

CLDN18.2 related *in vivo* models



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2020.07

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- CLDN18.2 biology
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- CLDN18.2 related CDX model summary
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■ Engineered cell line/model of MIA PaCa2 overexpressing hCLDN18.2

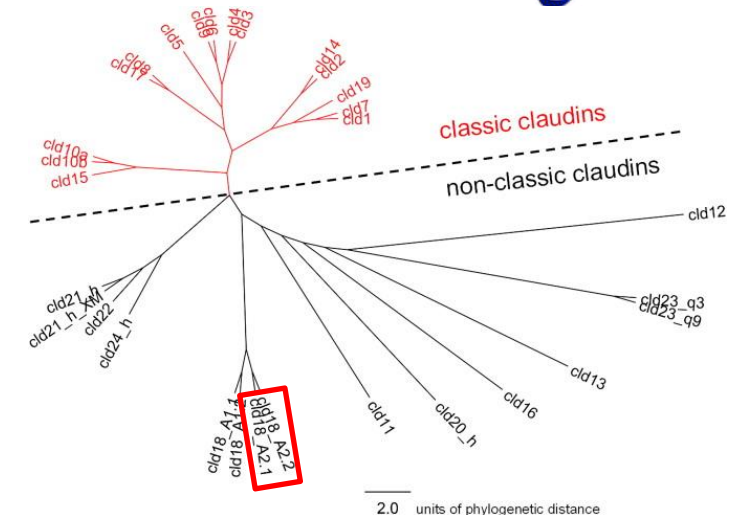
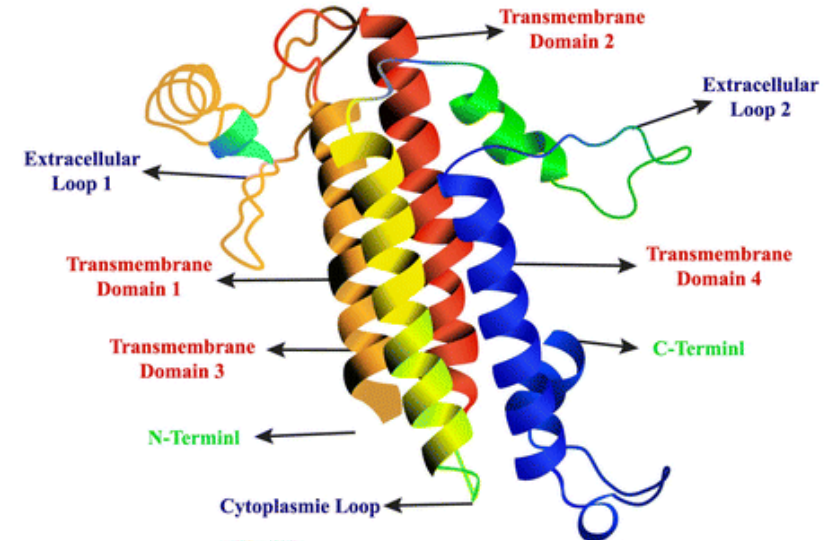
- Human CLDN18.2/MIA PaCa-2 engineered cell line summary
- Human CLDN18.2/MIA PaCa-2 stable cell line

■ CLDN18.2 related PDX models

- CLDN18.2 related PDX model summary

- Claudin-18 is encoded by the CLDN18 gene at 3q22.3 in human, and belongs to the large claudin family of proteins, which form the important components of the tight cell junctions.
- Claudins family establish a paracellular barrier which controls the flow of molecules between the cells and represent a useful target for various therapeutic strategies.
- The transmembrane domains of claudins include a N-terminus and a C-terminus in the cytoplasm. Different claudins are expressed on different tissues, their altered function has linked to formation of cancers of respective tissues.
- Claudin-1 expression has been shown to have prognostic value in colon cancer, claudin-10 in hepatocellular carcinoma, and claudin-18 in gastric cancer.

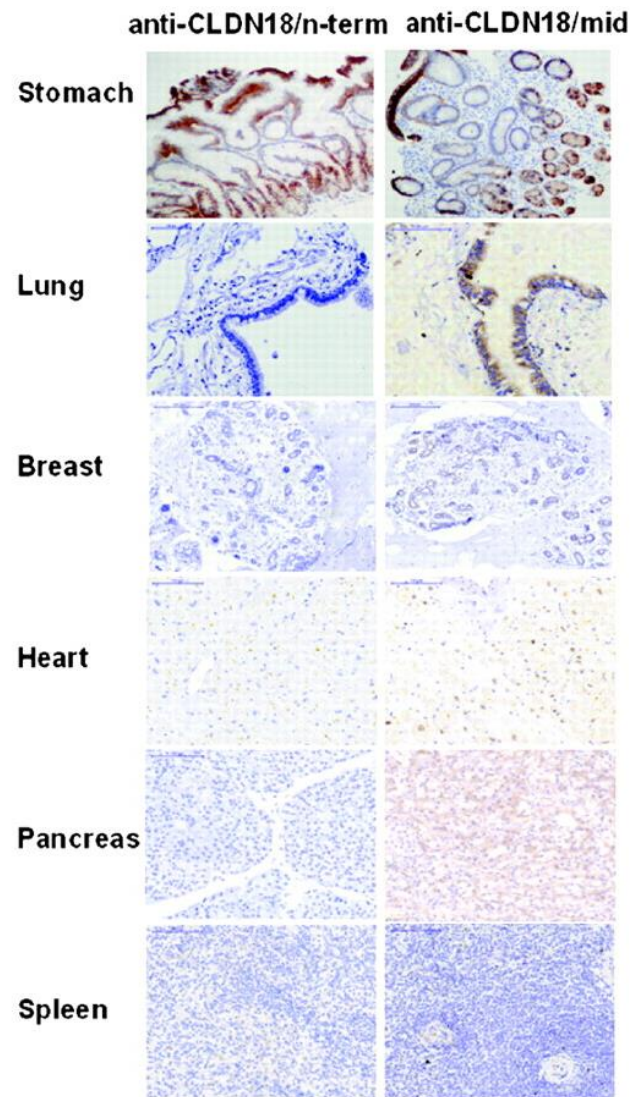
Model structure of claudin protein



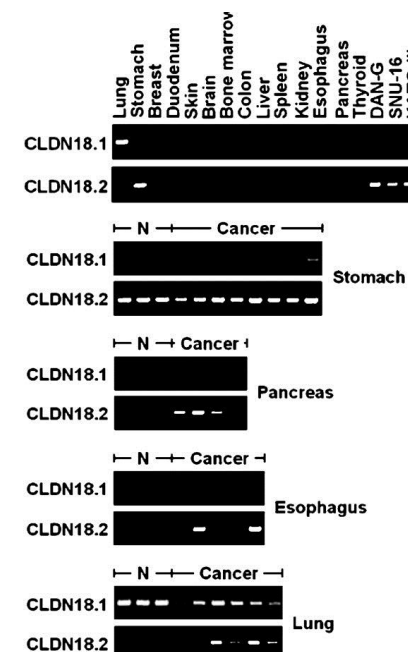
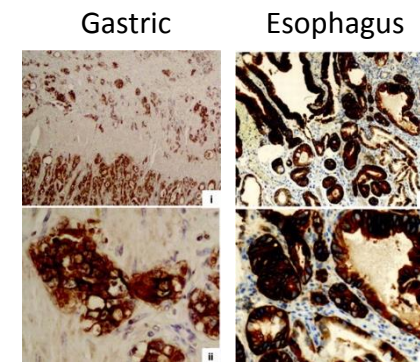
Claudin 18 isoform 2 (CLDN18.2) biology

- Isoform 2 of the tight junction molecule claudin-18 (CLDN18.2) as a highly selective cell lineage marker.
- CLDN18.2 was retained on malignant transformation and was expressed in a significant proportion of primary gastric cancers and its metastases.
- CLDN18.2 is overexpressed in up to 80% of gastrointestinal adenocarcinomas (primary and metastasized) and 60% pancreatic tumors in addition to other solid cancers.
- CLDN18.2 is involved in tumor development and progression and located in the outer cell membrane. It has exposed extracellular loops and is available for monoclonal antibody binding.

CLDN18 expression in normal tissue.

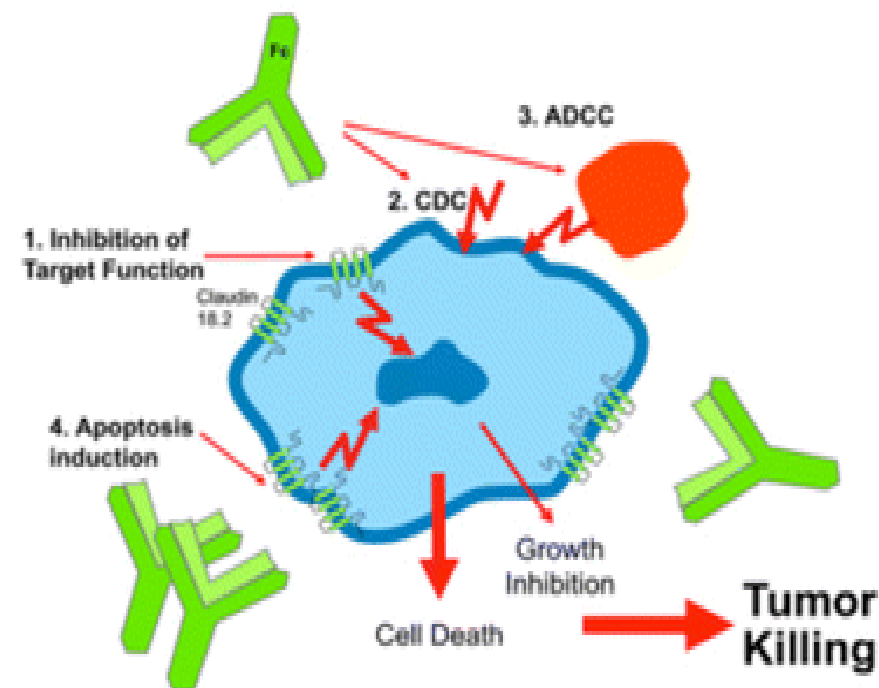


CLDN18.2 expression in cancer tissue.



CLDN18.2-targeted antibodies

- The biological characteristics of CLDN18.2 suggested that it is an ideal molecule for targeted therapy and led to the further development of monoclonal antibodies, such as claudiximab (IMAB362).
- Claudiximab is a chimeric IgG1 antibody specifically binds to CLDN18.2, which exerts its mechanism of action by activation of complement-dependent cellular cytotoxicity (CDCC) and antibody-dependent cellular cytotoxicity (ADCC).
- Additionally, it may enhance T cell infiltration or induce pro-inflammatory cytokines in combination with chemotherapy.



Journal of Hematology & Oncology. 10:105. (2017)

CLDN18.2-targeted antibodies

Clinical trials involving claudiximab (IMAB362)

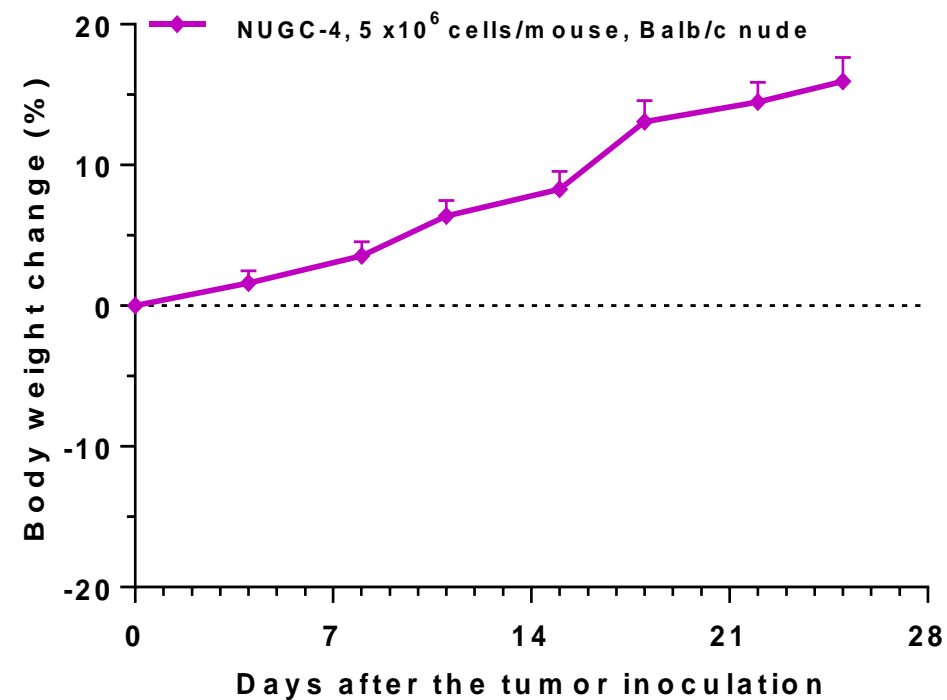
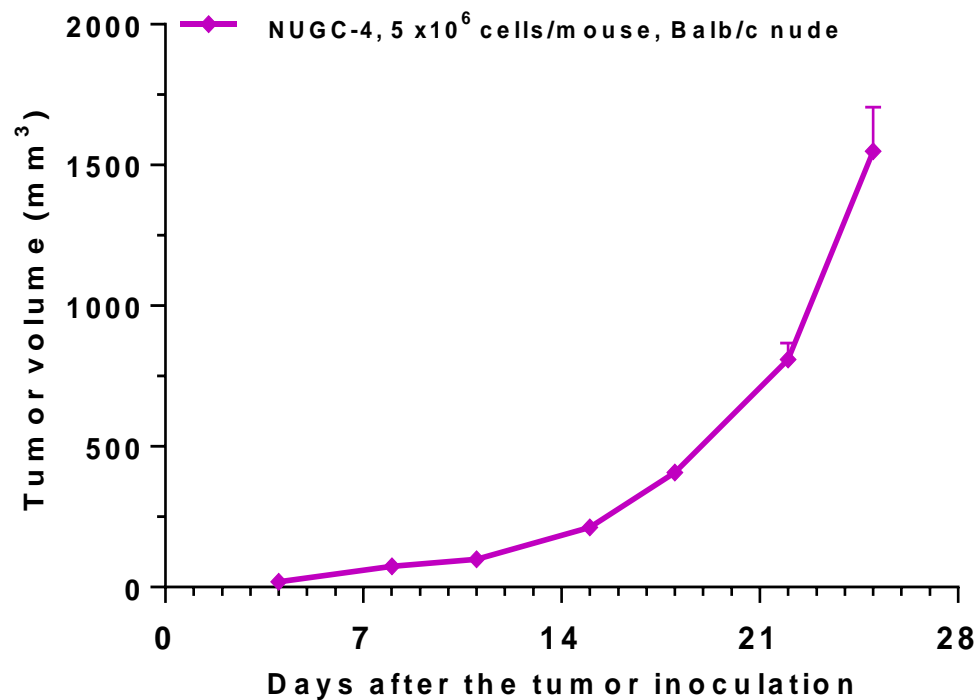
Drug	Inventor	Target(s)	Indications	Status	Description
IMAB362	Astellas Pharma Inc	CLDN18.2	Positive, Metastatic or Advanced Unresectable Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma	Phase II Recruiting	NCT03505320
IMAB362	Astellas Pharma Inc	CLDN18.2	Advanced Gastroesophageal Cancer	Phase II completed	NCT01197885
IMAB362 + mFOLFOX6	Astellas Pharma Inc	CLDN18.2	Claudin (CLDN) 18.2 Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma	Phase III Recruiting	NCT03504397
IMAB362 + Zoledronic acid + interleukin-2	Astellas Pharma Inc	CLDN18.2	CLDN18.2-positive Gastric Adenocarcinoma CLDN18.2-positive Adenocarcinoma of Esophagus CLDN18.2-positive Adenocarcinoma of the Gastroesophageal Junction	Phase I completed	NCT01671774

CLDN18.2 related CDX models

Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI	Model genomics
Gastric Cancer	NUGC4	yes	IMAB362	10 mg/kg	54%	CLDN18.2 overexpression
	SNU-601*	No				
	HuG1-N*	No				
	GSU*	No				
SCLC	DMS 454*	No				
	NCI-H146*	No				
NSCLC	NCI-H854*	No				

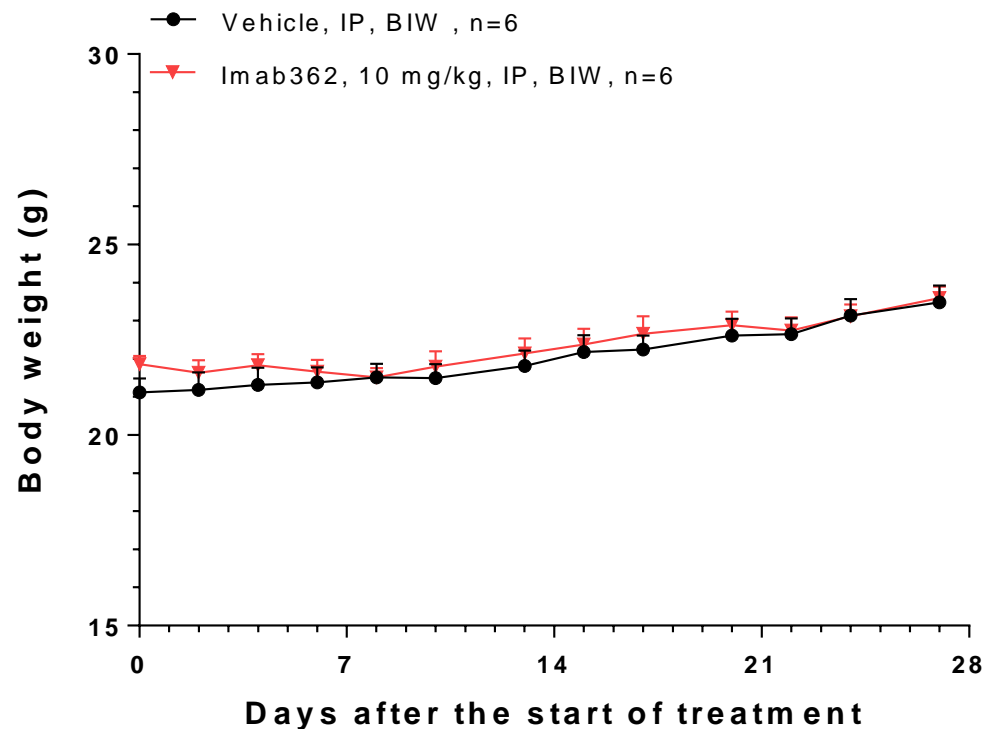
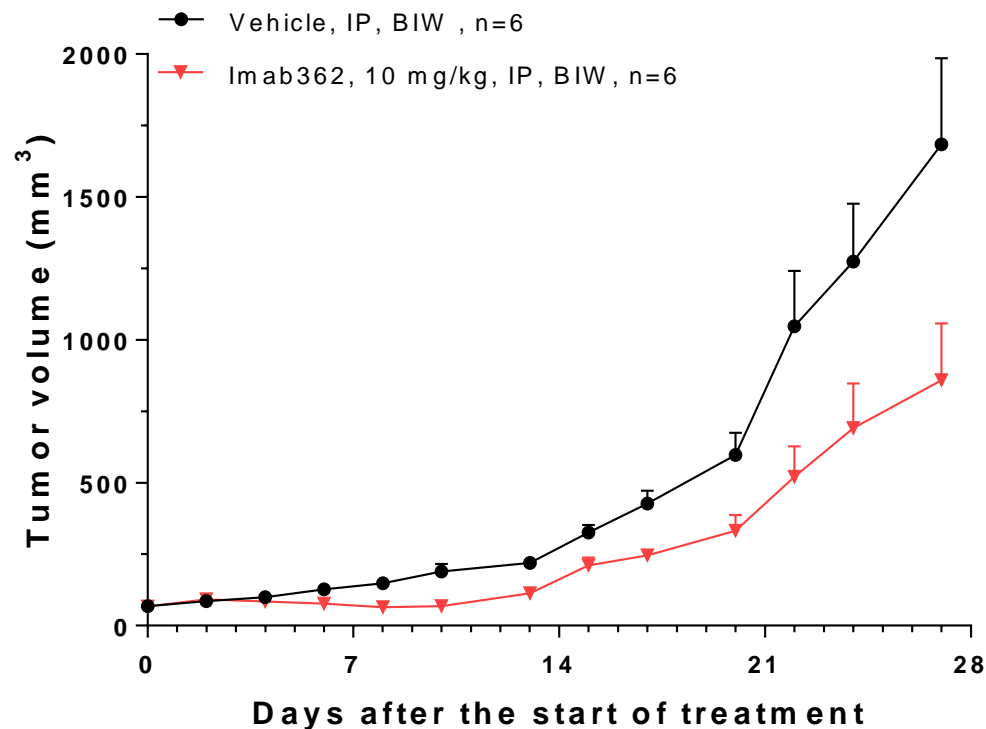
* Cells not available, information from CCLE.

NUGC4 human gastric cancer xenograft model



NUGC4 human gastric cancer xenograft model

Treated with an IMAB362 analogue



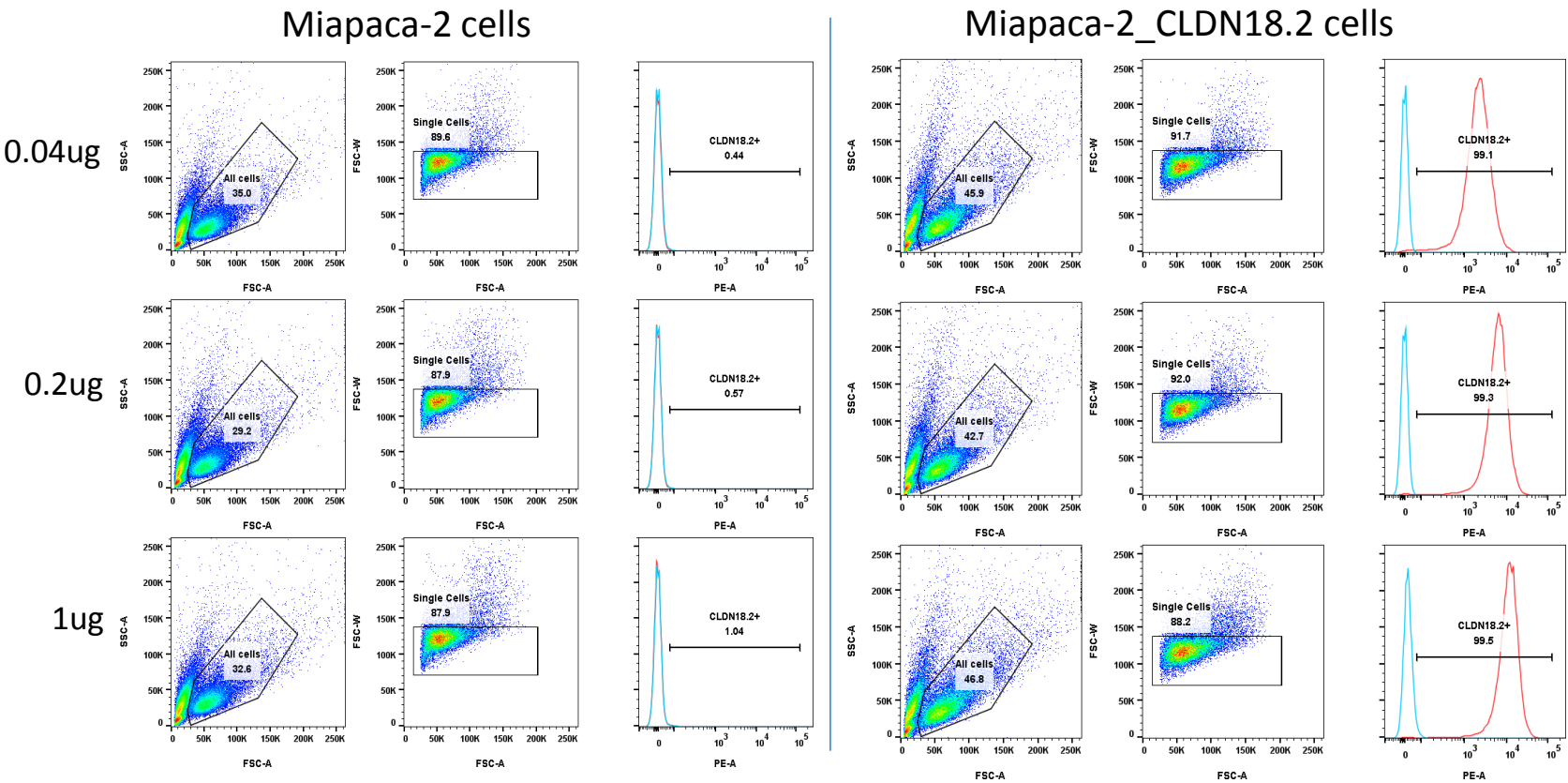
Engineered cell line/model of MIA PaCa-2 overexpressing hCLDN18.2

Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI
Pancreatic Cancer	CLDN18.2 /MIA PaCa-2	Be available soon	In plan		

Human CLDN18.2/MIA PaCa-2 stable cell line

- MIA PaCa-2 stable cell clone expressing full-length human CLDN18.2 receptor
- Host Cell: MIA Paca-2, a human pancreatic carcinoma cell line

FACS analysis result



Isotype
Panel

Type	percentage
CLDN18.2+ Miapaca-2_CLDN18.2 cells	99.1%

Type	percentage
CLDN18.2+ Miapaca-2_CLDN18.2 cells	99.3%

Type	percentage
CLDN18.2+ Miapaca-2_CLDN18.2 cells	99.5%

CLDN18.2 related PDX models

Cancer type	Model ID	CLDN 18 mRNA expression (FPKM)	Model genomics
Pancreatic	PC-07-0004	895.0	CLDN 18 overexpression
	PC-07-0033	864.5	
	PC-07-0044	694.6	
	PC-07-0052	558.1	
	PC-07-0034	516.7	
	PC-07-0016	483.1	
	PC-07-0016	427.5	
	PC-07-0039	351.5	
Gastric	ST-02-0079	710.2	
	ST-02-0318	657	
	ST-02-0328	484.5	
	ST-02-0238	419.5	
	ST-02-0393	407.6	



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