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# Identification and preliminary validation in mouse models of circulating biomarkers of pancreatic cancer.

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal oncological malignancies in humans. Not-specific symptoms and lack of early diagnostic strategies, frequently lead to late diagnosis which limited therapeutic possibilities (Korc, 2007). The present study aimed at identifying novel potential serum biomarkers for early detection of PDAC.

In the first phase, two different mouse models of PDAC were characterized: genetically engineered mice (GEMs) (Hingorani et al., 2003) which developed PanIN (pancreatic intraepithelial neoplasia) lesions and three PDAC patient-derived xenograft.

In the second phase the two mouse models were used to evaluate the reliability of 3 circulating molecules as early diagnostic biomarkers of PDAC. The plasma levels of matrix metalloproteinase-7 (MMP-7), tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) and thrombospondin-2 (THBS-2) were tested on GEMs and PDAC-PDXs bearing mice by ELISA tests, during tumor development, and at sacrifice by immunohistochemistry performed on pancreatic tissue.

The three established PDAC-PDXs were found to better reproduce the tumor of origin after intra-pancreas transplantation compared to the subcutaneous ones, and to maintain molecular and morphological features over different passages.

At sacrifice, histopathological analysis demonstrated different stages of PanIN lesions in GEMs and the presence of a well-developed pancreatic tumor in all the mice orthotopically inoculated with the PDAC-PDXs.

Plasma levels of MMP-7, TIMP-1 and THBS-2 were progressively upregulated, over the time, in GEMs and in PDAC-PDX bearing mice.

In both animal models, immunohistochemistry revealed stromal immunoreactivity for TIMP-1 and THBS-2 (Figure 1), while MMP-7 expression was mainly localized on epithelial cells. All the markers showed progressive increase of staining intensity along with PanIN progression.

In conclusion, the investigated circulating molecules represent promising biomarkers for early diagnosis of PDAC and to monitor the response to treatment in human patients. Both tumoral



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cells and associated stroma play a role in the production and release of such biomarkers which, in addition, represent also biologically relevant molecules in remodeling the tumor microenvironment, by a complex network of interacting molecules.

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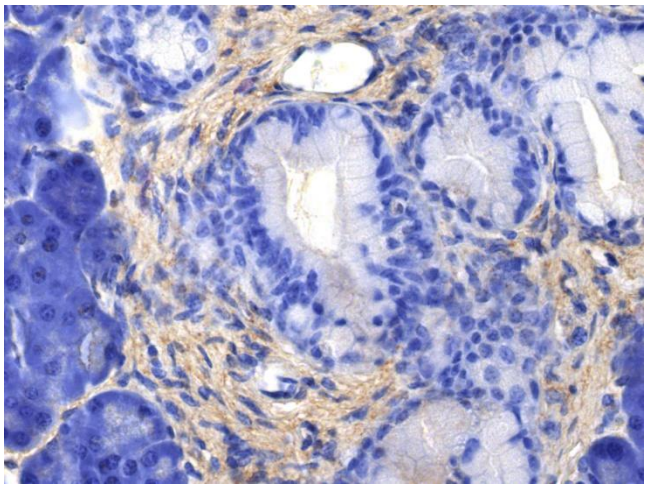
**Figure 1:** Mouse (GEM model of PDAC), pancreas. Diffuse immunoreactivity for THBS-2 in the stroma surrounding a PanIN-1A lesion. Immunohistochemistry for Thrombospondin-2, 400x magnification.



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