DMTX invaScan

Diagnosis of invasive carcinomas

Many carcinomas present a desmoplastic reaction involving cellular and acellular components, such as fibroblasts, immune cells, endothelial cells, the extracellular matrix and soluble proteins such as cytokines and growth factors. This heterogeneous stroma seems to promote tumor growth, invasion, and resistance to chemotherapy.

Fibroblasts in the vicinity of the tumor, the so-called cancer-associated fibroblasts (CAF), play a role in stimulating tumor progression. One of the most significantly and consistently overexpressed genes in CAFs is collagen type XI α1 (COL11A1), a tumor-associated matrix collagen (1). Transforming growth factor beta triggers the activation of Smad2 signaling cascades, leading to transcription of COL11A1, collagen remodeling and tumor invasiveness. The specific expression of COL11A1 in cancer-associated fibroblasts might be an early indicator of tumor progression and invasion. **Overexpression of COL11A1 has been associated with progression and metastasis of various types of tumors (2-8), chemorresistance (9-12) and bad prognosis (4, 13-14)**. COL11A1 is involved in the desmoplastic reaction driven by the peritumoral fibroblasts, altering the composition of the extracellular matrix, and facilitating tumor invasion.

What is DMTX invaScan?

DMTX invaScan is a monoclonal antibody developed by ONCOMATRYX that specifically detects COL11A1 in tissues from patients with invasive cancer.

What are the clinical benefits?

DMTX invaScan facilitates diagnosis in small samples, aiding the selection of the most appropiate treatment for each patient.

What is it based on?

DMTX invaScan allows immunohistochemical staining of COL11A1. It has been optimized for the automated platforms commonly used in pathology labs.

Oncomatryx has developed a monoclonal antibody that is highly specific for human proCOL11A1, the precursor protein of COL11A1 (15). Based on this antibody, **ONCOMATRYX has developed DMTX invaScan, for the diagnosis of multiple invasive tumors, even in small biopsy samples, which are difficult to evaluate by traditional methods.**

DMTX invaScan specifically detects COL11A1 in different tissue samples, with high sensitivity, specificity and reproducibility. A very clear intense intracellular staining of peritumoral fibroblasts, allows an easy interpretation of results with no need for quantitation of the stain, nor complicated analysis of the morphological features of the positive cells. DMTX invaScan is optimized for its use in the common immunohistochemistry automated platforms used in Pathology lab services, allowing an user-friendly introduction in clinical routine.

The expression of COL11A1 in peritumoral stromal fibroblasts instead of tumor cells, enables the diagnosis of different types of tumors. Multicenter clinical validations in Europe and USA have already proven its clinical usefulness for breast, ovary, pancreas, head and neck, bladder and colon cancer.

1. Jia, D. et al; Cancer Lett. 2016; 28;382(2):203-214; 2.Kim, H. et al, BMC Medical Genomics 2010; 3:51; 3.Wang, K. et al, Oncogene 2002; 21:7598-7604; 4.Chong, IW. et al, Oncol Rep 2006;16(5):981-988; 5.Zhao, Y. et al, The anatomical record 2009; 292:692-700; 6.Fischer, H. et al, Carcinogenesis 2000;22(6):875-878; 7. Schmalbach, C. E. et al; Arch Otolaryngol Head Neck Surg, 2004; 130(3): 295-302 8.An, J. H. et al; J Proteome Res, 2009; 8(6): 2873-2881 9.Navabi, S. et al; BMC Genomics, 2016; 17(1):638; 10.Ten., P.N. et al; Br J Cancer, 2014; 110(1):123-132; 11.Shen, L. et al; Oncol Rep, 2016; 36(2):877-885; 12.Farmer, P. et al; Nat Med, 2009; 15(1)68-74; 13.Tothill, R. W. et al; Clin Can Res, 2008; 14:5198-5208; 14.Boguslawska, J. et al; J Urol, 2016; 195(6)1892-1902; 15. García-Ocaña et al, Int J Oncol. 2012 May;40(5):1447-54

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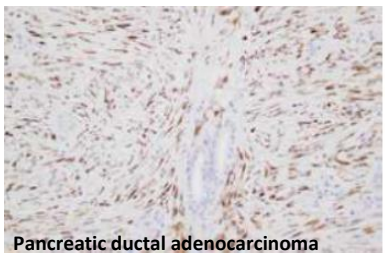
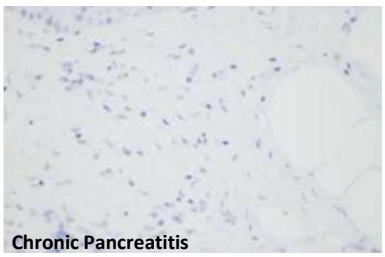
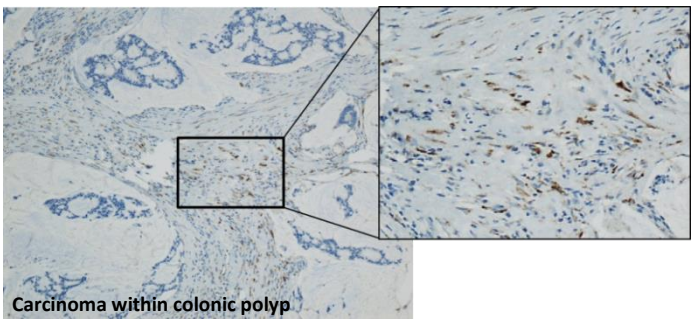
Clinical applications

- **PANCREATIC CANCER:** COL11A1 is found in the desmoplastic stroma of ductal adenocarcinomas, distinguishing them from chronic pancreatitis and ampullary carcinomas. DMTX invaScan has been validated by means of immunohistochemistry (IHC) on 51 PDAC and 18 CP tissues: sensitivity 92%, specificity 83%. (García-Pravia et al. 2013. PloS ONE 8(10): e78327)


Pancreatic ductal adenocarcinoma

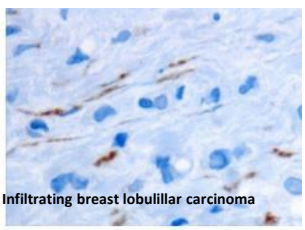

Chronic Pancreatitis

- **COLON CANCER:** COL11A1 is present in the stroma of colonic polyps with malignant component, distinguishing them from benign polyps. It has been validated by means of IHC on 66 endoscopically-removed colorectal polyps. COL11A1 was ex pressed in invasive carcinomas, including samples with cautery artifacts or mucin component (80%), while none of the minimally invasive carcinomas nor benign lesions, such as adenomas with benign misplaced glands and tubulovillous adenomas, where positive (0%); sensitivity 72%, specificity 100% (Zhang,D. et al. 2016. Pathol Res Pract 212(6):545-8).

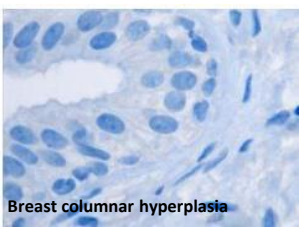

Carcinoma within colonic polyp

- **BREAST CANCER:** COL11A1 is present in the desmoplastic stroma of infiltrating carcinomas, distinguishing them from benign inflamatory and sclerosing complex lesions. DMTX invaScan has shown to allow diagnosis of infiltrating breast tumors in biopsy core samples with high sensitivity and specificity. It has been validated by means of IHC on core needle biopsies of 92 infiltrating breast carcinomas and 97 non-invasive lesions (*in situ* carcinomas, benign lesions and healthy breast samples): sensitivity 96%, specificity 97%. DMTX invaScan has shown higher sensitivity than myoepithelial markers (p63 and calponin) in detecting tumor invasion in core needle biopsies, diagnosing 25/25 infiltrating tumors that were misdiagnosed by current biomarkers (Freire et al. 2014. Pathol Res Pract. pii: S0344-0338(14)00225-8.)


Infiltrating breast ductal carcinoma


Infiltrating breast lobulillar carcinoma


Breast ductal carcinoma *in situ*


Breast columnar hyperplasia

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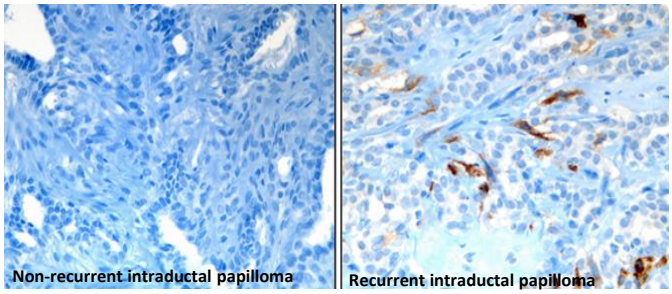
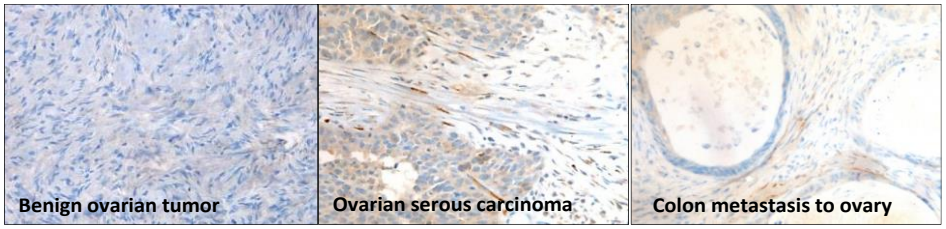
Clinical applications

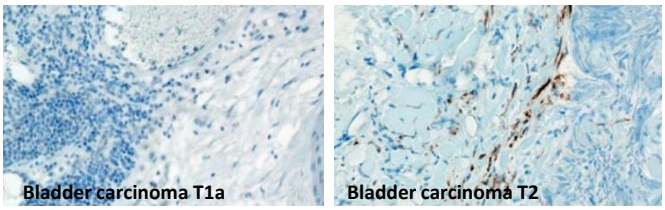
- **BREAST PAPILLOMAS:** Prognosis of recurrence and malignant recurrence of breast non-malignant papillary lesions. It has been validated by means of IHC on core needle biopsies of 51 breast intraductal papillomas that were excised and followed up for longer than 5 years: sensitivity for prognosis of malignant recurrence 90%, specificity 68%. (Freire, J. et al. Biomed Res.Int.2015. 2015:812027).



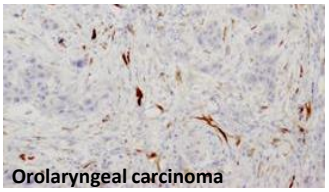
- **OVARIAN CANCER:** COL11A1 is present in malignant ovarian tumors, distinguishing them from benign tumors and non-malignant lesions. Collagen-XI-α1 is also useful for the assessment of the invasiveness of borderline tumor implants. It has been validated by means of IHC on 27 malignant tumors (15 serous, 3 endometrioid, 3 mucinous, 3 non-specified and 3 metastasis of colon tumors) and 4 non malignant tumors or other lesions: sensitivity 74%, specificity 75%. Increasing COL11A1 expression has been correlated with tumor invasiveness, metastasis and recurrence (Cheon, DJ. et al. Clin Cancer Res. 2014. 20(3):711-23)



- **BLADDER CANCER:** Collagen-XI-α1 is present in the stroma of invasive bladder carcinomas (pT2), distinguishing them from superficial tumors and benign lesions. It has been validated by means of IHC on 43 transurethral resection samples: sensitivity 91%, specificity 96%. (Freire et al. 2014. Pathology Journal of the RCPA. 46:S135)



- **HEAD AND NECK CANCER:** Collagen-XI-α1 is found in the desmoplastic stroma of squamous carcinomas in any localization, distinguishing them from benign lesions such as fibrosis, inflammation, leucocheratosis, ulcer, hyperplasia, etc. It has been validated by means of IHC on 50 infiltrating tumors and 47 non-invasive lesions (*cis* and displasias, even severe displasias): sensitivity 90%, specificity 85%.



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Publications

1. ***Characterization of a novel mouse monoclonal antibody, clone 1E8.33, highly specific for human procollagen 11A1, a tumor-associated stromal component.*** García-Ocaña M. et al. Int J Oncol. 2012. 40 (5): 1447-145

2. ***Overexpression of COL11A1 by cancer-associated fibroblasts: clinical relevance of a stromal marker in pancreatic cancer.*** García-Pravia C. et al. PLoS ONE. 2013. 8(10): e78327

3. ***A collagen-remodeling gene signature regulated by TGF-β signaling is associated with metastasis and poor survival in serous ovarian cancer.*** Cheon, DJ. et al. Clin Can Res. 2014. 20(3):711-23

4. ***Collagen, type XI, alpha 1: An accurate marker for differential diagnosis of breast carcinoma invasiveness in core needle biopsies.*** Freire J. et al. Pathol Res Pract. 2014 Aug 8

5. ***Validation of COL11A1/procollagen 11A1 expression in TGF-β1-activated immortalised human mesenchymal cells and in stromal cells of human colon adenocarcinoma***. Galván, J.A. *et al. BMC Cancer. 2014 Nov 23;14:867*

6. ***Collagen, Type XI Alpha 1 Expression in Intraductal Papillomas Predicts Malignant Recurrence.*** Freire, J. et al. Biomed Res. Int.2015. 2015:812027

7. ***Overexpression of COL11A1 Aids in the Diagnosis of Invasive Carcinoma in Endoscopically Removed Malignant Colorectal Polyps.*** Zhang,D. et al. 2016. Pathol Res Pract 212(6):545-8

8. ***COL11A1/(pro)collagen 11A1 expression is a remarkable biomarker of human invasive carcinoma-associated stromal cells and carcinoma progression.*** Vázquez-Villa, F. *et al. Tumor Biol. (2015) 36:2213–2222*

9. Immunohistochemical analysis of the expression of cancer-associated fibroblast markers in esophageal cancer with and without neoadjuvant therapy. Galván, JA et al., Virchows Arch 2019.

10. A new aggressive xenograft model of human colon cancer using cancer-associated fibroblasts. Fernando-Macías, E. et al., *PeerJ.* 2020 Jun 3;8:e9045

11. OMTX705, a Novel FAP-Targeting ADC Demonstrates Activity in Chemotherapy and Pembrolizumab-Resistant Solid Tumor Models. Fabre, M. et al., *Clin Can Res* 2020 Jul 1;26(13):3420-3430

12. ***Usefulness of COL11A1 as prognostic mrker of tumor infiltration.*** *Freire, J. et al. Biomedicines, 11:2*496.

Patents

Country	Application /Patent No.	Indication	Status
Spain	ES2398328B1	Invasive tumors: pancreas, breast, colon, bladder, head and neck	Granted
Worldwide	WO2013/021088A3	Invasive tumors: pancreas, breast, colon, bladder, head and neck, renal, lung	Pending
US	US 9,702,879 B2	Invasive tumors: pancreas, breast, colon, bladder	Granted
Mexico	MX352680B	Invasive tumors: pancreas, breast, colon, bladder	Granted
Europe	EP2743697/A2	Colon cancer and diagnosis in polyps	Granted
Spain	ES2485615B1	Breast intraductal papillomas	Granted
Europe	EP2957913	Breast intraductal papillomas	Granted
Worldwide	WO2014/125144	Breast intraductal papillomas	Pending
Spain	P201331488	Ovarian cancer and borderline tumors	Granted
Europe	EP3052938B1	Ovarian cancer and borderline tumors	Granted
Worldwide	WO2015/049282A1	Ovarian cancer and borderline tumors	Pending