



## PROJECT

**Supervisor:** ----- CARLA TAVEGGIA -----

**Title:** \_ Molecular Mechanisms regulating perineural invasion in  
pancreatic adenocarcinoma -----

**Curriculum:** ----- NEN -----

Link to the personal page  
of the University or  
relevant hospital site  
website: \_ <https://research.hsr.it/en/divisions/neuroscience/units/carla-taveggia.html>

## Description of the Project (max 3,000 characters including spaces)

### **Background/gap of knowledge**

Direct cross communications between cancer cells and peripheral nerves actively influence the tumor microenvironment as well as tumor progression and metastasis<sup>1,2</sup>. However, the events controlling how nerves and cancer cells influence each other are complex<sup>3</sup>, and likely regulated by the tumor microenvironment and by the type of nerve fibers innervating the tumor<sup>4,5</sup>. Regardless of the mechanism, the communication between tumor cells and nerves regulates cancer initiation, invasion and metastasis, often through the release of neurotransmitters<sup>6</sup>.

### **Rationale and hypothesis**

The centrality of nerves in cancer is particularly compelling in perineural invasion (PNI), an alternative route for cancer cell dissemination in addition to lymphatic and hematogenous spreading<sup>7</sup>. PNI has its higher incidence in pancreatic adenocarcinoma (PDAC), in which it is present in almost 80%-100% of tumors<sup>8,9</sup>. 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<sup>10</sup>. In PDAC, PNI is a recognized risk factor of poor survival after surgery and correlates with pain<sup>9,11,12</sup>. Thus, characterizing the molecular events at the basis of PNI in PDAC could lead to the development of new therapies that might effectively limit disease progression.

In PDAC, Schwann cells (SCs), the glial cells of the peripheral nervous system (PNS), colonize the tumors before cancer invasion<sup>13</sup> and actively degrade the extracellular matrix and instruct cancer cell by directly contacting them<sup>3,14</sup>. Moreover, they can indirectly modulate the tumor microenvironment by acting onto angiogenesis and the inflammatory milieu<sup>15</sup>.

### **Objectives and specific aims**

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 PNS. Specifically, the candidate will be asked to



UniSR

Università Vita-Salute  
San Raffaele

**APPLICATION TO ACT AS SUPERVISOR AND  
RESEARCH PROJECT PROPOSAL**

**MO 20-5**  
ed. 02 of 16/01/2026  
PO 20  
Page 6 of 10

evaluate how the interaction between nerve and pancreatic cancer cells initiates and sustains cancer spreading, using ad hoc designed in vitro system with neuron/SCs and PDAC organoids. To investigate the relationship between SCs, axons and cancer cells he/she will capitalize on, and adapt our expertise to study SCs' biology in physiological and pathological settings. We have already developed a new *in vitro* culture system in which we could successfully model the interaction between cancer cells (organoids or 2D cells) and SCs and sensory neurons (either embryonic or adult). To characterize all events at the basis of PNI, the candidate will also exploit a newly developed animal model, already available in the Institute that develops PDAC and PNI and analyze the role of the nerve repair program in vivo in tumor formation by spatial transcriptomic analyses.

**Expected outcomes**

The results of these studies might pave the way to identify new therapeutic strategies to counteract PNI formation in PDAC.

**Skills that the student should acquire** (max. 600 characters including spaces):

We expect the student to become skillful with complex in vitro culture systems, generation and maintenance of pancreatic organoids and in vivo analyses. Thus, he/she will acquire expertise in mouse genetics and in morphological analyses of the nervous system and of the pancreas. Further, he/she will become proficient in cell biology, mainly primary cultures and in the biochemical/functional characterization of nerve-glia cells-tumor cells interaction in tumor formation and spreading.

**References** (max. 15)

1. Magnon C. *et al.* Autonomic nerve development contributes to prostate cancer progression. *Science* **341**, 1236361, doi:10.1126/science.1236361 (2013).
2. Bunimovich, Y. L., Keskinov, A. A., Shurin, G. V. & Shurin, M. R. Schwann cells: a new player in the tumor microenvironment. *Cancer Immunol Immunother* **66**, 959-968, doi:10.1007/s00262-016-1929-z (2017).
3. Pascual, G. *et al.* Dietary palmitic acid promotes a prometastatic memory via Schwann cells. *Nature* **599**, 485-490, doi:10.1038/s41586-021-04075-0 (2021).
4. Hayakawa, Y. *et al.* Nerve Growth Factor Promotes Gastric Tumorigenesis through Aberrant Cholinergic Signaling. *Cancer Cell* **31**, 21-34, doi:10.1016/j.ccell.2016.11.005 (2017).
5. Renz, B. W. *et al.* Cholinergic Signaling via Muscarinic Receptors Directly and Indirectly Suppresses Pancreatic Tumorigenesis and Cancer Stemness. *Cancer Discov* **8**, 1458-1473, doi:10.1158/2159-8290.CD-18-0046 (2018).
6. Gysler, S. M. & Drapkin, R. Tumor innervation: peripheral nerves take control of the tumor microenvironment. *The Journal of clinical investigation* **131**, doi:10.1172/JCI147276 (2021).
7. Liebig, C., Ayala, G., Wilks, J. A., Berger, D. H. & Albo, D. Perineural invasion in cancer: a review of the literature. *Cancer* **115**, 3379-3391, doi:10.1002/cncr.24396 (2009).



UniSR

Università Vita-Salute  
San Raffaele

**APPLICATION TO ACT AS SUPERVISOR AND  
RESEARCH PROJECT PROPOSAL**

**MO 20-5**

ed. 02 of 16/01/2026

PO 20

Page 7 of 10

8. Demir, I. E. *et al.* Neural invasion in pancreatic cancer: the past, present and future. *Cancers (Basel)* **2**, 1513-1527, doi:10.3390/cancers2031513 (2010).
9. Rahib, L. *et al.* Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* **74**, 2913-2921, doi:10.1158/0008-5472.CAN-14-0155 (2014).
10. 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* **26**, 105-115, doi:10.1016/j.suronc.2017.01.007 (2017).
11. Gasparini, G. *et al.* Nerves and Pancreatic Cancer: New Insights into a Dangerous Relationship. *Cancers (Basel)* **11**, doi:10.3390/cancers11070893 (2019).
12. Crippa, S. *et al.* Implications of Perineural Invasion on Disease Recurrence and Survival After Pancreatectomy for Pancreatic Head Ductal Adenocarcinoma. *Ann Surg*, doi:10.1097/SLA.0000000000004464 (2020).
13. Demir, I. E. *et al.* Investigation of Schwann cells at neoplastic cell sites before the onset of cancer invasion. *J Natl Cancer Inst* **106**, doi:10.1093/jnci/dju184 (2014).
14. Deborde, S. *et al.* Schwann cells induce cancer cell dispersion and invasion. *The Journal of clinical investigation* **126**, 1538-1554, doi:10.1172/JCI82658 (2016).
15. Shurin, M. R., Shurin, G. V., Zlotnikov, S. B. & Bunimovich, Y. L. The Neuroimmune Axis in the Tumor Microenvironment. *J Immunol* **204**, 280-285, doi:10.4049/jimmunol.1900828 (2020).