AACR poster # 3942

Differential expression of a novel transport receptor, SORT1 (sortilin), in cancer versus healthy tissues that can be utilized for targeted delivery of anti-cancer drugs

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Introduction

- Sortilin (SORT1), or neurotensin receptor-3, is a scavenger receptor in the Vacuolar Protein Sorting 10 protein (Vps10p) family.
- SORT1 is involved in the rapid transport of molecules across the cell membrane with an internalization half-life of ≤4 min of its ligands (neurotensin and progranulin).[1] SORT1 is thus an ideal candidate for the internalization of peptide-drug conjugates (PDCs).
- The role of SORT1 in cancer continue to be investigated; it is associated with progression, invasion, and more aggressive disease. The PDC TH1902, a new drug in development has been shown to exert its anti-cancer effects in triple-negative breast cancer (TNBC), ovarian, and endometrial cancers.[2-5]
- The pattern and prevalence of SORT1 expression in different healthy and cancer tissues is still not well understood, but it has been shown to be highly expressed in many cancers such as breast and ovarian.[6-9]
- The goal of this study was to **gain better understanding of the expression of SORT1 in healthy tissues and multiple cancer types.**

Materials and Methods

- Screening of healthy and cancer tissue microarrays (TMAs) was undertaken using a qualified immunohistochemistry (IHC) method.
- IHC staining for SORT1 was performed using the primary antibody ab188586 (Abcam) for the detection in formalin-fixed, paraffin-embedded (FFPE) human tissues. Nuclei are counterstained using hematoxylin (blue stain) to assess cell and tissue morphology.
- Assay testing utilized the TechMate IHC platform (Roche Diagnostics).
- List of TMAs screened:

Tumor Indication	Biomax ID	No. Cores/ TMA	No. Cores/ Indication
Endometrial Cancer	EM1021C	102	97 5 normal
Thyroid	BCC15014	40	110 10 normal
	TH8010a	80	
Melanoma	ME2082d	192	176 16 normal
Lung	LC121b	120	110 NSCLC 44 SCLC 10 normal
	LC703a	44	
Bladder	BL601a	60	120 20 normal
	BL802b	80	
Testis	TE481	48	40 8 normal
Small Intestine	SM802	80	54 11 others 15 normal

Tumor Indication	Biomax ID	No. Cores/ TMA	No. Cores /Indication
Eye	BC35111a	40	28 12 normal
Cervix	CR1101	110	388 10 normal
	CR2089a	208	
	CR806	80	
Prostate	PR807C	80	153 27 hyperplasia 21 normal
	PR1211	121	
Liver	BC03117a	80	123 22 cirrhosis 15 normal
	LV808	80	
Multi-Normal	BCN921	92	92 normal

Total cores screened: 1737
Total tumor cores screened: 1,443
Total of evaluable tumor cores: 1,394
Total normal or adjacent tissues screened: 234
Total other conditions tissues screened: 60

▸ Scoring method in cancer tissues (H-score)

The H-score is calculated by summing the percentage of cells with intensity of expression staining multiplied by their corresponding differential intensity on a four-point semi-quantitative scale (0, 1+, 2+, 3+). Thus, scores range from 0 to 300.

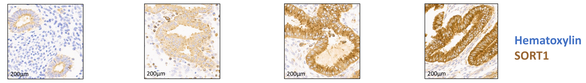
H-score = [(% at 1+) x 1 **] + [** (% at 2+) x 2 **] + [** (% at 3+) x 3 **]**

▸ Normal tissues

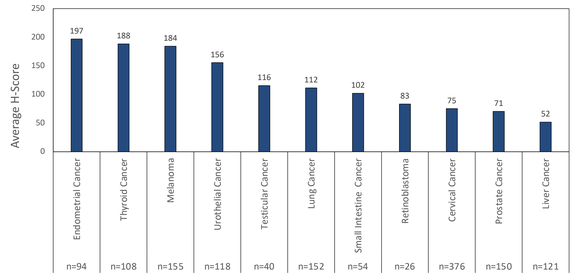
Due to the heterogeneity of cells in normal tissue (i.e. presence of multiple cell types), it was not possible to attribute an H-score representative of the tissue core. A descriptive approach was taken to identify the cell type and its staining intensity in normal tissues.

Results

A. EXAMPLE OF DIFFERENTIAL STAINING IN ENDOMETRIAL CANCER



B. PAN-TUMOR SORT1 EXPRESSION IN HUMAN CANCERS

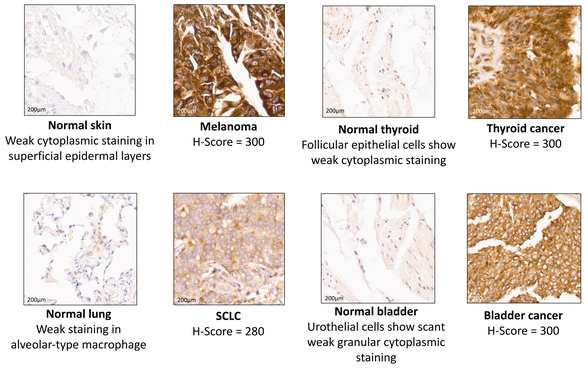


C. BREAKDOWN OF SORT1 REACTIVITY IN TUMOR TYPES BY H-SCORE

Breakdown of SORT1 reactivity for tumor types with n ≥50 and H-Score ≥100 (total of n = 681 in this sub-analysis)

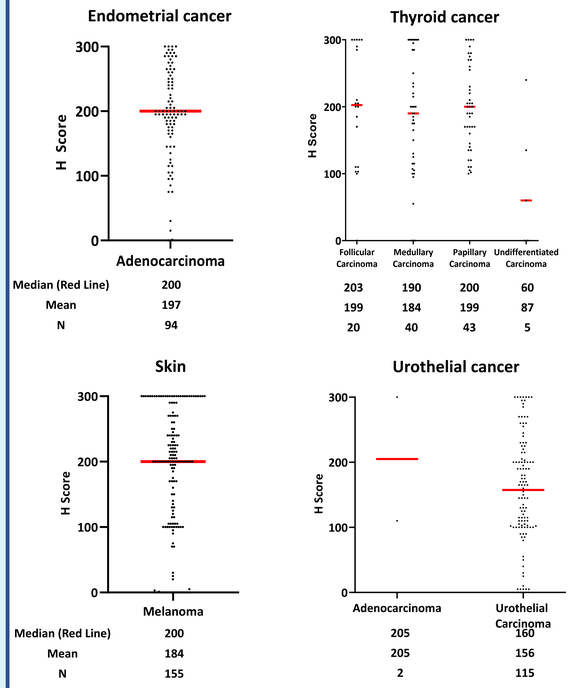
Cancer	No. of Evaluable Cases	H-Score 0 to <100		H-Score 100 to <200		H-Score 200 to 300		% of Indication H-score ≥100	Average H-Score
		No. of Cases	% of Indication	No. of Cases	% of Indication	No. of Cases	% of Indication		
Endometrial	94	9	10	37	39	48	51	**90**	**197**
Thyroid	108	9	8	45	42	54	50	**92**	**188**
Melanoma	155	26	17	37	24	92	59	**83**	**184**
Urothelial	118	23	19	54	46	41	35	**81**	**156**
Lung	152	64	42	54	36	34	22	**58**	**112**
NSCLC	108	62	57	32	30	14	13	**43**	**82**
SCLC	44	2	5	22	50	20	46	**95**	**183**
Small intestine	54	20	37	29	54	5	9	**63**	**102**

D. SORT1 EXPRESSION IN NORMAL VS. TUMOR TISSUES



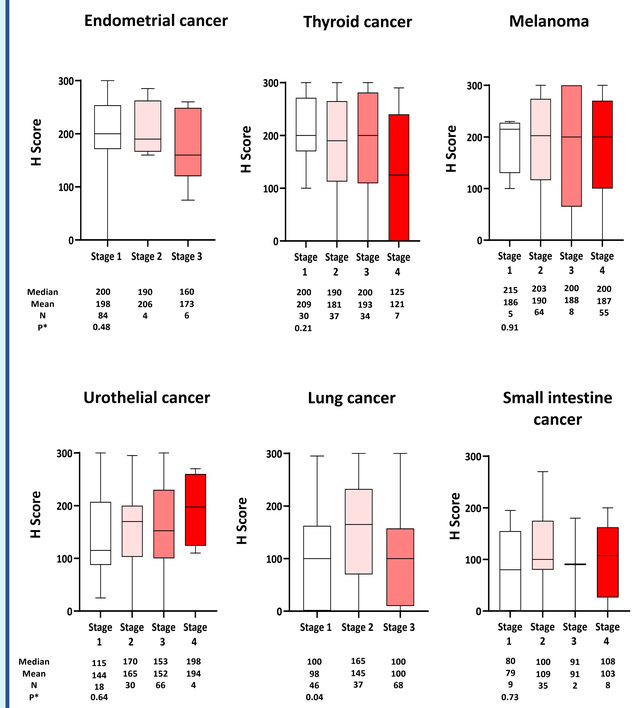
Results (cont'd)

E. SUB-ANALYSIS OF SORT1 EXPRESSION IN DIFFERENT PATHOLOGICAL SUB-TYPES



Results (cont'd)

F. SUB-ANALYSIS OF SORT1 EXPRESSION IN DIFFERENT CANCER STAGES



*Kruskal-Wallis test: A nonparametric approach to compare three or more groups on a dependent variable

Conclusions

- SORT1 is significantly over expressed in different cancers compared to normal tissues, high expression is maintained from stages 1 to 4.
- Expression of SORT1 is null or weak in most normal tissues, e.g. skin, thyroid, lung, bladder etc.
- These data will be used to support ongoing preclinical and clinical programs of Theratechnologies SORT1+ Technology™ platform. TH1902 is currently being evaluated in a Phase 1 clinical trial (clinicaltrial.gov: NCT04706962).
- This assessment of SORT1 expression across a variety of TMAs representing multiple tumor types such as bladder, thyroid, lung, small intestine, cervix, liver, testicular, and retinoblastoma has been confirmed in two separate studies.[9]
- SORT1 can be an important target for personalized approach in the treatment of solid tumors.

[1] Hu F, et al., *Neuron*. 2010;68(4):654-67. [2] Demeule M, et al., *Pharmaceutics*. 2022;14(9):1910. [3] Currie JC, et al., *Cancers (Basel)*. 2022;14(8):1877. [4] Charfi C, et al., *Front. Oncol.* 2021;11:760787. [5] Demeule M, et al., *Cancer Sci.,* 2021;112(10):4317-4334. [6] Roselli S, et al., *Oncotarget.* 2015;6(12):10473-10486. [7] Hemmati S, et al., *Avicenna J Med Biotechnol.*, 2009;1(2):125-131. [8] Ghaemimanesh F, et al., *Avicenna J Med Biotechnol*. 2014;6(3):169-177. [9]Roy G et al. EORTC-NCI-AACR-2022, abstract #328 .