

SITC 2019

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& Convention Center

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Podocalyxin is a therapeutic target in cancer

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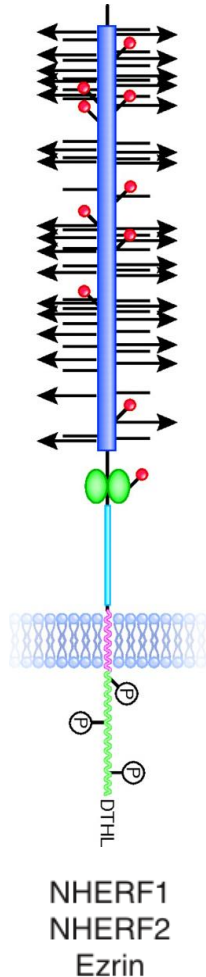
PhD Candidate

Overview

1. Podocalyxin, a new candidate for targeted therapeutics
2. Tumor specific α -PODXL antibody development
 - 2a. PODO83, a function-blocking antibody
 - 2b. PODO447, a highly tumor specific antibody
 - PODO 447 Antibody Drug Conjugate
5. Summary

Podocalyxin is a CD34-family sialomucin

Podocalyxin structure



Normal tissue expression pattern of podocalyxin

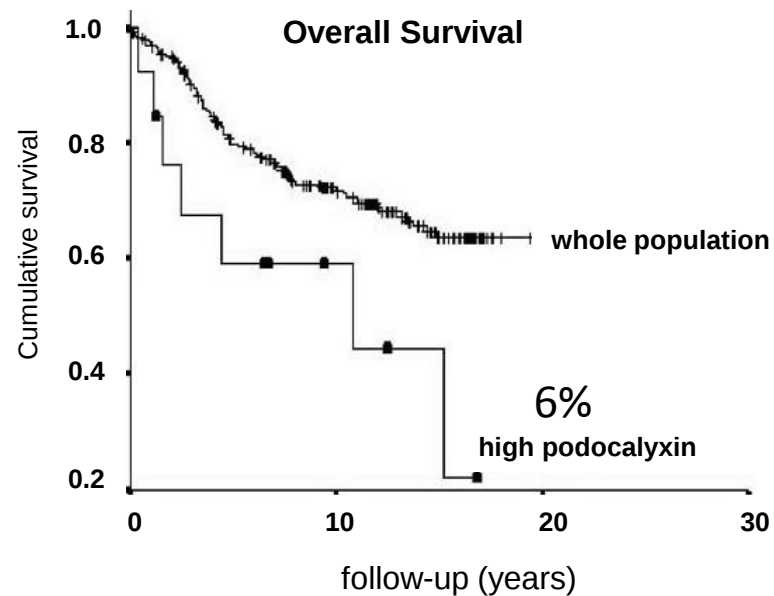
- Vascular Endothelia
- Kidney Podocytes (specialized epithelia)

Proposed functions

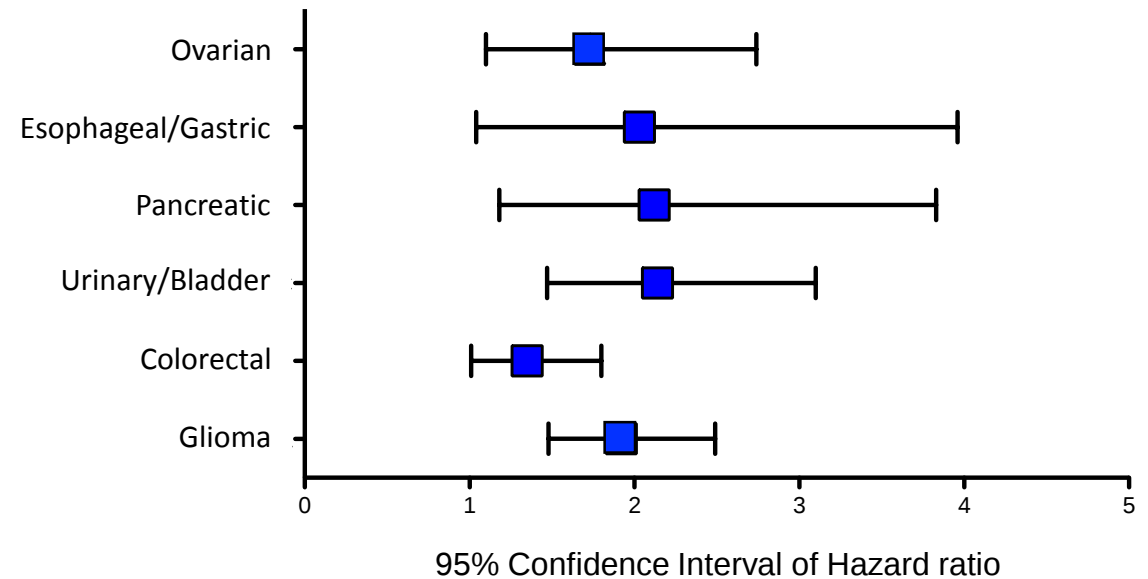
- Blocks adhesion
- Involved in cell migration
- Apical domain expansion
- Establishment of cell polarity
- Lumen formation

High podocalyxin expression is associated with poor prognosis in several cancer types

Breast Cancer



Meta-analysis of high PODXL overall survival



Most common cancers

Male			
Estimated New Cases	→ Prostate	164,690	19%
	Lung & bronchus	121,680	14%
	→ Colon & rectum	75,610	9%
	→ Urinary bladder	62,380	7%
	Melanoma of the skin	55,150	6%
	→ Kidney & renal pelvis	42,680	5%
	Non-Hodgkin lymphoma	41,730	5%
	Oral cavity & pharynx	37,160	4%
	Leukemia	35,030	4%
	Liver & intrahepatic bile duct	30,610	4%
	All sites	856,370	100%



Female			
	→ Breast	266,120	30%
	Lung & bronchus	112,350	13%
	→ Colon & rectum	64,640	7%
	Uterine corpus	63,230	7%
	Thyroid	40,900	5%
	Melanoma of the skin	36,120	4%
	Non-Hodgkin lymphoma	32,950	4%
	→ Pancreas	26,240	3%
	Leukemia	25,270	3%
	→ Kidney & renal pelvis	22,660	3%
	All sites	878,980	100%



Responsible for most deaths

Male			
Estimated Deaths	Lung & bronchus	83,550	26%
	→ Prostate	29,430	9%
	→ Colon & rectum	27,390	8%
	→ Pancreas	23,020	7%
	Liver & intrahepatic bile duct	20,540	6%
	Leukemia	14,270	4%
	→ Esophagus	12,850	4%
	→ Urinary bladder	12,520	4%
	Non-Hodgkin lymphoma	11,510	4%
	→ Kidney & renal pelvis	10,010	3%
	All sites	323,630	100%

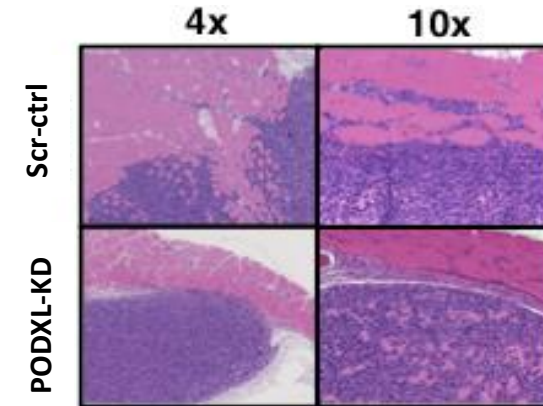
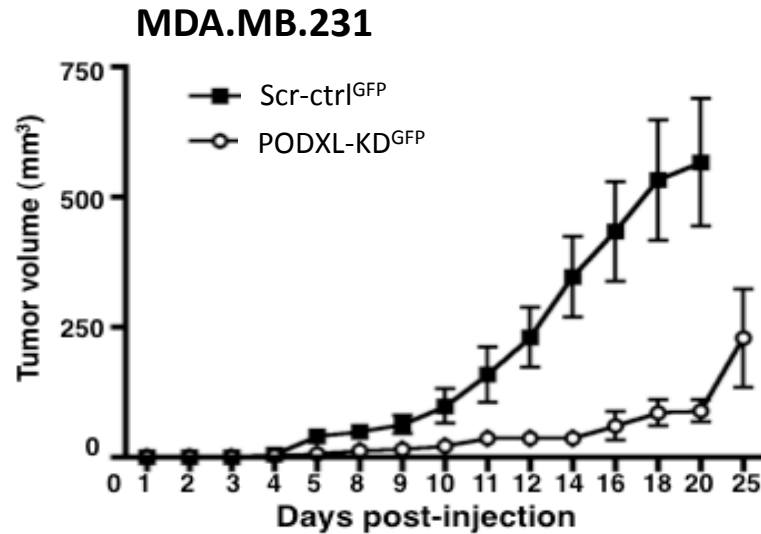


Female			
	Lung & bronchus	70,500	25%
	→ Breast	40,920	14%
	→ Colon & rectum	23,240	8%
	→ Pancreas	21,310	7%
	→ Ovary	14,070	5%
	Uterine corpus	11,350	4%
	Leukemia	10,100	4%
	Liver & intrahepatic bile duct	9,660	3%
	Non-Hodgkin lymphoma	8,400	3%
	→ Brain & other nervous system	7,340	3%
	All sites	286,010	100%

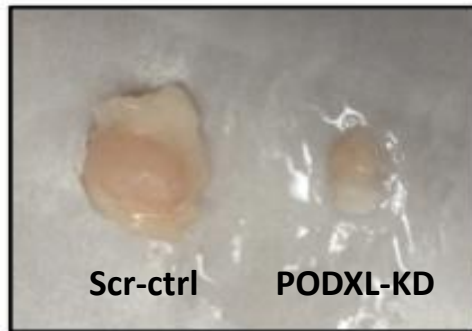
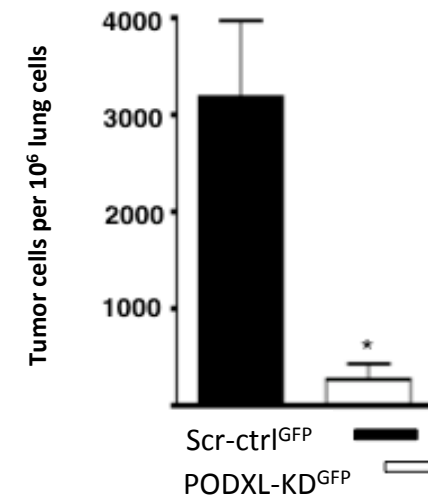


Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

Podocalyxin expression promotes tumor growth and metastasis *in vivo*

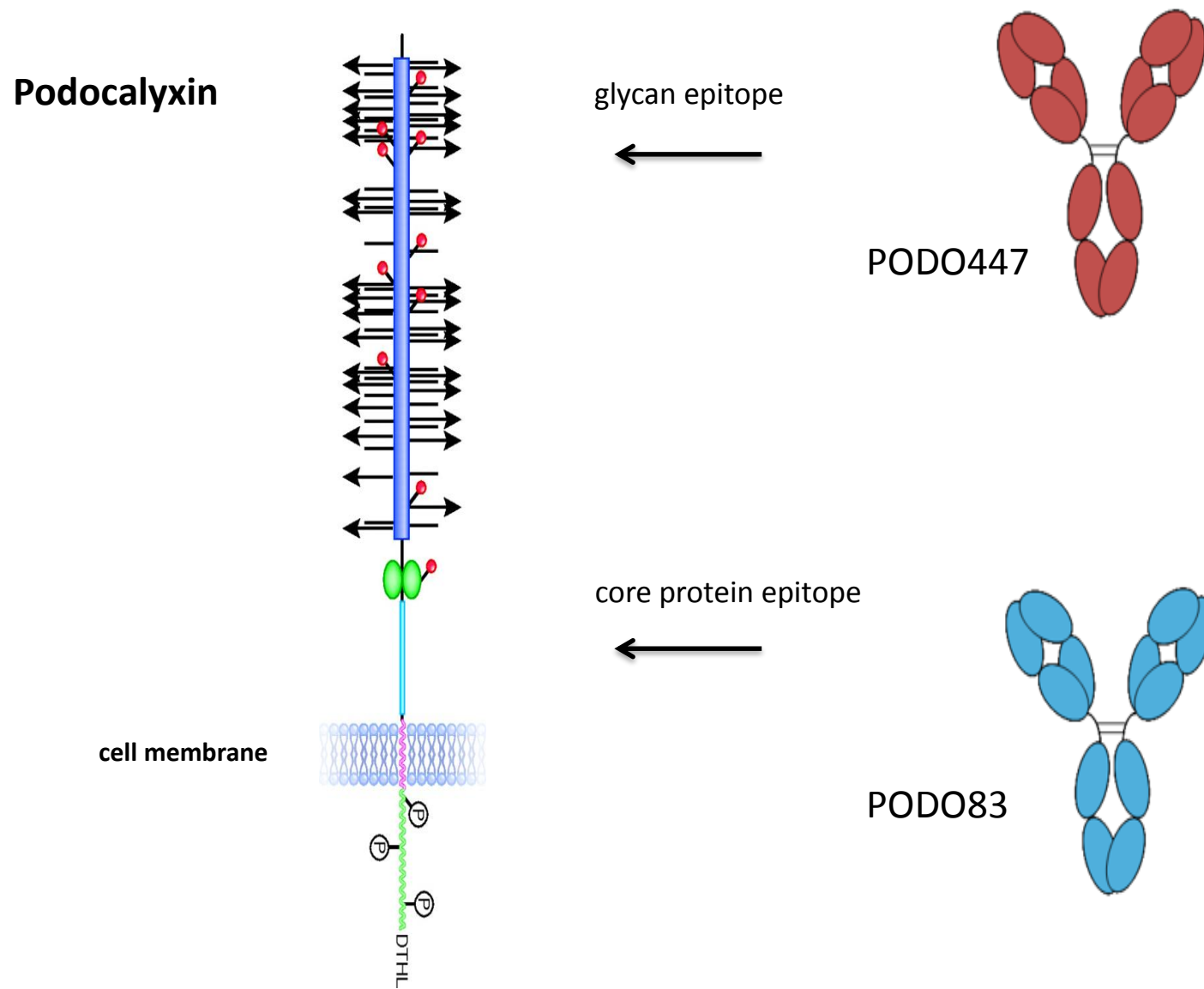


Number of GFP+ cells in the lung

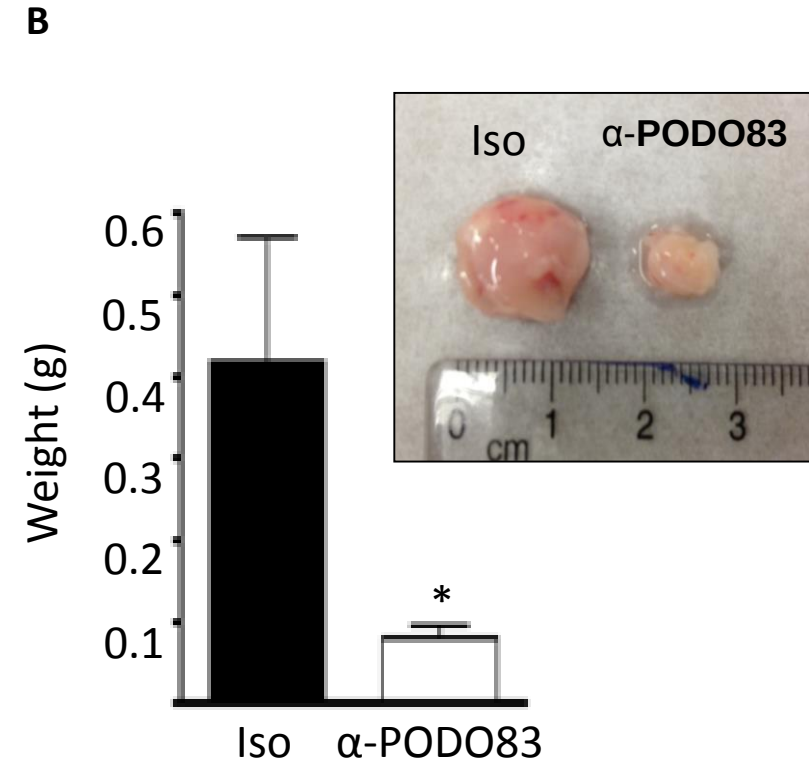
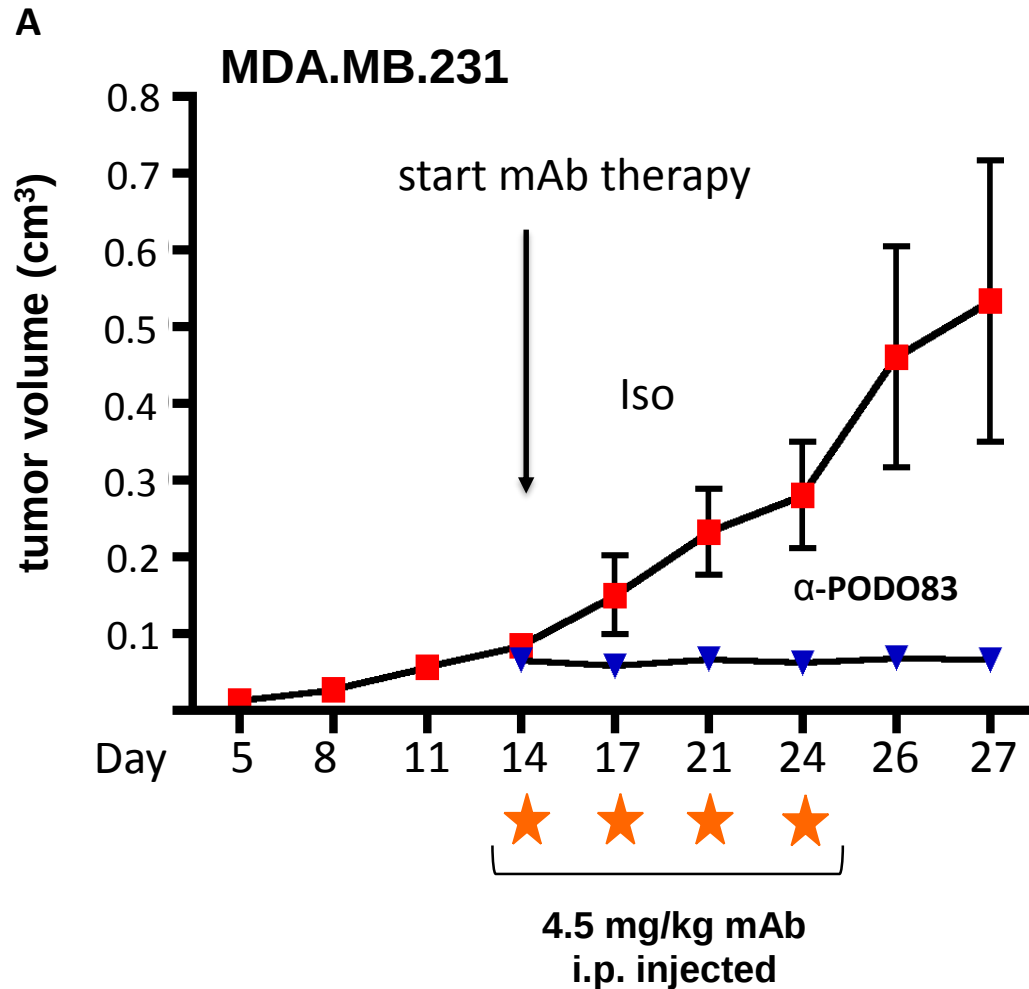


Resected s.c. tumors

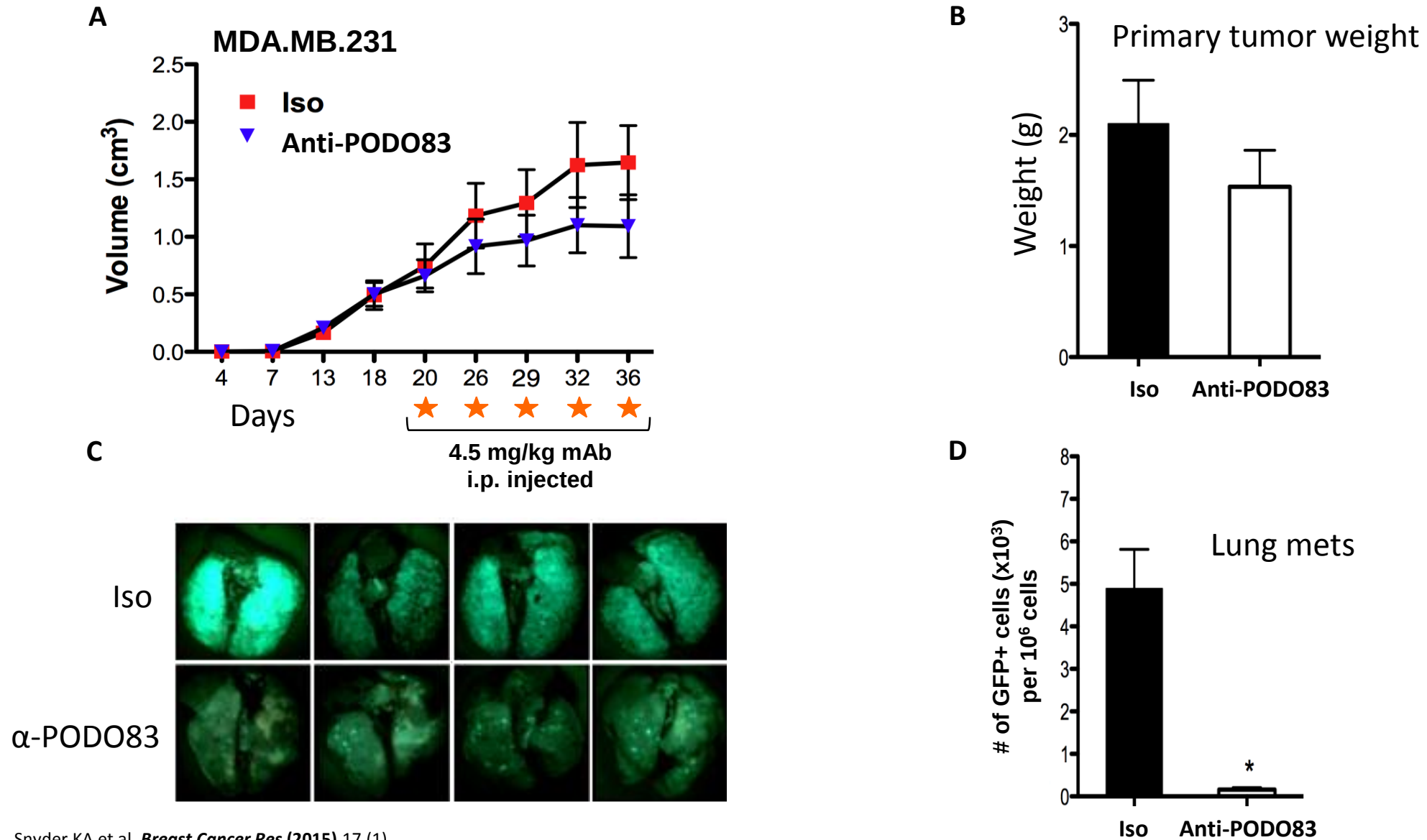
Lead α -Podocalyxin antibodies



PODO83 mAb blocks tumor growth and metastasis



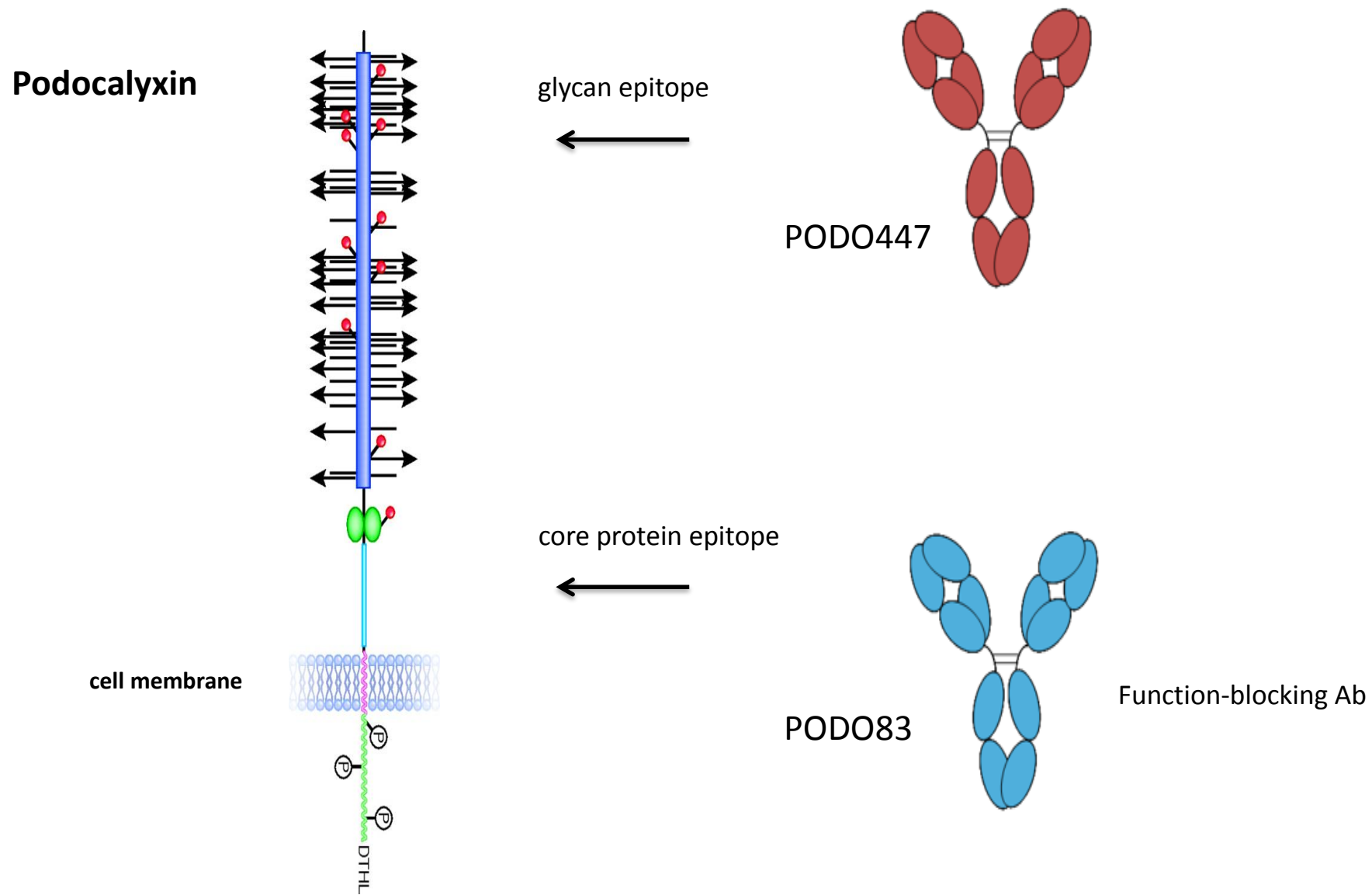
PODO83 therapy blocks metastasis in mice with established tumor burden (~ 1 cm³)



Summary part 2a

- Podocalyxin expression is associated with poor survival in many cancers, and is important for primary tumor growth and metastasis
- Anti-podocalyxin antibody development produced two lead candidates, PODO83 and PODO447.
- PODO83 is a function-blocking antibody that:
 - Delays primary tumor growth
 - Blocks metastasis in mice with an established tumor burden.

Lead α -Podocalyxin antibodies

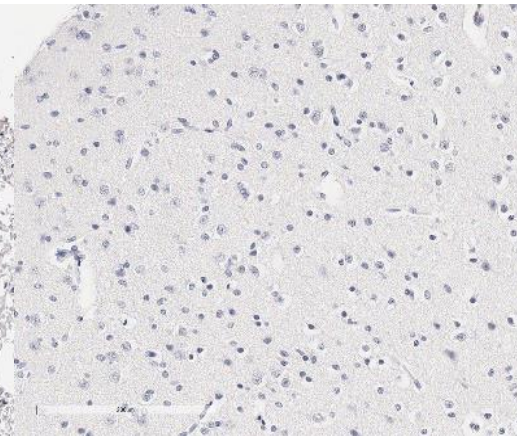
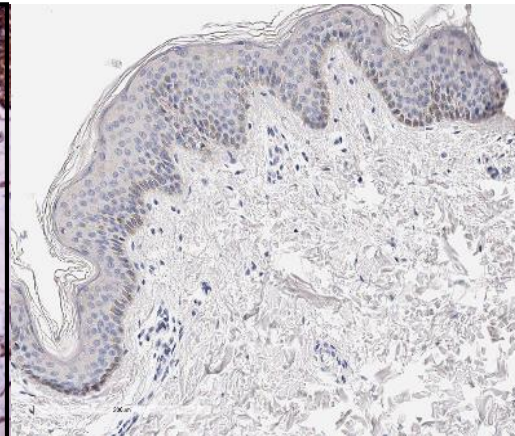
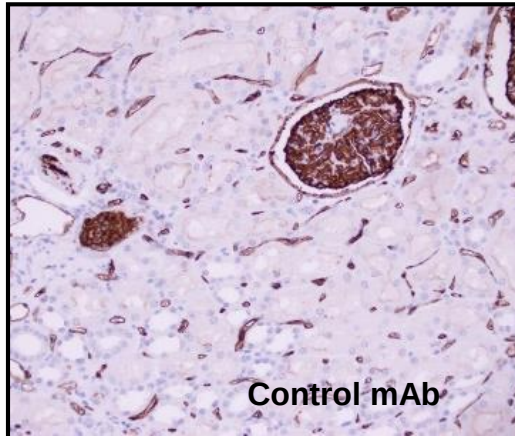


PODO447 does not recognize PODXL in healthy tissue

Kidney

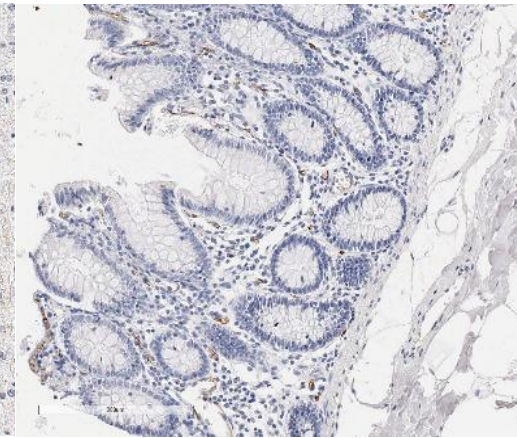
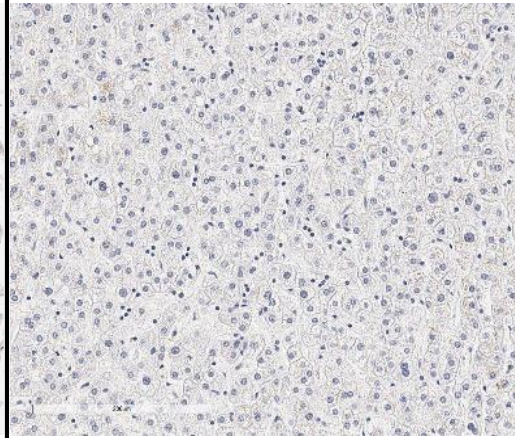
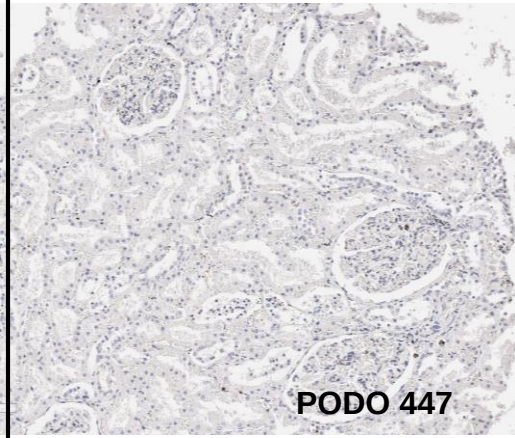
Skin

Cerebrum



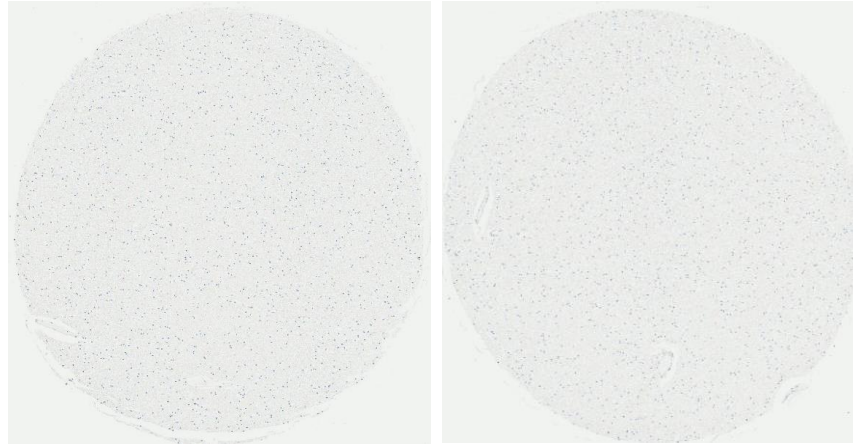
Liver

Colon



PODO447 does not recognize PODXL in healthy tissue but recognizes a tumor specific target

Normal Cerebellum

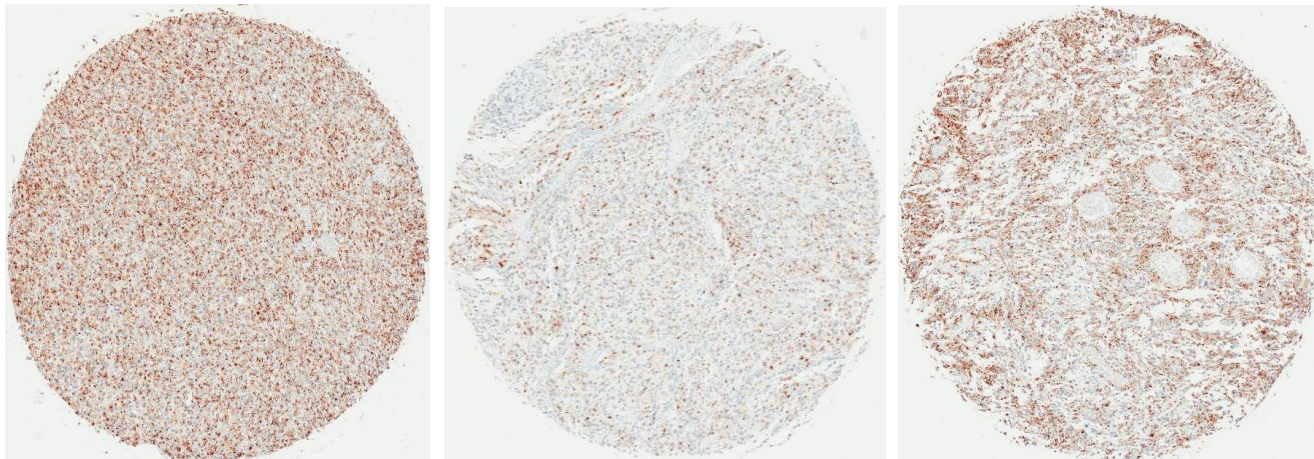


**Glioblastoma
TMA staining:**

Normal 0/10

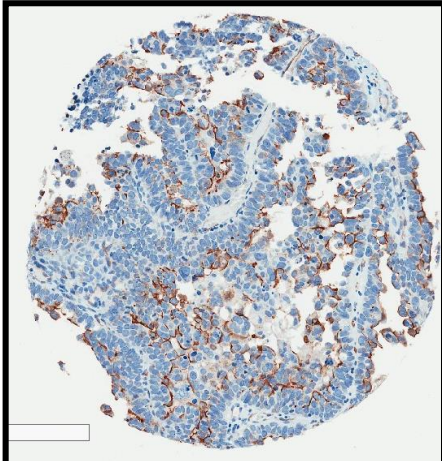
Malignant 22/60

Malignant Tissue

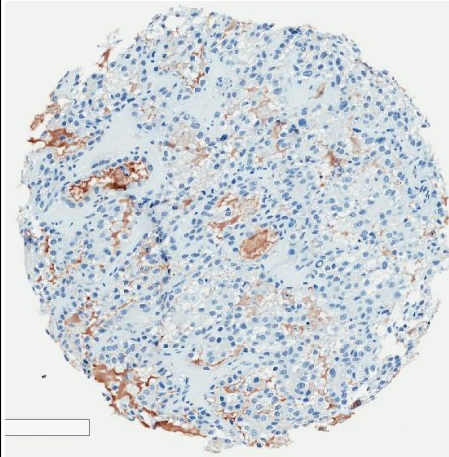


PODO447 does not recognize PODXL in healthy tissue but recognizes a tumor specific target

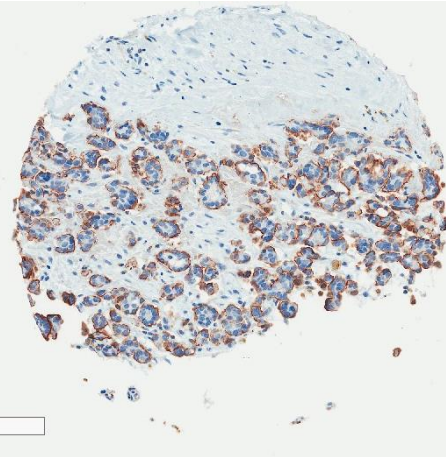
High Grade Serous



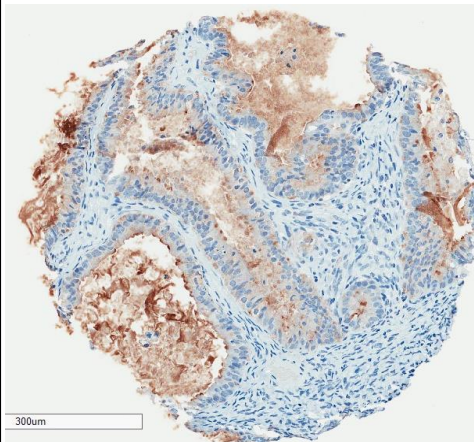
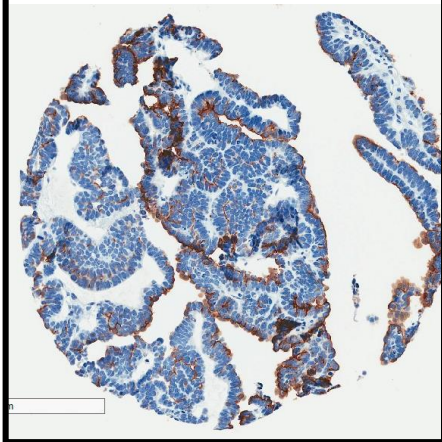
Clear Cell



Low grade serous



Endometrioid

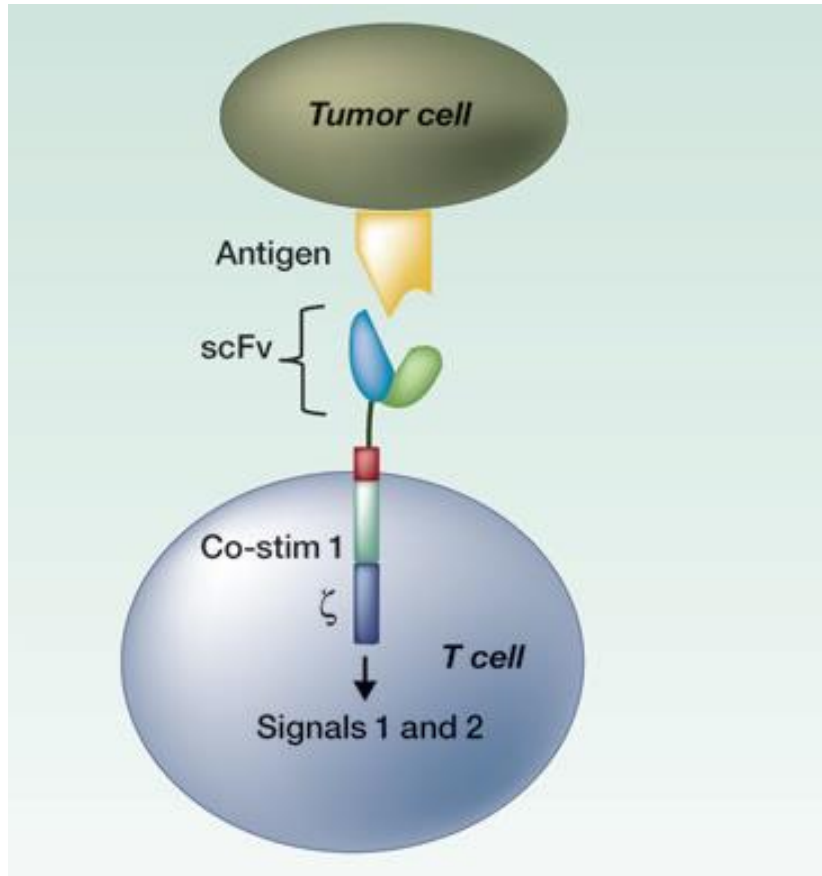


Ovarian Carcinoma TMA staining (n):

High grade serous	64.1% (125)
Clear cell	73.1% (19)
Endometrioid	80.6% (29)
Mucinous	55.6% (5)
Low grade serous	87.5% (7)

Turning PODO447 into a therapeutic

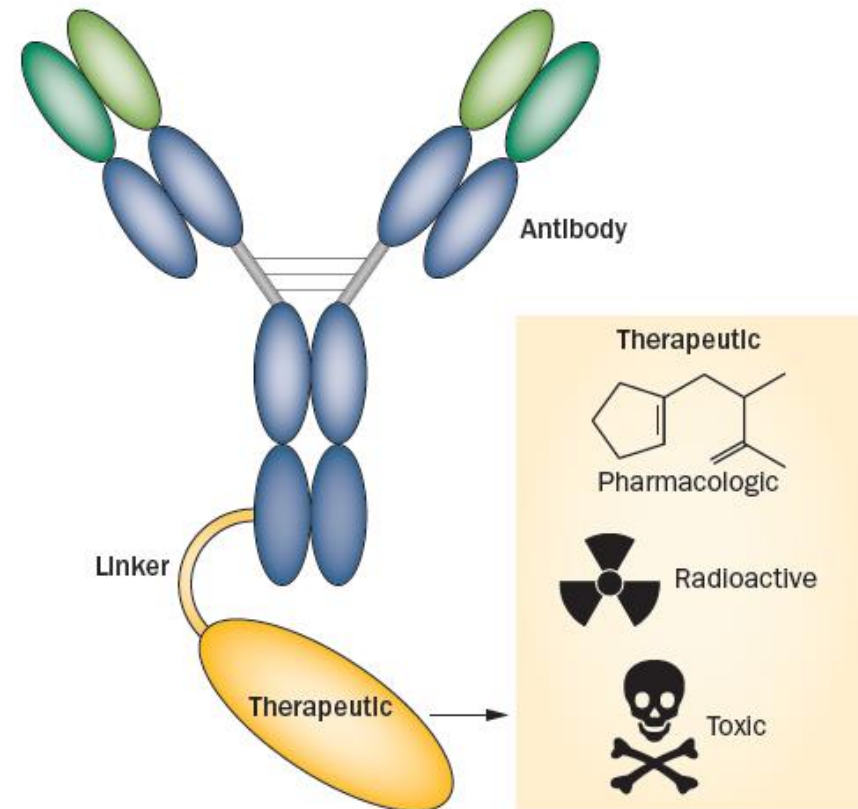
Engineered T cells: PODO 447 CART



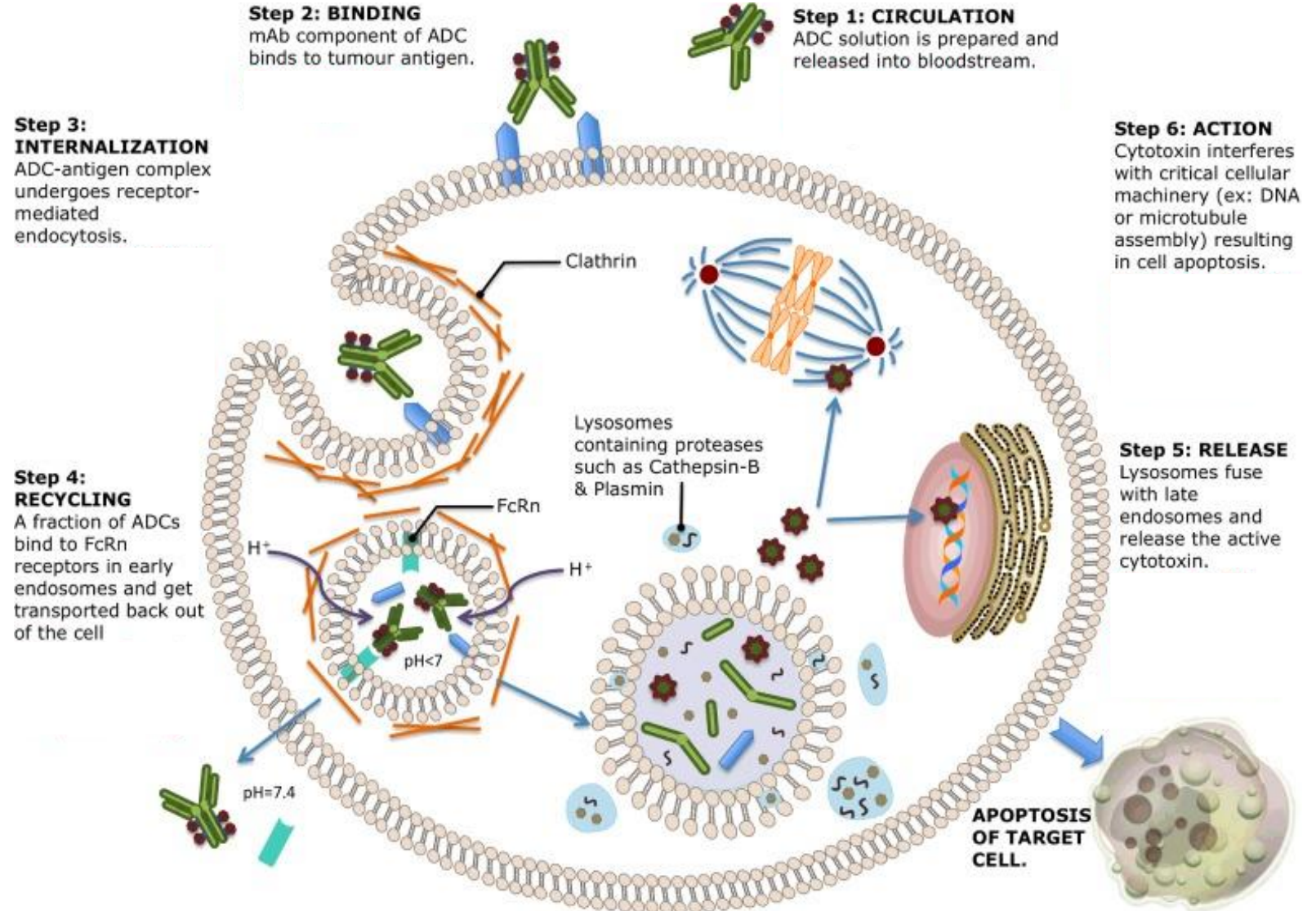
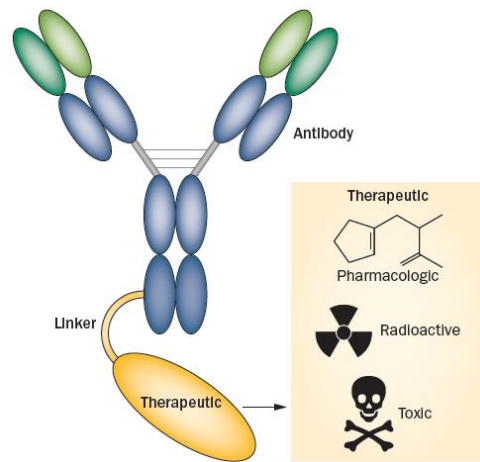
Antibody Conjugated Drug: PODO447 ADC

PODO447-CTx (Cytotoxic payload)

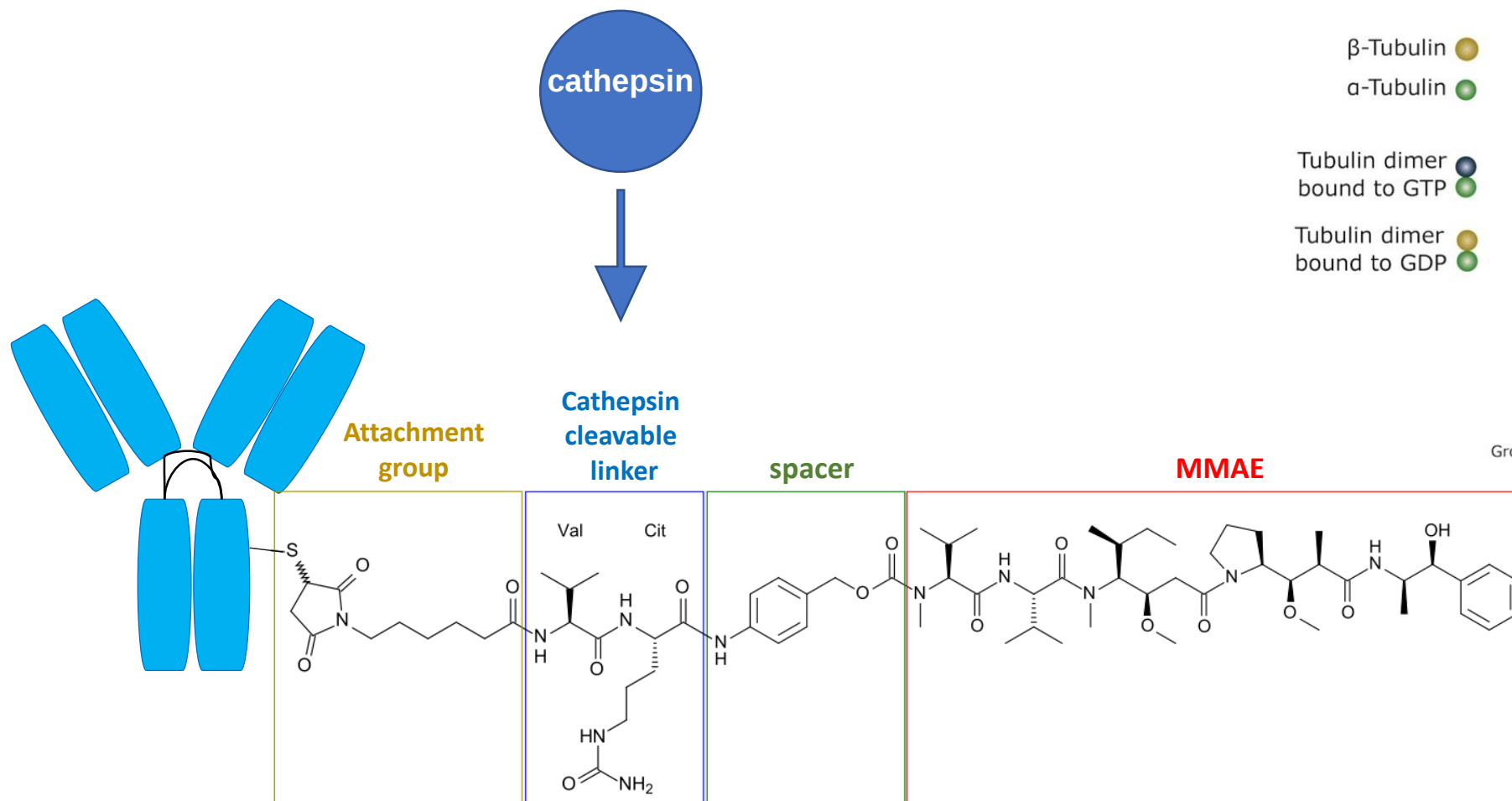
PODO447-Radionucleotide



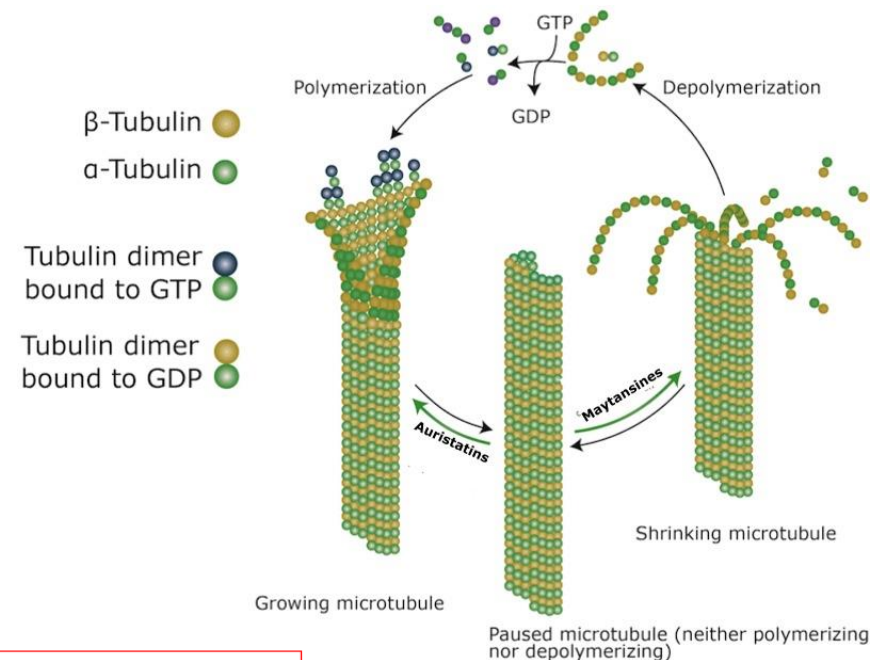
Antibody Drug Conjugate (ADC)



PODO447 Antibody Drug Conjugate

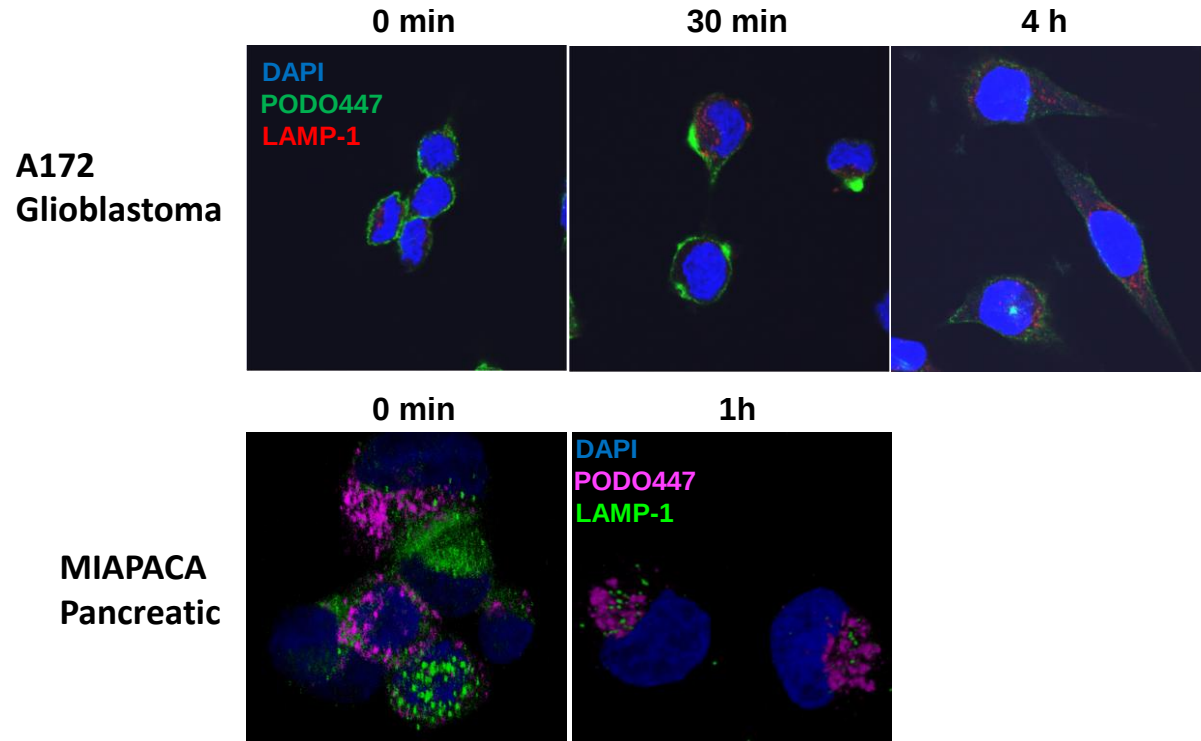


Vedotin (Val-Cit-PABC-MMAE)

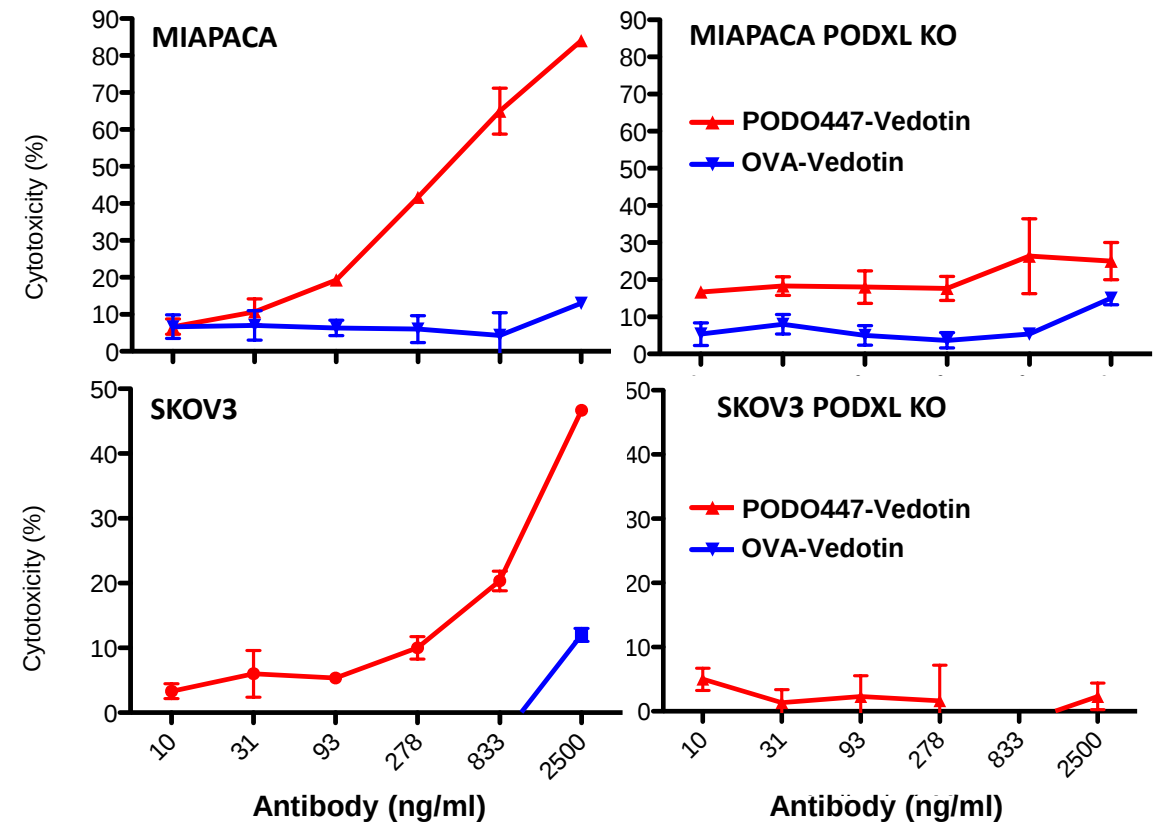


PODO447 ADC internalizes and has cytotoxic activity *in vitro* and *in vivo*

A PODO447 Internalization

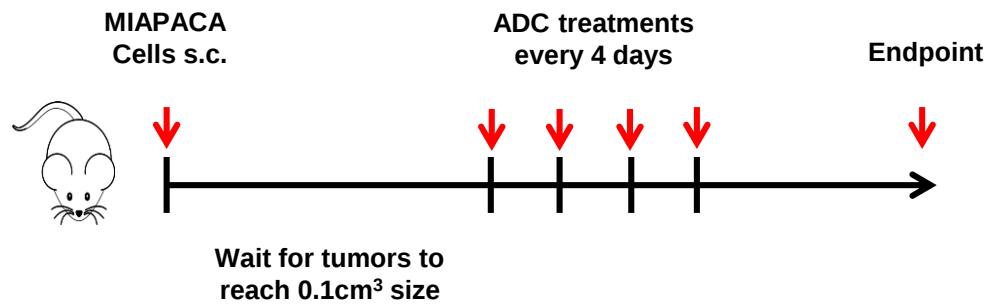


B PODO447-Vedotin *in vitro* cytotoxicity



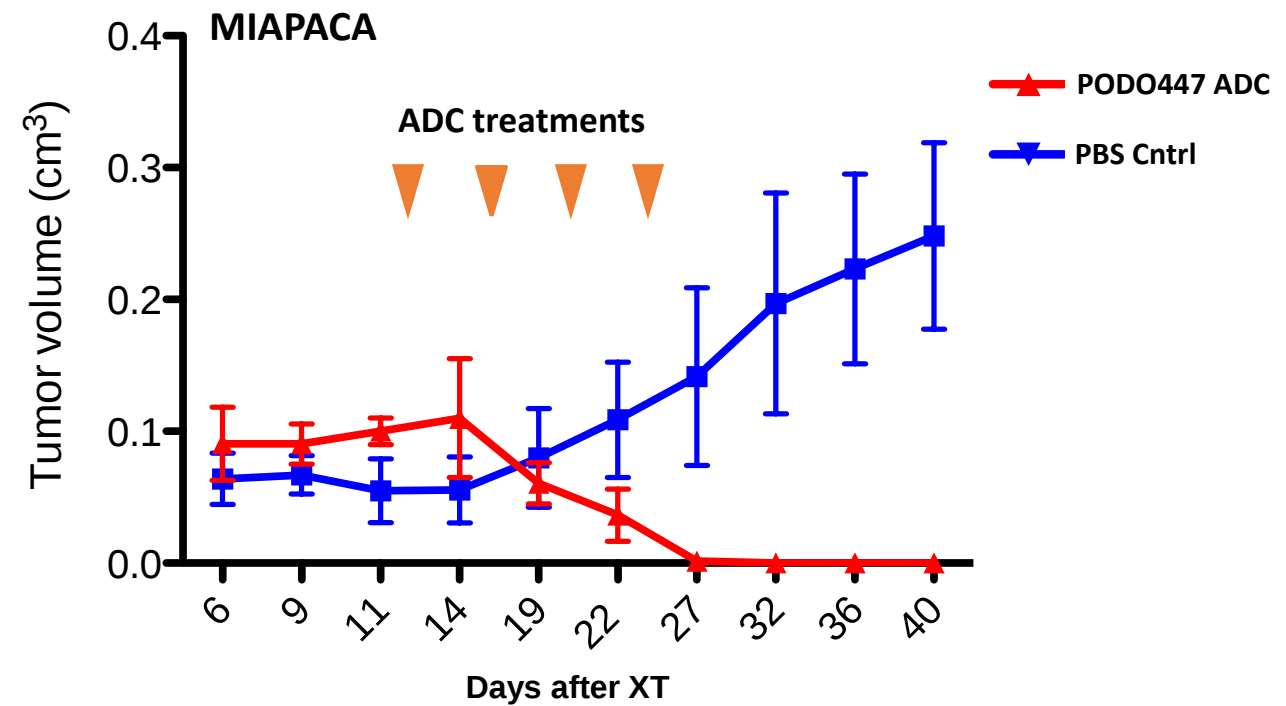
PODO447 ADC clears tumor burden *in vivo*

A



B

PODO447-ADC *in vivo* cytotoxicity



Final Overview

- Podocalyxin is great candidate for targeted therapeutics for a variety of cancers.
- We have developed two novel α -PODXL antibodies.
- PODO83 can delay primary tumor growth and block metastasis.
- PODO447 is highly tumor-specific and it can be turned into a therapeutic through conjugation of a toxic payload (i.e. MMAE).

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