proprietary peptide, TH19P01, can be conjugated to well characterized anticancer agents, such as docetaxel (TH1902) and doxorubicin (TH1904), for which efficacy and safety have been well established in the clinical setting.
- TH1902 peptide-drug conjugate is internalized via a sortilin-dependent endocytic mechanism and produces strong inhibition of tumor growth across multiple tumor types which is superior to that of docetaxel alone. Efficacy of TH1902 is even seen in tumors where docetaxel is not routinely used as a standard of care (e.g CRC).
- Tissue microarrays and IHC staining for sortilin demonstrate strong expression across a variety of human cancers, which correlates strongly with increasing stage of disease.
- Once internalized, TH1902 induces apoptosis to a greater extent than docetaxel alone in breast cancer cells (MDA-MB-231) and this process can be reversed by competing natural ligands for sortilin (neurotensin and progranulin).
- TH1902 alters microtubule polymerization and the effect on the microtubules is presumably due to the free docetaxel that is released from the conjugate once it is internalized and cleaved from linker.
- TH1902 demonstrated better and sustained efficacy at doses equivalent to the MTD of docetaxel in various s.c. xenograft tumor models (breast cancer, melanoma, colorectal and pancreatic). Improved efficacy was also seen at doses lower than MTD docetaxel (1/4 of the equivalent MTD). Safety profile (neutropenia) was also significantly improved over that seen with docetaxel. This could be important clinically as neutropenia is a dose limiting toxicity that affects dosing, efficacy and tolerability.
- This preclinical data demonstrates that SORT1+ Technology™ is a precision medicine approach for delivery of established anticancer drugs directly inside the tumor cells, thereby optimizing efficacy, limiting toxicity and improving the therapeutic window of the cytotoxic overall.

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