

Role of the Sialyl-Tn antigen in cancer metastasis and survival



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Agenda

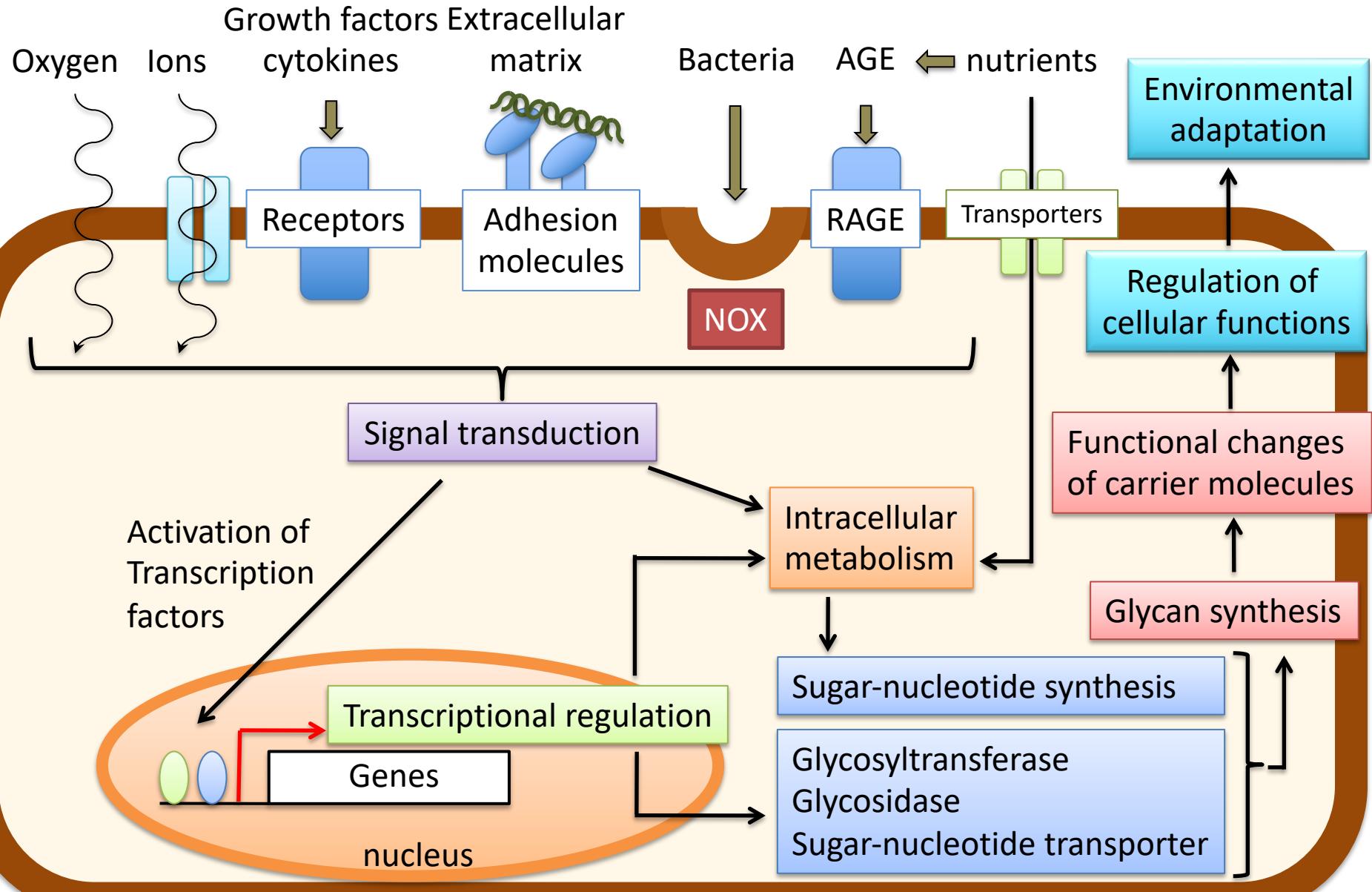
Induction of Sialyl-Tn antigen in hypoxic conditions

sTn antigen expression and cancer metastasis

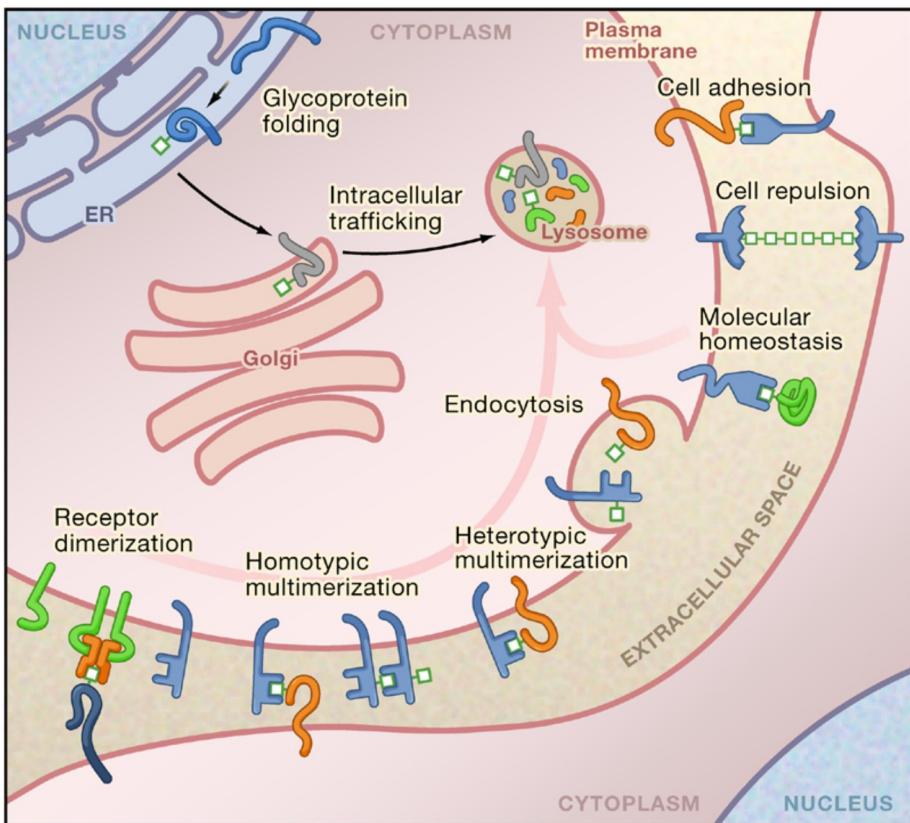
sTn antigen and tumor microenvironment remodeling

Potential for targeting sTn antigen for cancer therapy

Glycan synthesis in response to alterations in the cellular microenvironment.

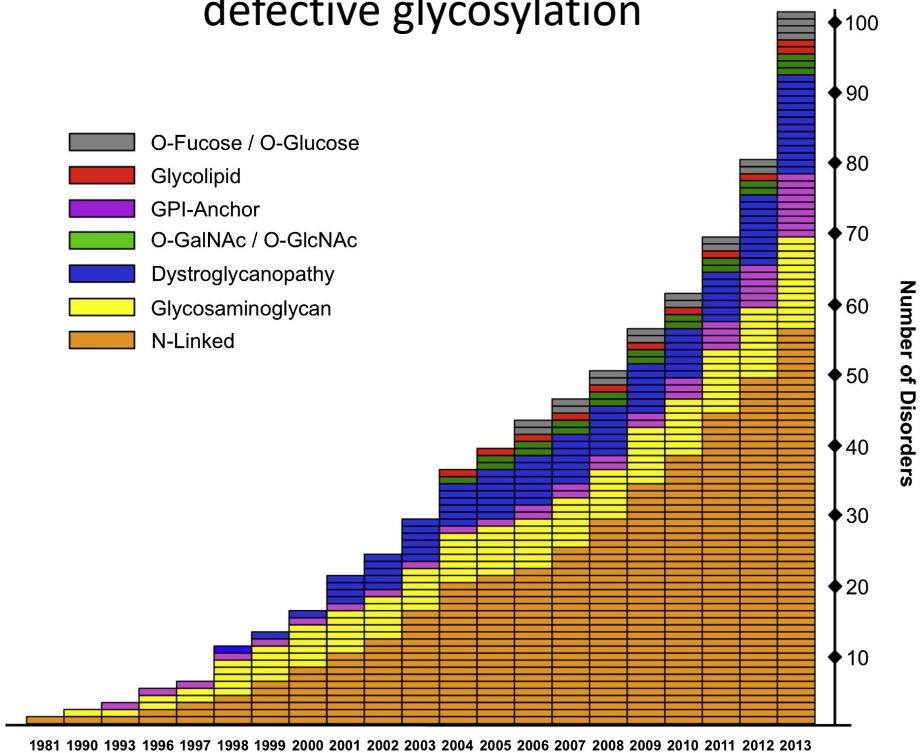


Misglycosylation and diseases



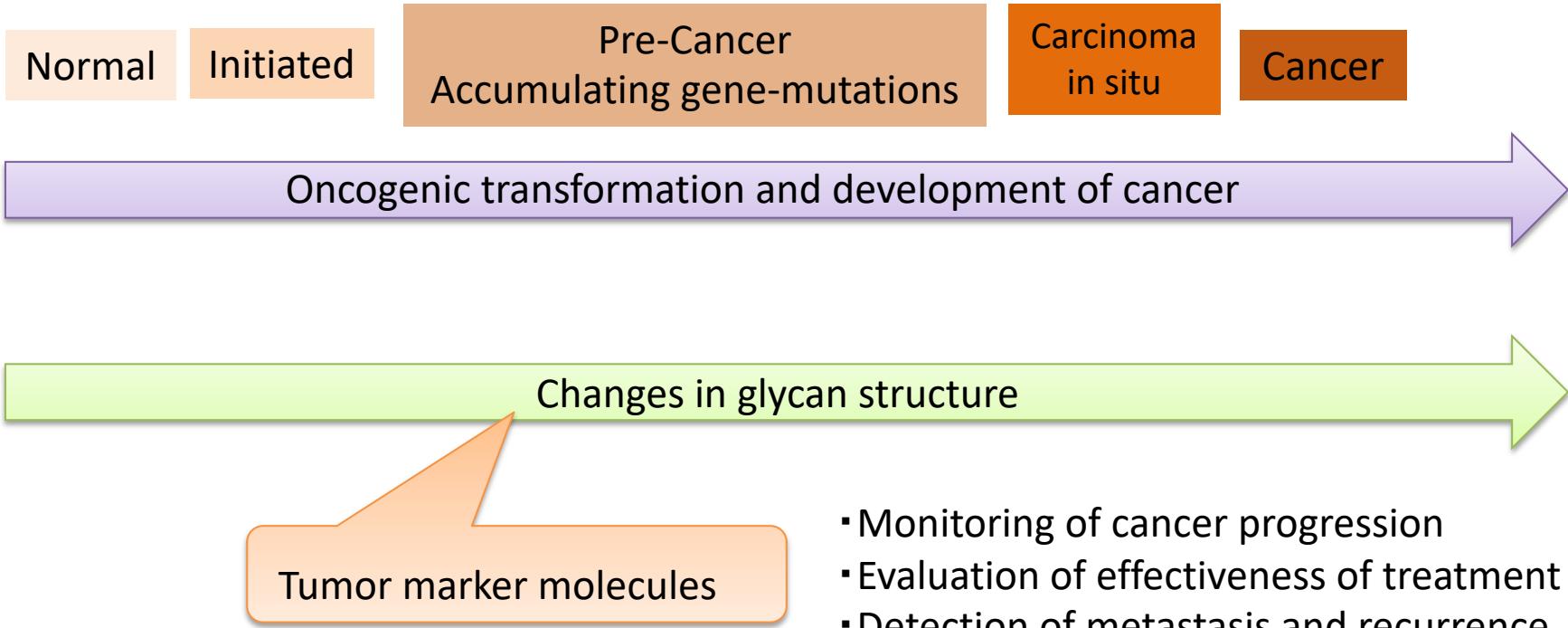
Ohtsubo, K. and Marth JD. *Cell* 126: 855-867, 2006

Number of diseases caused by defective glycosylation

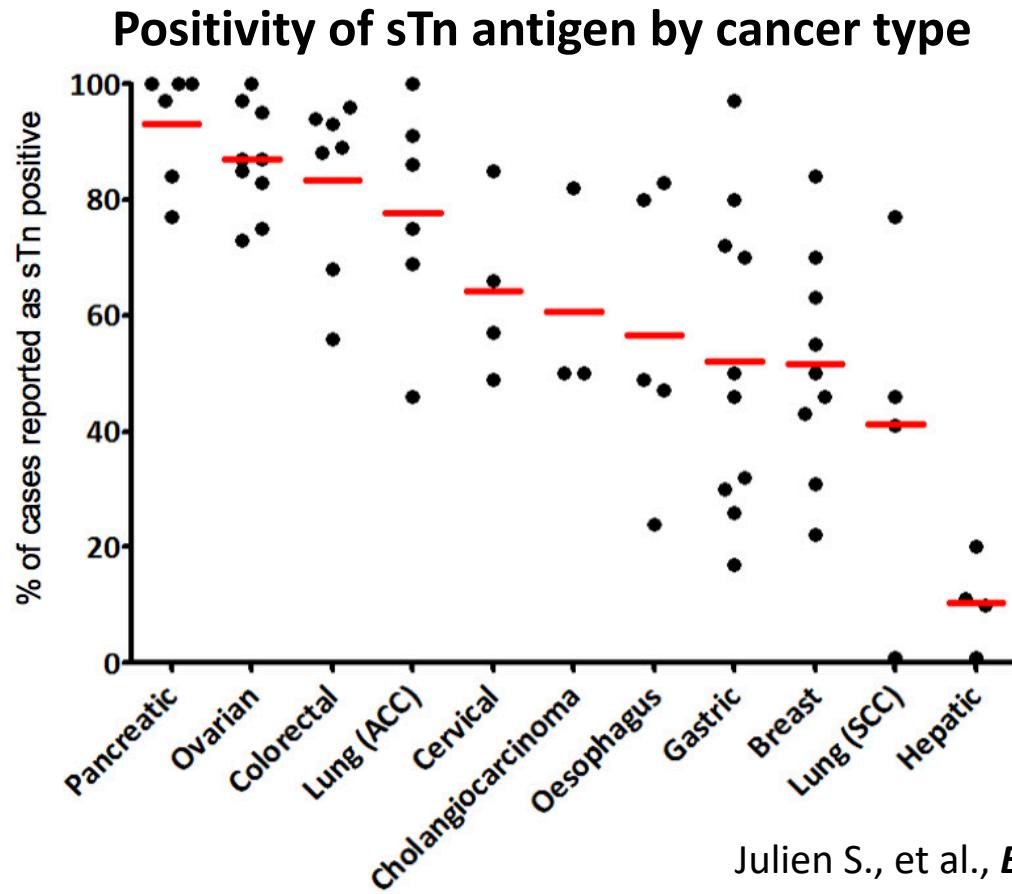


Hudson H. F. et al. *AJHG* 94:161-175, 2014

Alteration of glycan structure in the disease process of cancer



Cancer distribution of Sialyl-Tn (sTn) carbohydrate antigen



Julien S., et al., *Biomol.* 2:435-66, 2012

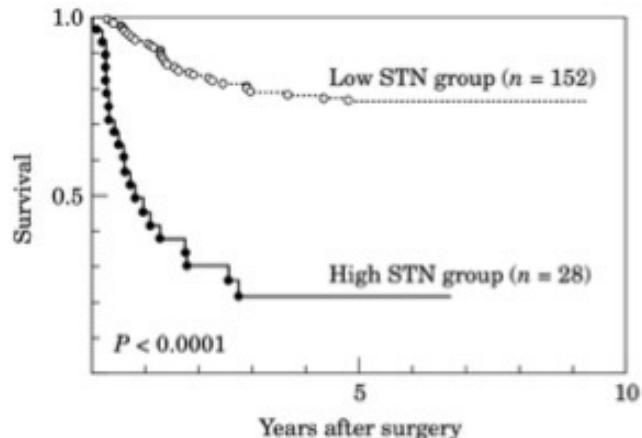
The expression is observed irrespective of cancer type



No expression in normal tissues

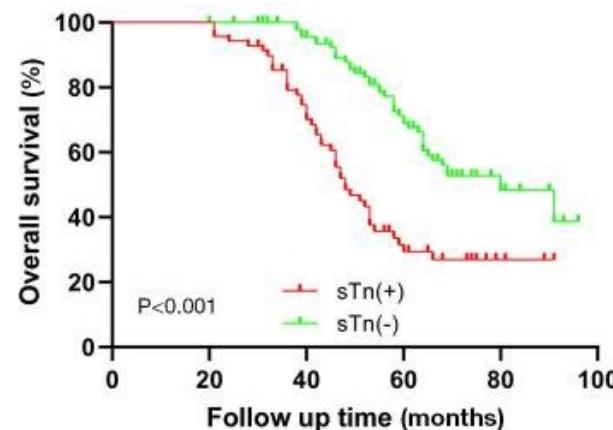
sTn antigen expression and prognosis of cancer patients

Gastric cancer



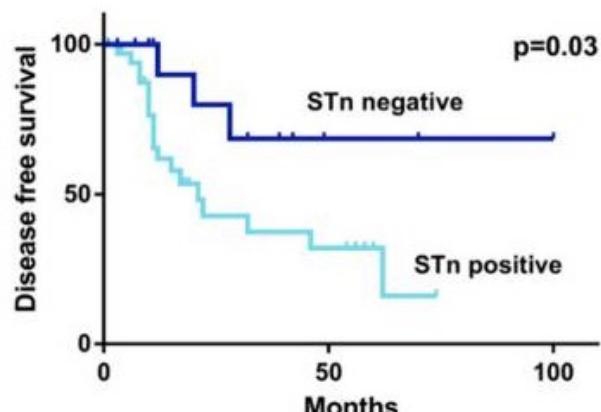
Nakagoe, T., et al, *EJSO* 27: 731-739, 2001

Breast cancer



Xu, F., et al, *Gland surgery* 10: 2673-2685, 2021

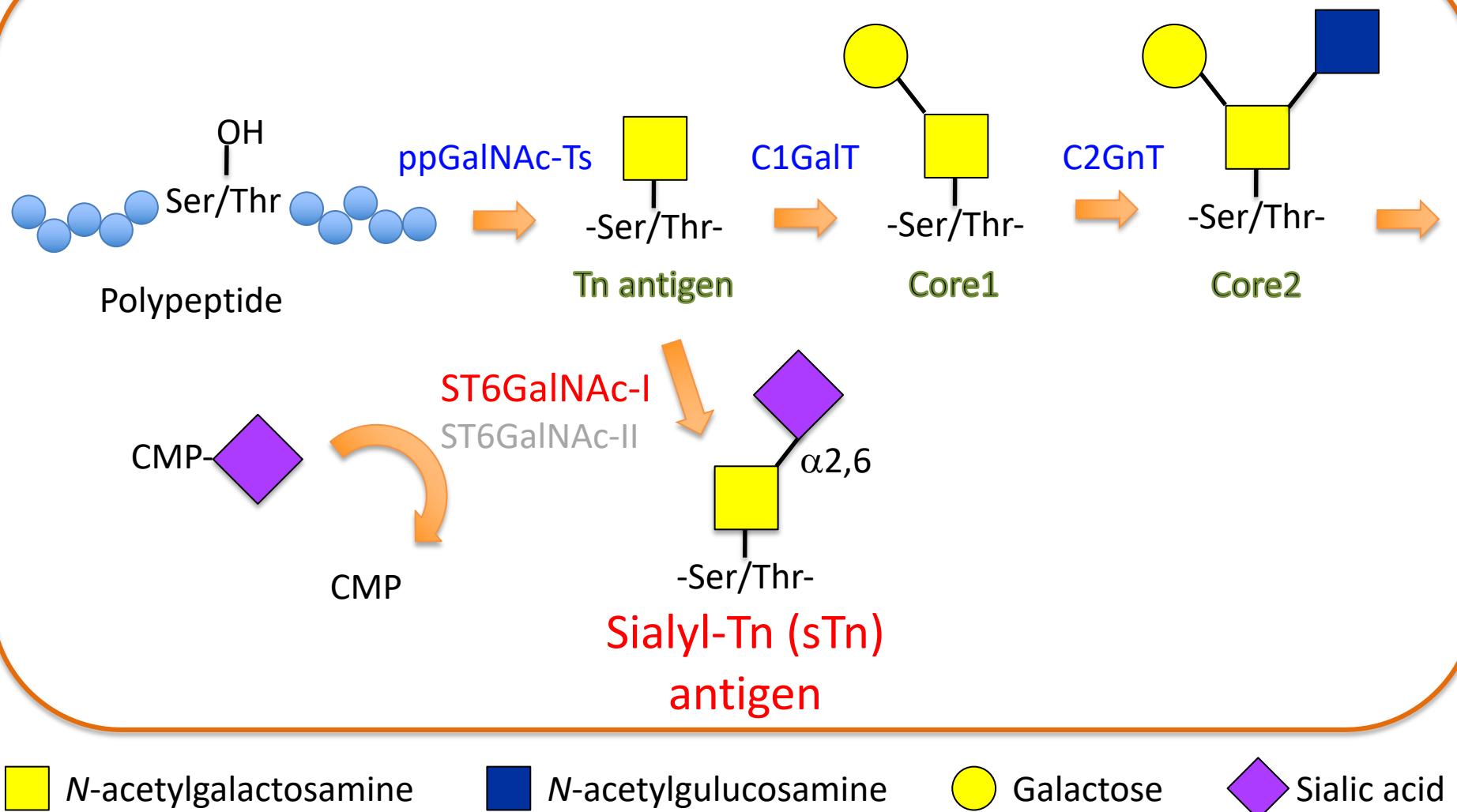
Esophageal cancer



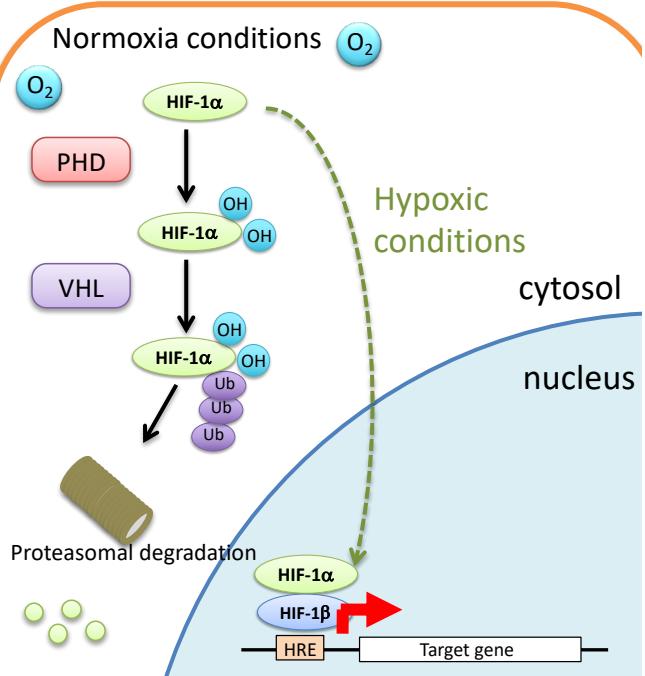
Cotton, S., et al, *Int J Mol Sci.* 22: 1664, 2021

Synthesis pathway of sTn antigen

The early steps of *O*-glycan synthesis pathway



Hypoxic induction of sTn antigen

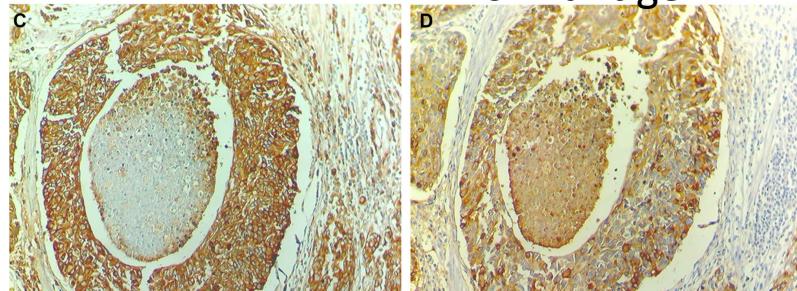


PDH:prolyl hydroxylase, VHL:von Hippel–Lindau

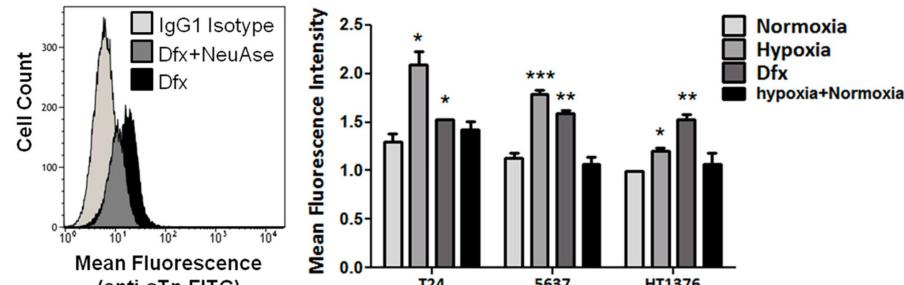
sTn antigen expression and nuclear localization of HIF-1 α in bladder cancer

HIF-1 α

sTn antigen

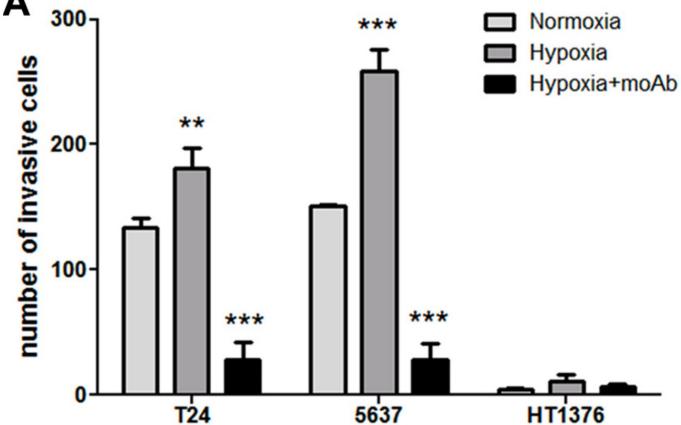


Hypoxic induction of sTn antigen



Enhanced invasion of hypoxic tumor cells, and inhibitory effect of sTn antibody

A



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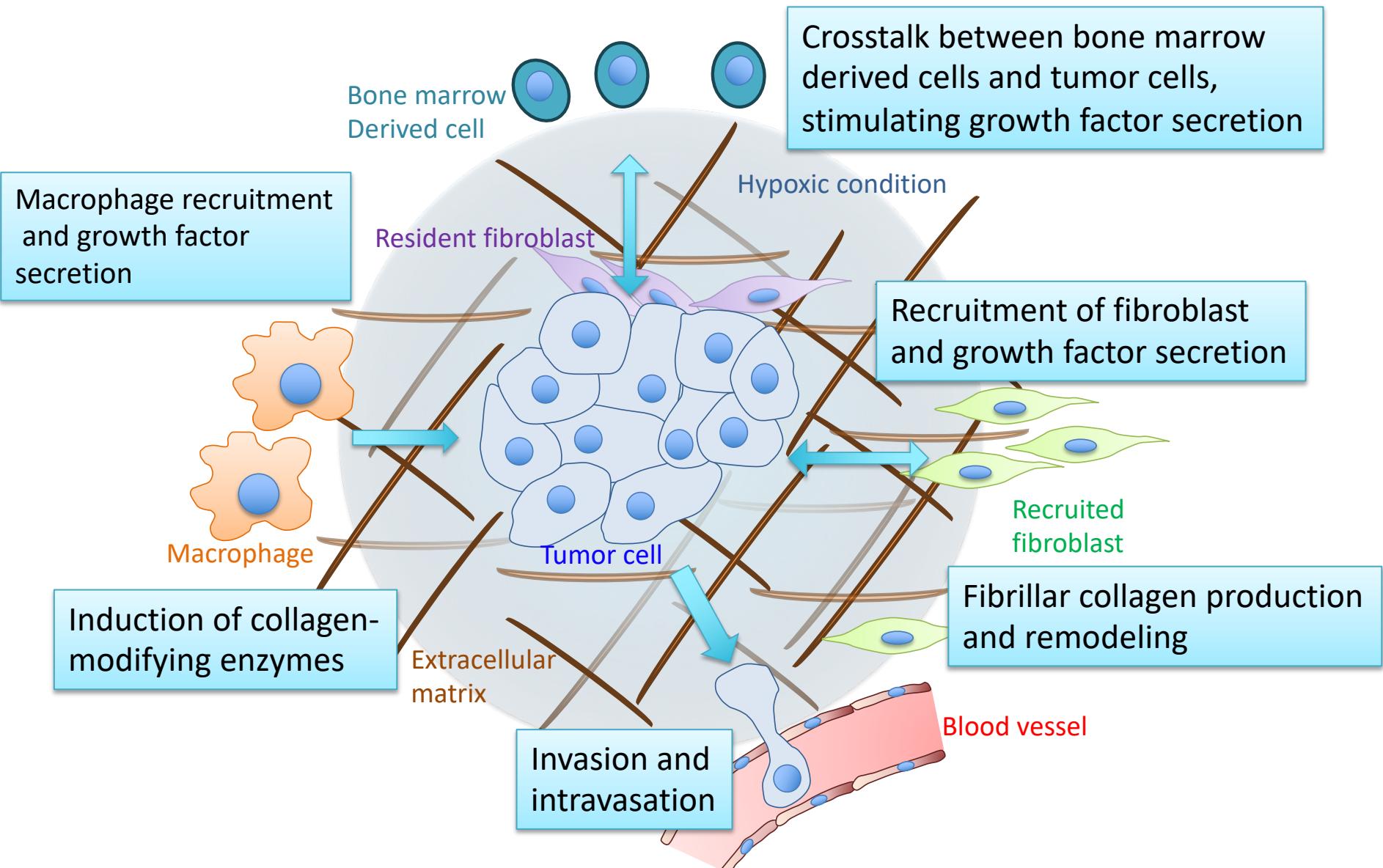
Induction of Sialyl-Tn antigen in hypoxic conditions

sTn antigen expression and cancer metastasis

sTn antigen and tumor microenvironment remodeling

Potential for targeting sTn antigen for cancer therapy

Hypoxic tumor microenvironments promoting cancer metastasis



sTn antigen expression and metastasis

Serum sialyl-Tn antigen level as a prognostic indicator in patients with gastric-cancer.

Maeda K, Chung Y, Onoda N, Nakanishi I, Nitta A, Arimoto Y, Yamada N, Kondo Y, Kato Y, Sowa M.
Int J Oncol. 1994 Jan;4(1):129-32. PMID: 21566901

sTn antigen expression
and lymphatic metastasis
of gastric cancer

Correlation between sialyl Tn antigen and lymphatic metastasis in patients with Borrmann type IV gastric carcinoma.

Kakeji Y, Maehara Y, Morita M, Matsukuma A, Furusawa M, Takahashi I, Kusumoto T, Ohno S, Sugimachi K.
Br J Cancer. 1995 Jan;71(1):191-5. doi: 10.1038/bjc.1995.39. PMID: 7819038

sTn antigen expression
and lymphatic metastasis
of gastric cancer

Immunohistochemical expression of sialyl Tn and sialyl Lewis(a) antigens in stromal tissue correlates with peritoneal dissemination in stage IV human gastric cancer.

Ikeda Y, Mori M, Kamakura T, Saku M, Sugimachi K.
Eur J Surg Oncol. 1995 Apr;21(2):168-75. doi: 10.1016/s0748-7983(95)90369-0. PMID: 7720892

sTn antigen expression
and peritoneal dissemination
of gastric cancer

Expression of sialyl-Tn in breast cancer. Correlation with prognostic parameters.

Soares R, Marinho A, Schmitt F.
Pathol Res Pract. 1996 Dec;192(12):1181-6. doi: 10.1016/S0344-0338(96)80148-8. PMID: 9182286

sTn antigen expression
and lymphatic metastasis
of breast cancer



Experimental demonstration of metastatic characteristics of sTn antigen-expressing cells

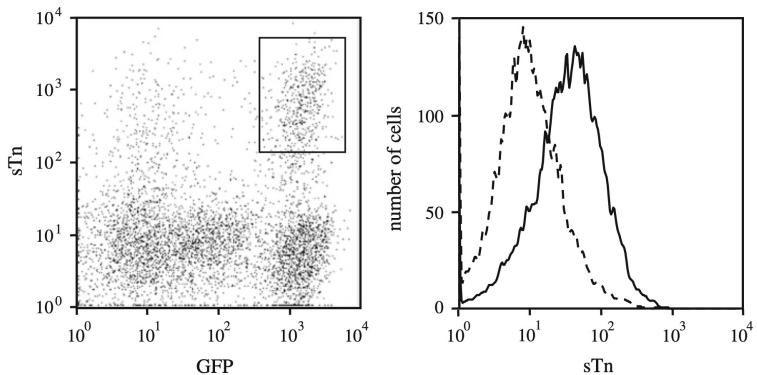
Cloning and expression of a human gene encoding an N-acetylgalactosamine-alpha2,6-sialyltransferase (ST6GalNAc I): a candidate for synthesis of cancer-associated sialyl-Tn antigens.

Ikehara Y, Kojima N, Kurosawa N, Kudo T, Kono M, Nishihara S, Issiki S, Morozumi K, Itzkowitz S, Tsuda T, Nishimura SI, Tsuji S, Narimatsu H.
Glycobiology. 1999 Nov;9(11):1213-24. doi: 10.1093/glycob/9.11.1213.

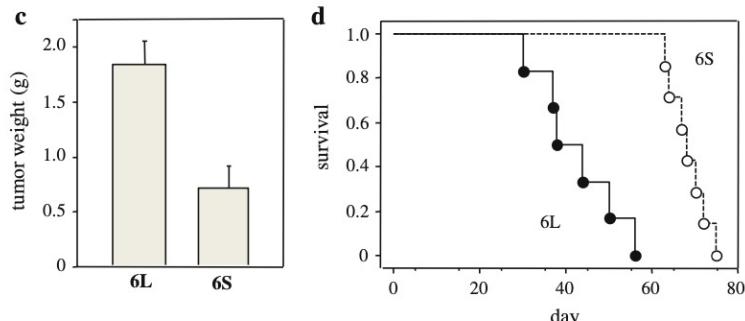
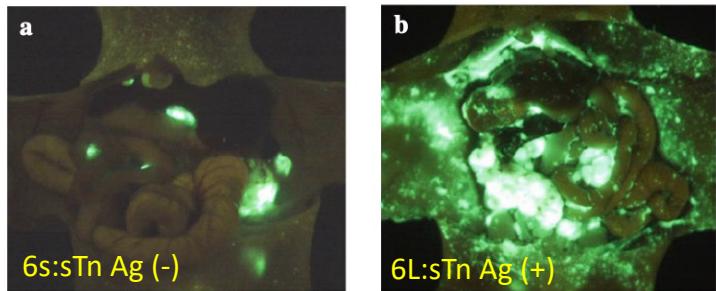
Cloning of ST6GalNAc-I gene

sTn antigen expression and metastasis

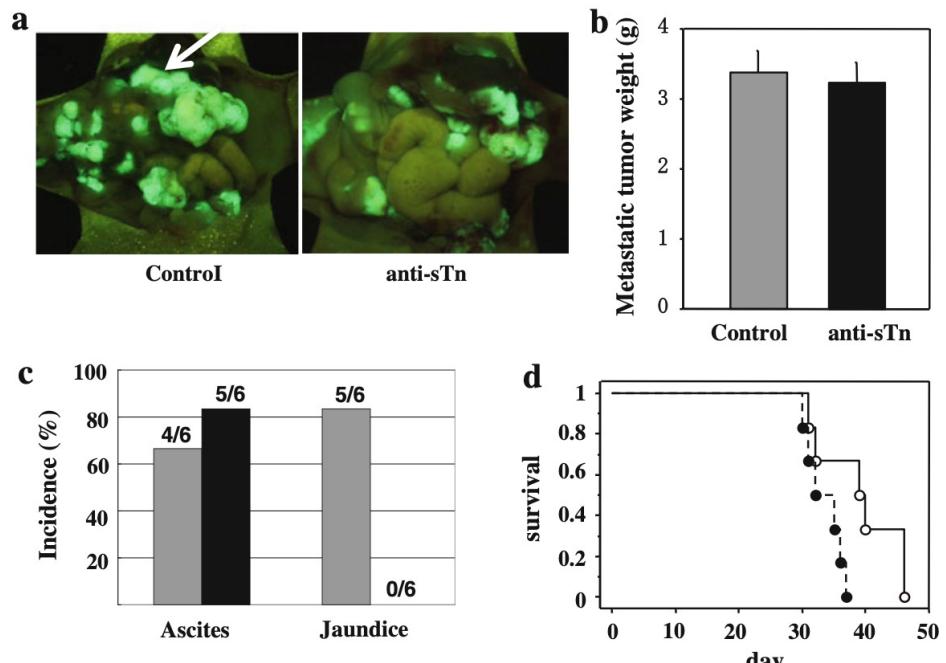
Establishment of cells expressing GFP and sTn antigen



Facilitated peritoneal dissemination of sTn antigen expressing cells



Suppression of peritoneal dissemination by sTn antibody treatment



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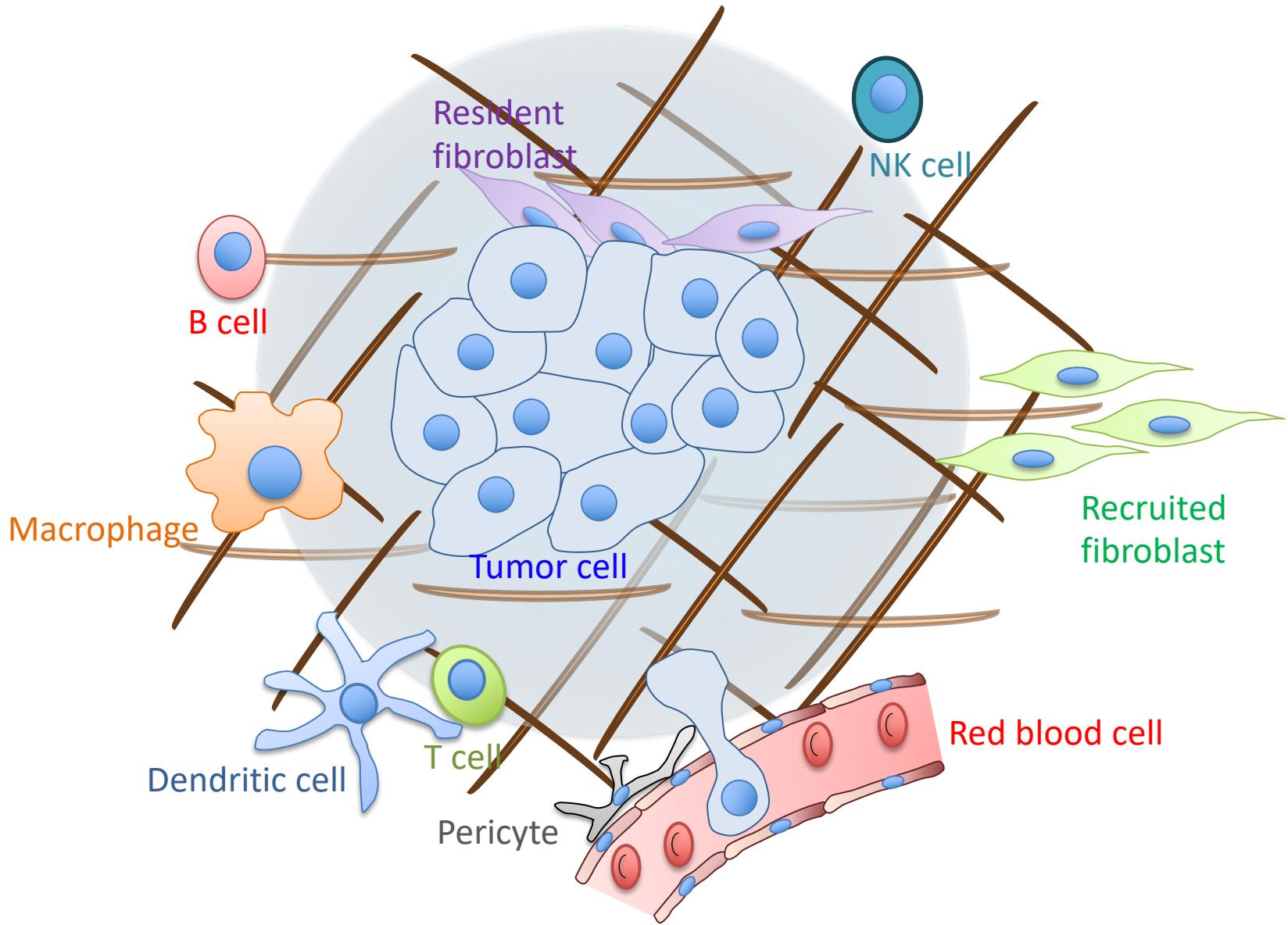
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sTn antigen and tumor microenvironment remodeling

Potential for targeting sTn antigen for cancer therapy

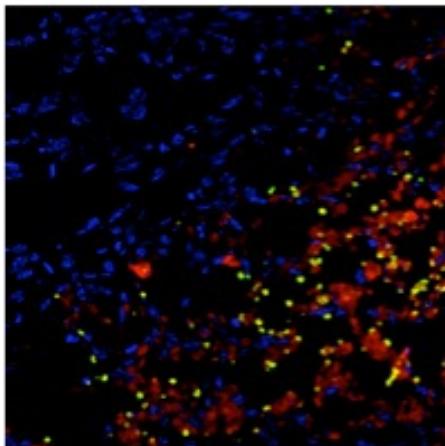
Cell types making up the tumor microenvironments



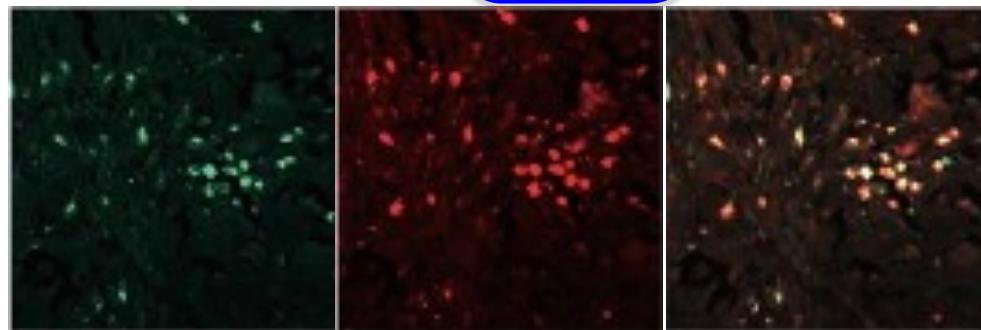
Macrophages associated with sTn antigen-expressing cancer cells express Siglec-15

Human lung cancer tissue

CD68/sTn/DAPI

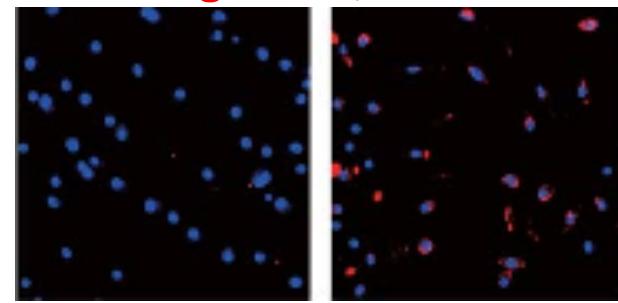


CD68/Siglec-15
recognizes
sTn antigen



Human monocyte
Treated with

Siglec-15/DAPI

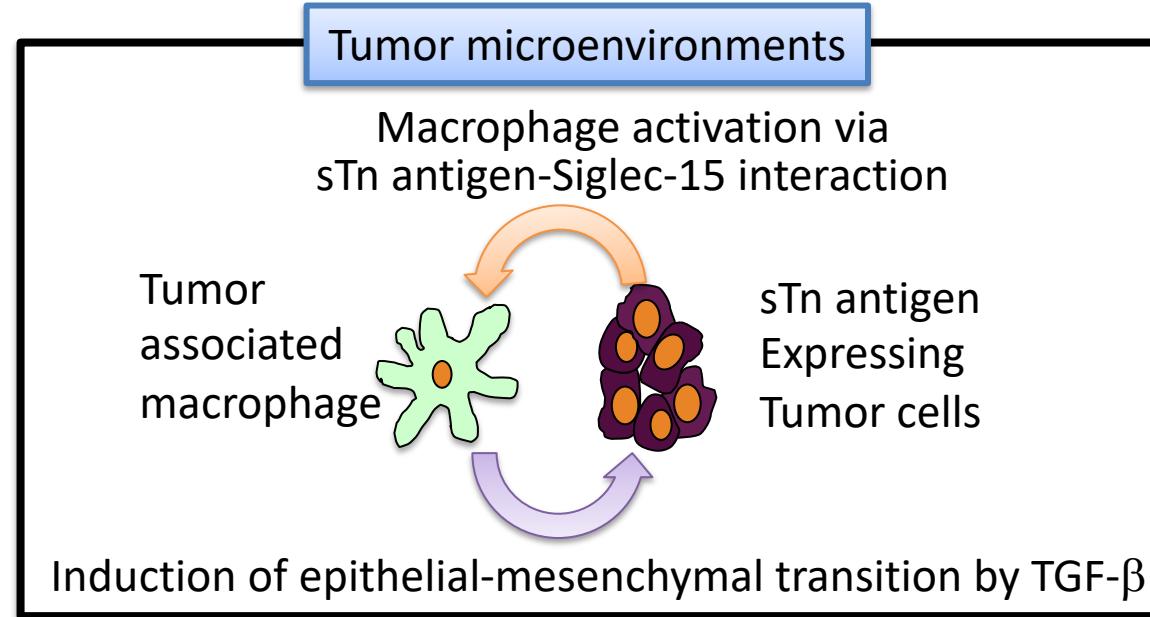
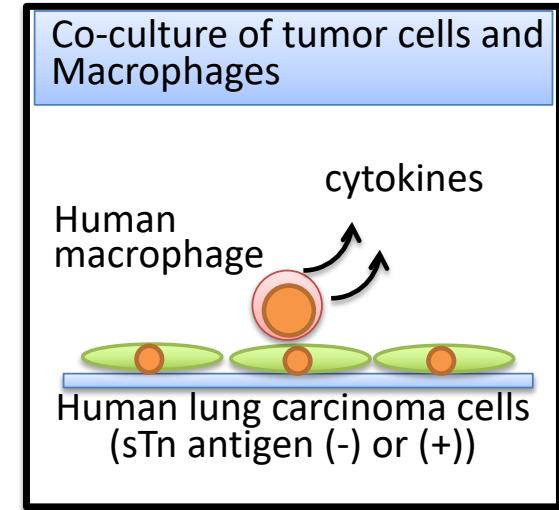
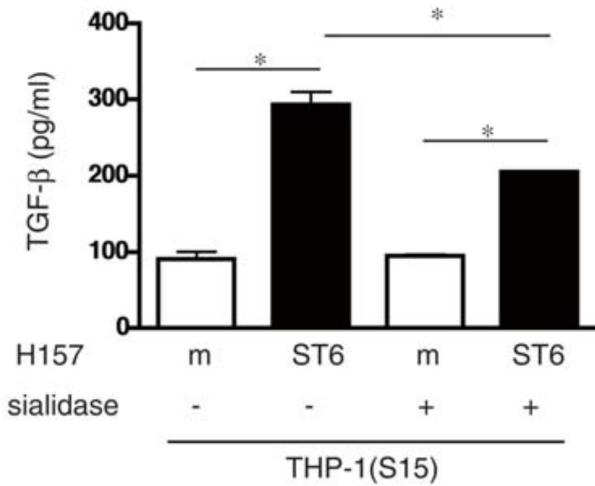
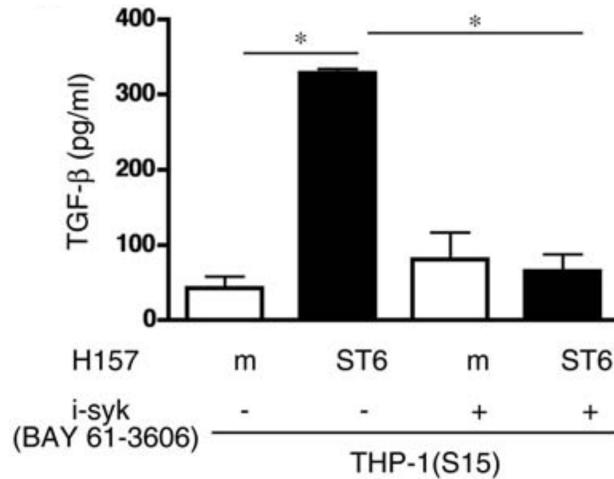
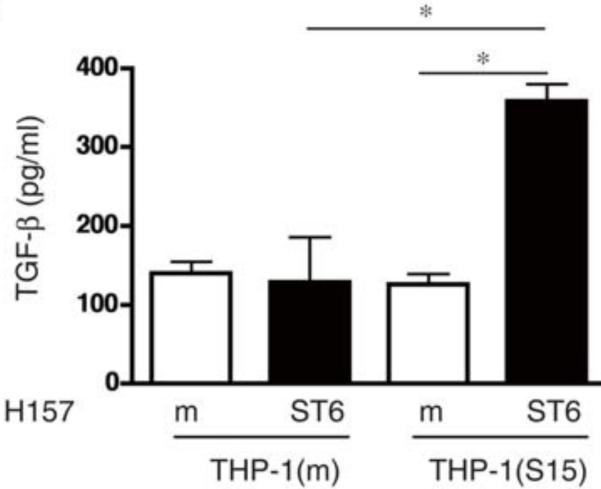


GM-CSF (M1)

M-CSF(M2)

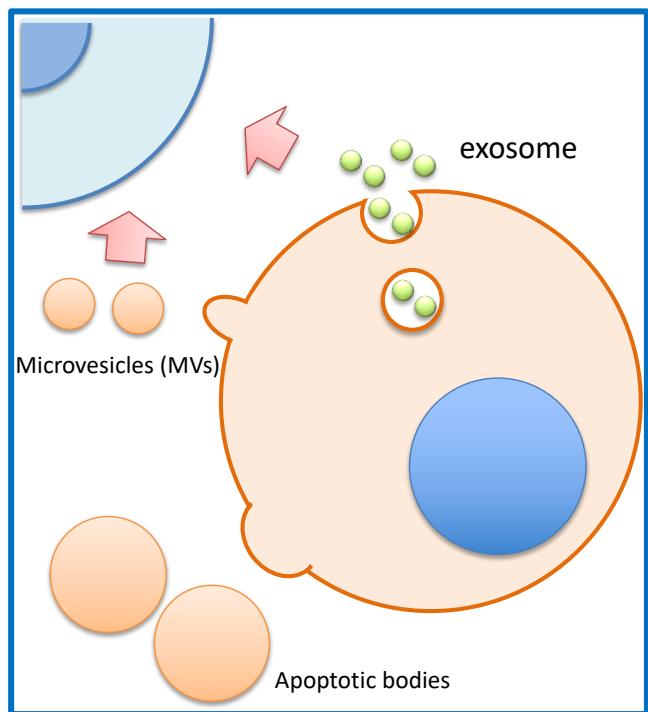
Induction of TGF- β production via Siglec-15

□ MOCK ■ ST6exp



Regulation of the hypoxic cancer microenvironments by cancer cell-derived extracellular vesicles

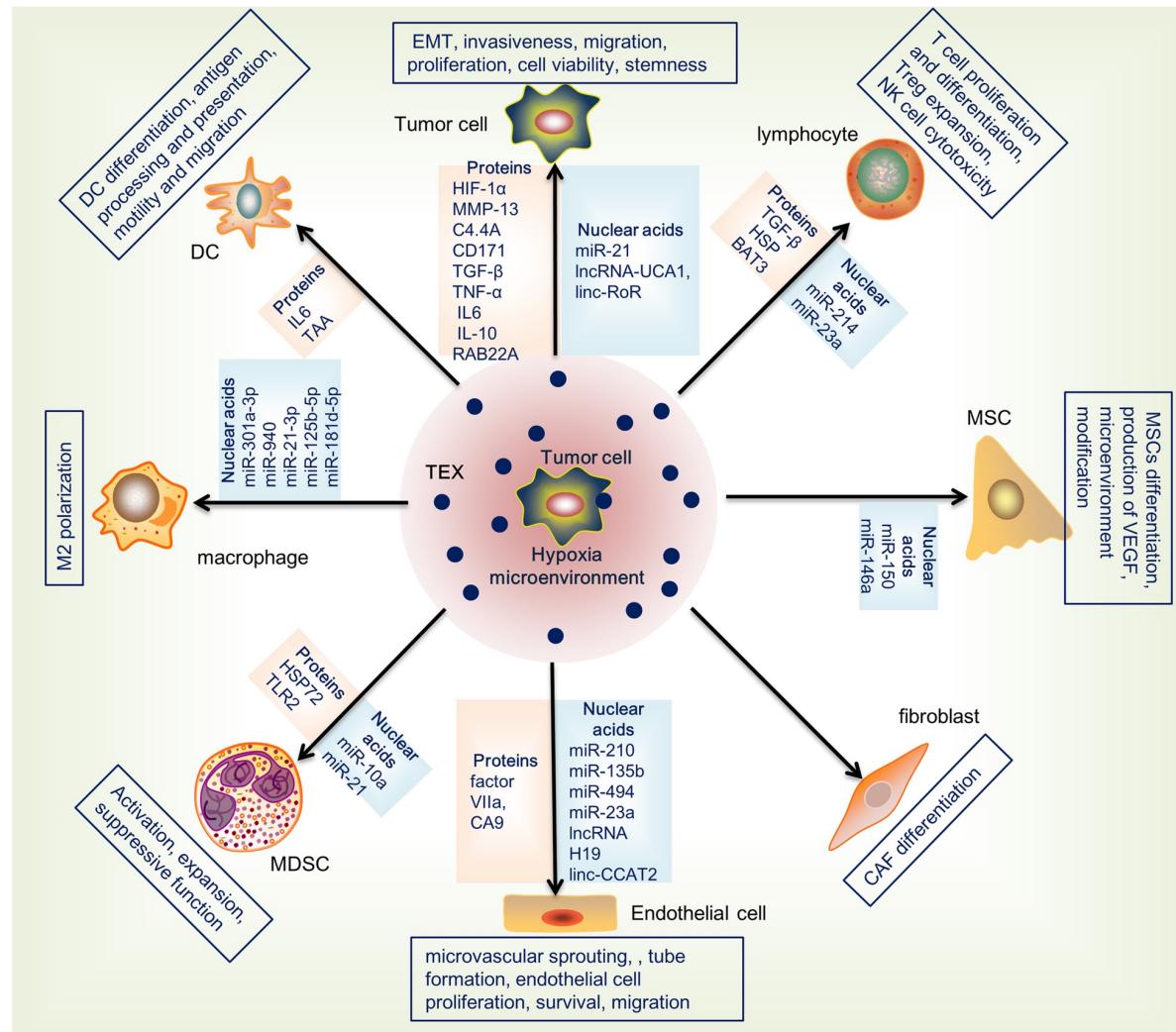
(Extracellular Vesicles; EVs)



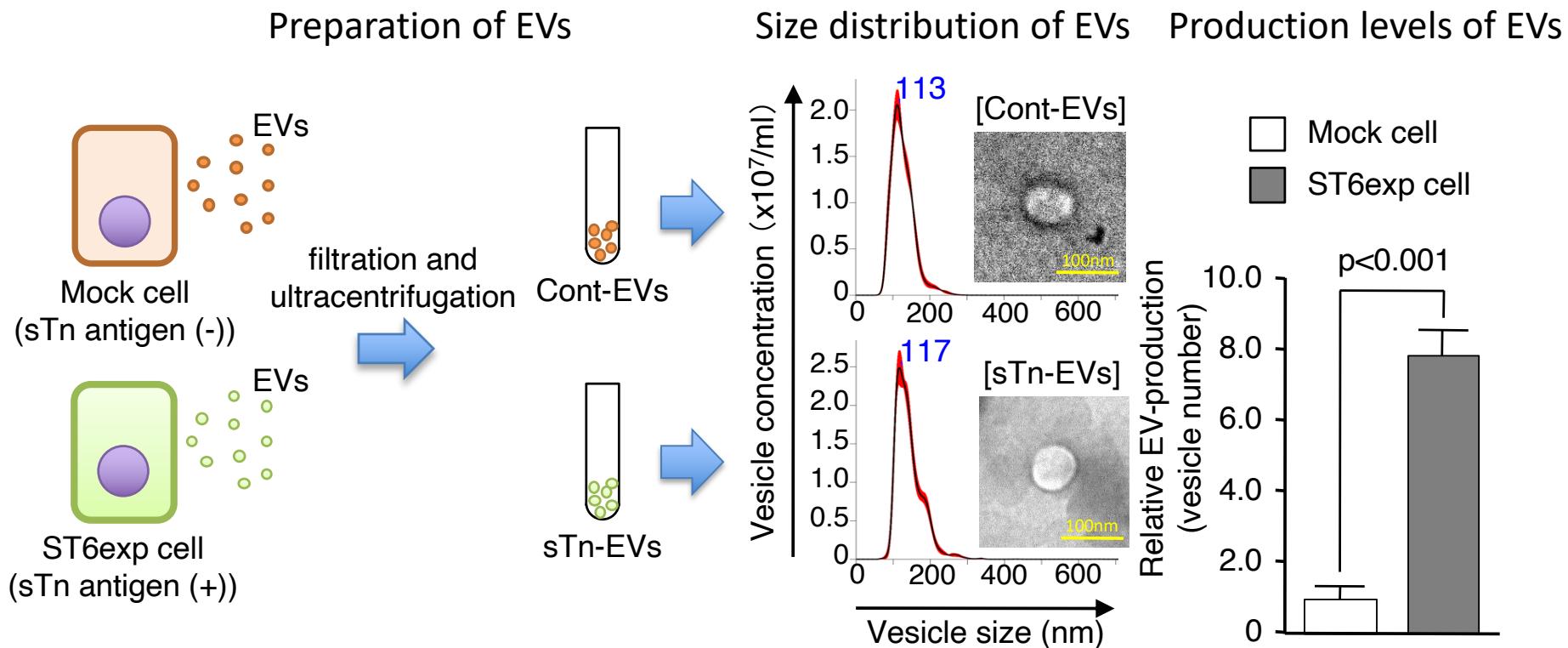
Exosome: 30~150nm

MV: 100~1000nm

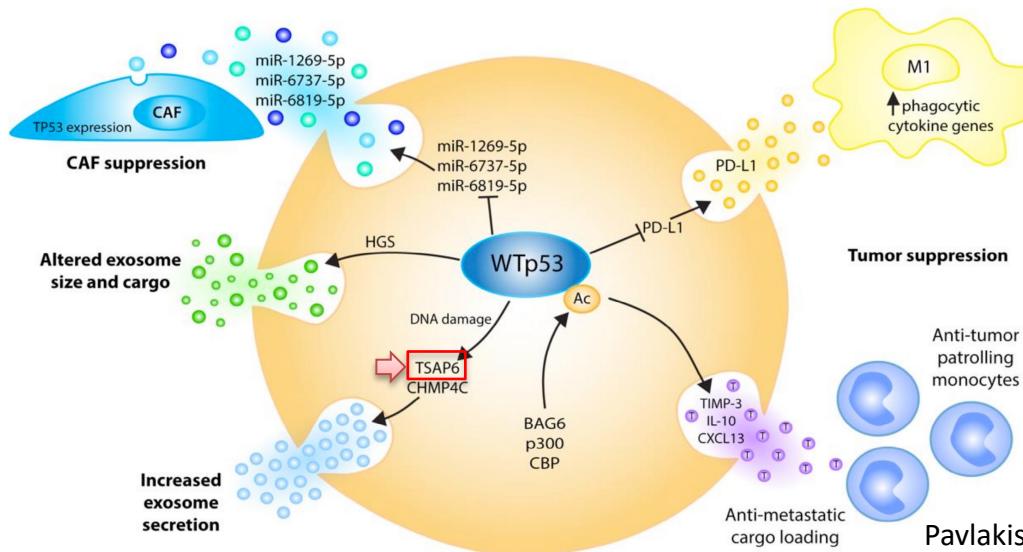
Apoptotic body: 50~5000nm



Increased production of EVs in sTn antigen-expressing cells



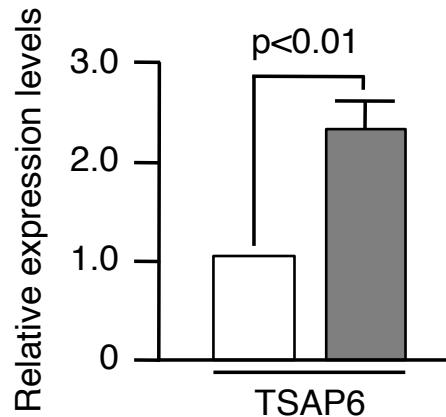
TSAP6-dependent EVs production



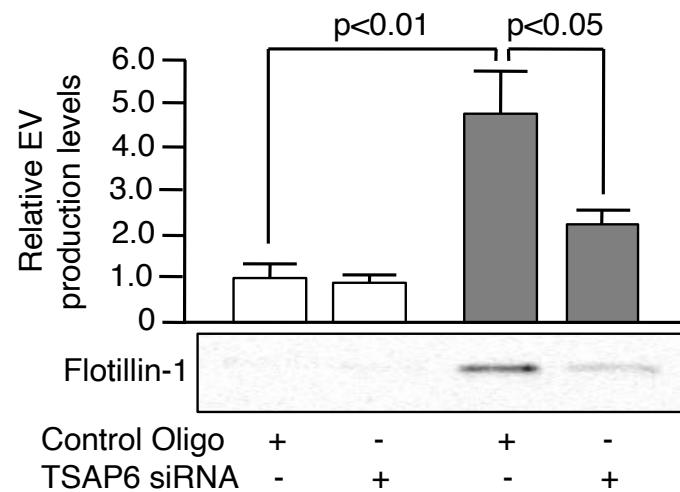
Pavlakis E. et al., *Int J Mol Sci* 21:9648, 2020

TSAP6 expression levels

□ Mock cell ■ ST6exp cell

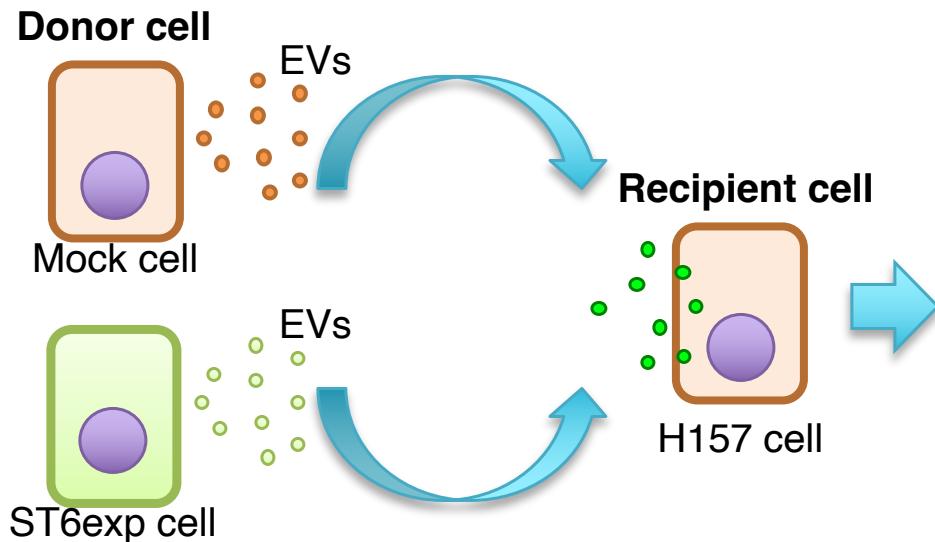


EV-production levels in TSAP6 knock down cells



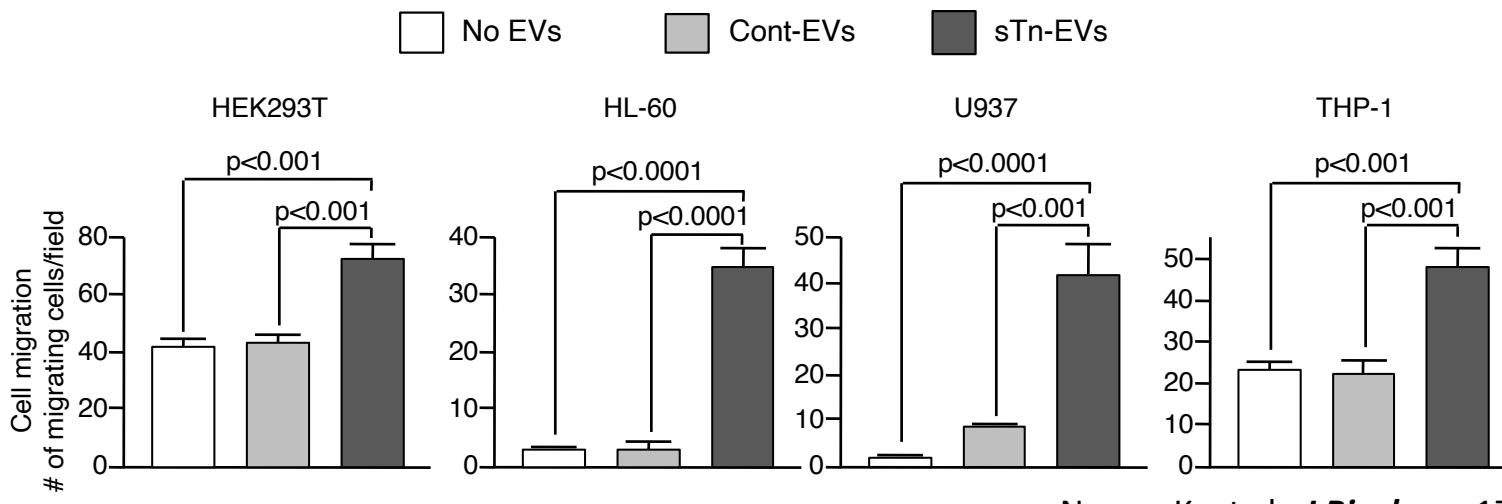
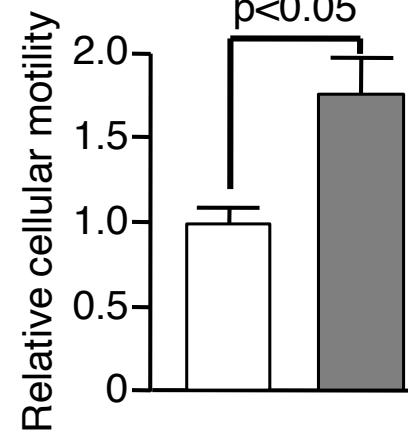
Nagao, K. et al., *J Biochem*. 171: 543-554, 2022

Enhanced motility of EV-recipient cells



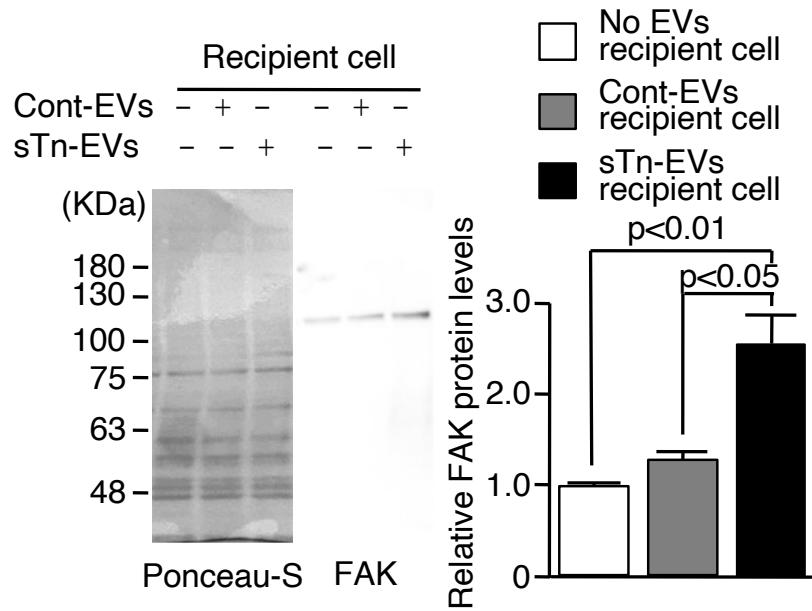
Cellular motility

□ Cont-EVs
recipient cell
■ sTn-EVs
recipient cell

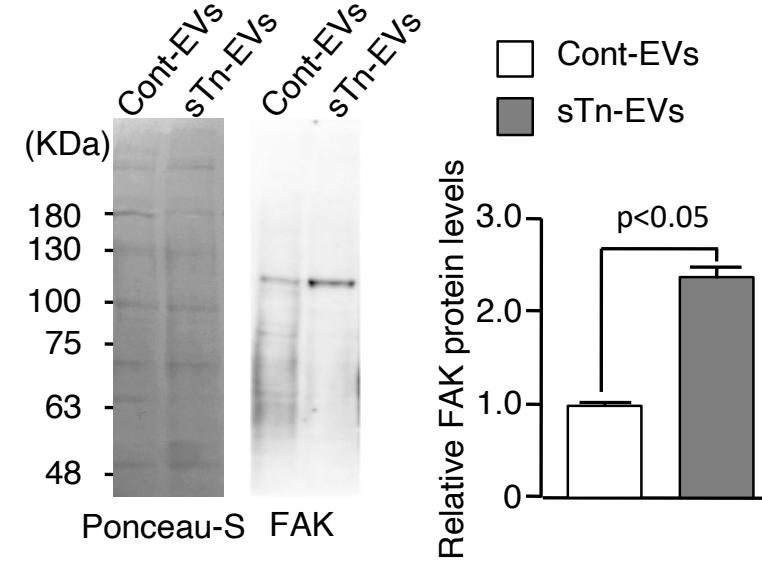


EVs transport FAK

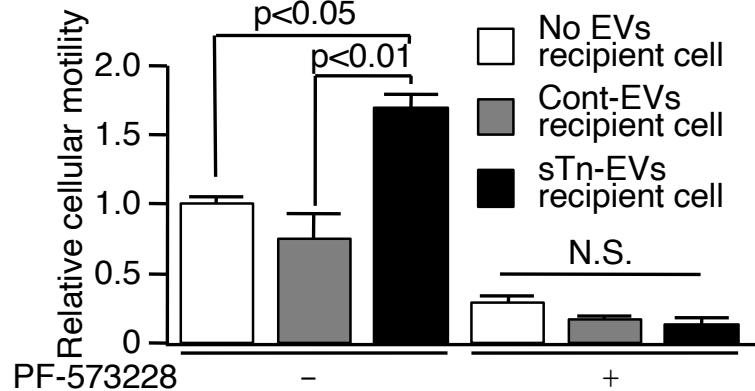
FAK protein levels in EV-recipient cells



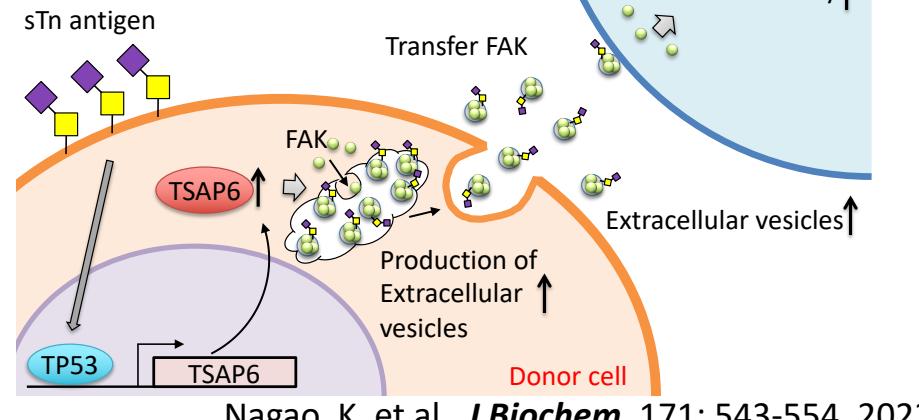
FAK protein abundance in EVs



Motility of EV-recipient cells under FAK inhibition conditions



sTn antigen facilitates extracellular vesicle-mediated FAK transfer



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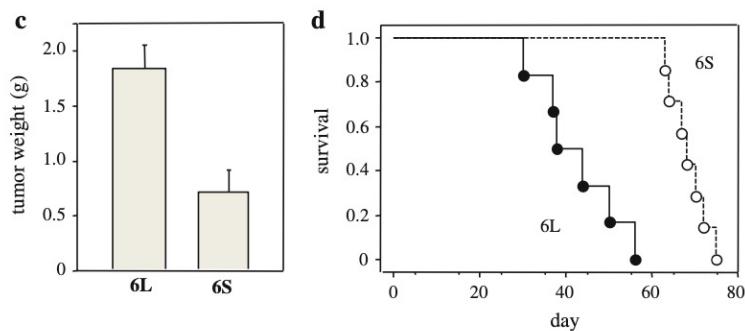
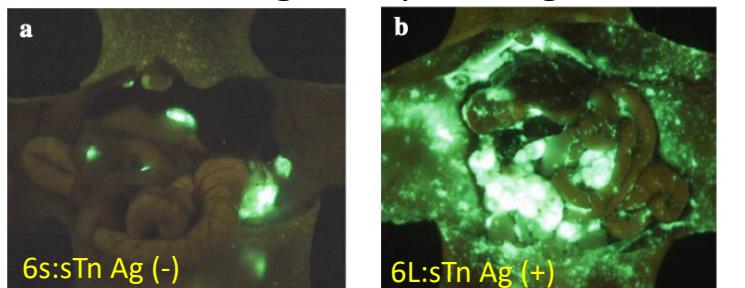
sTn antigen expression and cancer metastasis

sTn antigen and tumor microenvironment remodeling

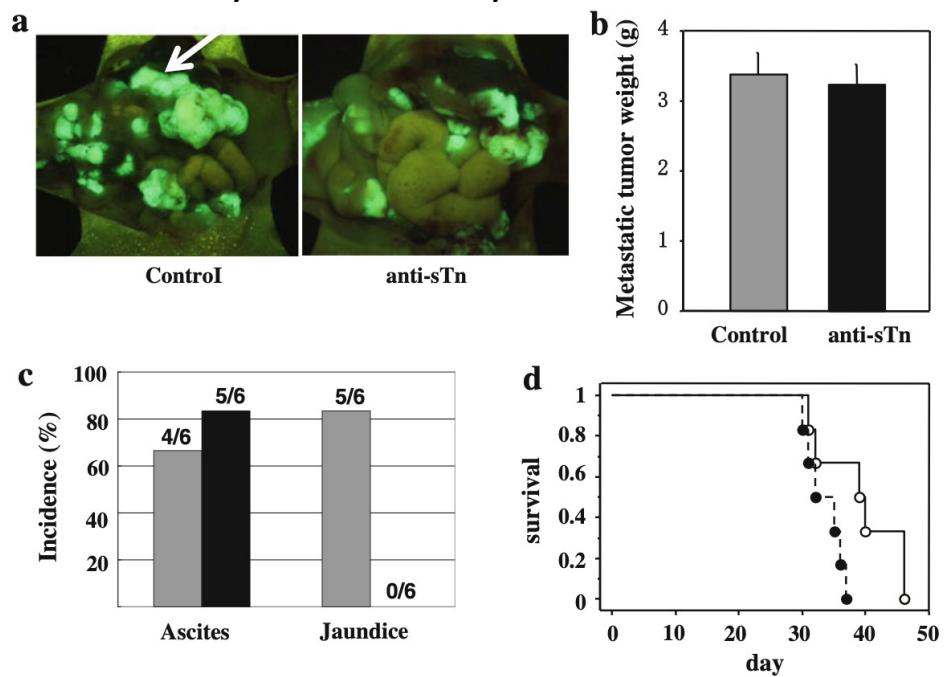
Potential for targeting sTn antigen for cancer therapy

Development of therapies (drug) targeting sTn antigen

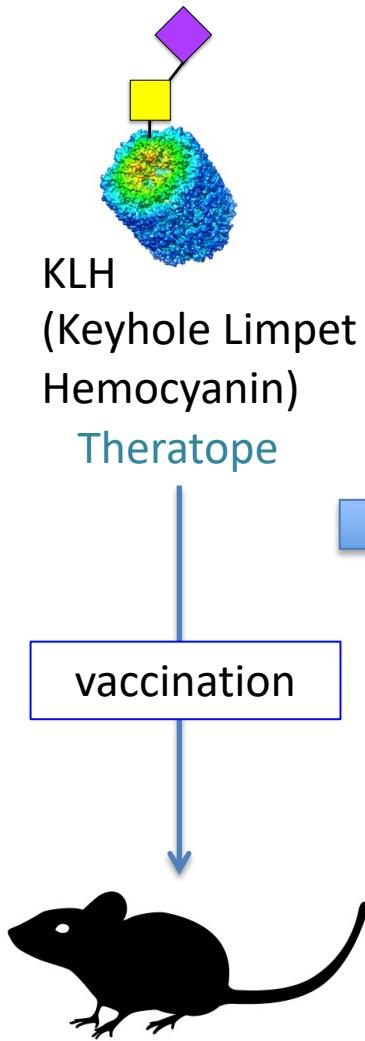
Facilitated peritoneal dissemination of sTn antigen expressing cells



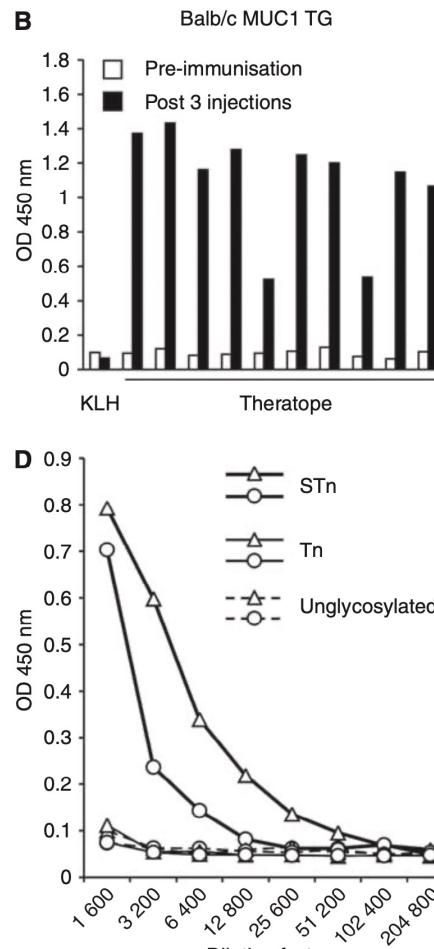
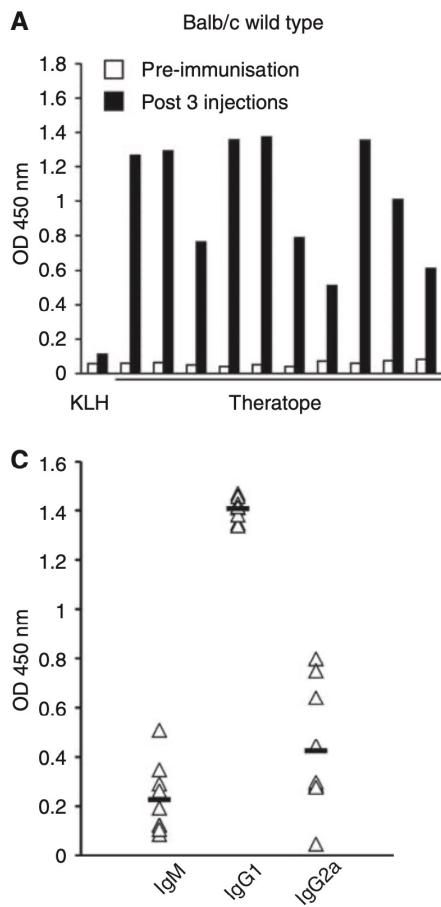
Suppression of peritoneal dissemination by sTn antibody treatment



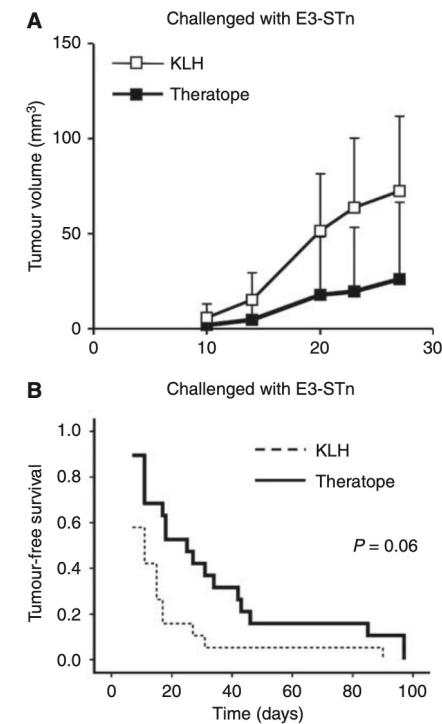
Development of vaccine therapies targeting the sTn antigen.



Induction of sTn antigen specific antibodies



Tumor suppression effect



References

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Freeze HH, Chong JX, Bamshad MJ, Ng BG. Solving glycosylation disorders: fundamental approaches reveal complicated pathways. *Am J Hum Genet.* 2014 Feb 6;94(2):161-75. doi: 10.1016/j.ajhg.2013.10.024.

Julien S, Videira PA, Delannoy P. Sialyl-tn in cancer: (how) did we miss the target? *Biomolecules.* 2012 Oct 11;2(4):435-66. doi: 10.3390/biom2040435.

Nakagoe T, Tsuji T, Jibiki M, Nanashima A, Yamaguchi H, Yasutake T, Ayabe H, Arisawa K, Ishikawa H. Pre-operative serum levels of sialyl Tn antigen predict liver metastasis and poor prognosis in patients with gastric cancer. *Eur J Surg Oncol.* 2001 Dec;27(8):731-9. doi: 10.1053/ejso.2001.1199.

Xu F, Li M, Li J, Jiang H. Diagnostic accuracy and prognostic value of three-dimensional electrical impedance tomography imaging in patients with breast cancer. *Gland Surg.* 2021 Sep;10(9):2673-2685. doi: 10.21037/gs-21-348.

Cotton S, Ferreira D, Soares J, Peixoto A, Relvas-Santos M, Azevedo R, Piairo P, Diéguez L, Palmeira C, Lima L, Silva AMN, Lara Santos L, Ferreira JA. Target Score-A Proteomics Data Selection Tool Applied to Esophageal Cancer Identifies GLUT1-Sialyl Tn Glycoforms as Biomarkers of Cancer Aggressiveness. *Int J Mol Sci.* 2021 Feb 7;22(4):1664. doi: 10.3390/ijms22041664.

Peixoto A, Fernandes E, Gaiteiro C, Lima L, Azevedo R, Soares J, Cotton S, Parreira B, Neves M, Amaro T, Tavares A, Teixeira F, Palmeira C, Rangel M, Silva AM, Reis CA, Santos LL, Oliveira MJ, Ferreira JA. Hypoxia enhances the malignant nature of bladder cancer cells and concomitantly antagonizes protein O-glycosylation extension. *Oncotarget.* 2016 Sep 27;7(39):63138-63157. doi: 10.18632/oncotarget.11257.

References

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- Julien S, Picco G, Sewell R, Vercoutter-Edouart AS, Tarp M, Miles D, Clausen H, Taylor-Papadimitriou J, Burchell JM. Sialyl-Tn vaccine induces antibody-mediated tumour protection in a relevant murine model. *Br J Cancer*. 2009 Jun 2;100(11):1746-54. doi: 10.1038/sj.bjc.6605083. Epub 2009 May 12.