

PROJECT 1**DoS:** Carla TaveggiaTitle: Genetic and molecular mechanisms in perineural invasion in pancreatic cancerCurriculum: Experimental and Clinical Medicine

Link to OSR/UniSR personal page:

<http://research.hsr.it/en/institutes/institute-of-experimental-neurology/axo-glia-interaction.html>**Project description** (Number of characters, including spaces: 2.000 - 3.000):

Perineural invasion (PNI) is the pathological identification of cancer cells along nerves within the epineurial, perineurial and endoneurial spaces (1). Although it is present in different tumors, PNI has its higher incidence in pancreatic ductal adenocarcinoma (PDAC), ranging between 80%-100% (2). PDAC is the fourth leading cause of cancer-related death, with a 5-year overall survival (OS) of only 5% in all affected patients and of 25% in those undergoing surgery (2). PNI is clinically relevant in PDAC as it is linked to pain, a symptom that impairs patients' quality of life, and it is a recognized risk factor of poor survival after surgery (1,2). Previous studies have implicated several molecules and pathways in PNI, including secreted neurotrophins and chemokines (3).

Despite these efforts, the molecular mechanisms at the basis of PNI are poorly understood. Recent data showed that PNI is the result of interactions between cancer cells, nerves and inflammatory cells (3). It has also been reported that activation of β -adrenergic receptor signaling in PDAC is related to augmented angiogenesis, increased PNI and tumor growth. Thus, considering the clinical relevance of PNI and its role in PDAC, it is impellent to better define pathological and molecular PNI characteristics to develop novel therapeutical approaches.

A PhD project is available to investigate the role of PNI in PDAC, by looking at the interactions between cancer cells and nerve/glial cells of the Peripheral Nervous System. To reach this objective we will exploit an *in vitro* neuronal-Schwann cells coculture system, in which PNI can be fully recapitulated. To further study the influence of pancreatic neoplastic ductal cell on neural cell we will also establish *in vitro* organoid cultures from surgically resected PDAC patients, in collaboration with the OSR Pancreatic Surgery Unit and we will correlate the effects of PNI invasion to the genetic mutations present in patients. The student will have to work in strict collaboration with the Pancreatic Surgery Unit and the Axo-Glial Interaction Unit. He/She will become skillful in complex *in vitro* culture systems, live-imaging, immunohistochemistry, genetic and biochemical analyses.

Skills to be acquired by the student:

Cell Biology, mainly primary cultures; Biochemical characterization of nerve-glial cells interaction/development. Morphological analyses of the nervous system and of the pancreas.

References (max. 3)

1. Bapat A et al. Perineural invasion and associated pain in pancreatic cancer. *Nat Rev Cancer* 2011;11:695-707
2. Schorn S et al. The influence of neural invasion on survival and tumor recurrence in pancreatic ductal adenocarcinoma. A systematic review and meta-analysis. *Surg Oncol* 2017;26:105-115
3. Demir IE et al. Neural plasticity in pancreatitis and pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2015;12:649-59.