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# Translational and clinical aspects of pancreatic cancer

## Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal 2119, Arvid Wallgrens backe Hus 2, Hälsovetarbacken, den 4 juni 2021, klockan 13.00

av

**Caroline Vilhav**

Fakultetsopponent:
Knut Jørgen Labori, Professor, Oslos Universitet, Norge

## Avhandlingen baseras på följande delarbeten:

I. **Vilhav C**, Engström C, Naredi P, Novotny A, Fagman JB, Iresjö BM, Asting AG, Lundholm K. Fractional uptake of circulating tumor cells into liver-lung compartments during curative resection of periampullary cancer. *Oncol Lett. 2018 Nov; 16(5): 6331–6338.*

II. Nilsson LM*****, **Vilhav C***, Karlsson JW, Fagman JB, Naredi P, Engström C, Nilsson JA
* Shared authorship.
Genetics and therapeutic responses to TIL therapy of pancreatic cancer PDX models. 2021. *In manuscript.*

III. Karimi N*****, **Vilhav C***, Fagman JB, Naredi P, Lötvall J[#], Lässer C[#]
*# Shared authorships.
Proteomic profiling of extracellular vesicles in tumour tissue from pancreatic cancer patients. 2021. *In manuscript*

IV. **Vilhav C**, Fagman JB, Holmberg E, Naredi P, Engström C.
C-reactive protein identifies patients at risk of postpancreatectomy hemorrhage. 2021. *Submitted manuscript.*

**SAHLGRENSKA AKADEMIN**
**INSTITUTIONEN FÖR KLINISKA VETENSKAPER**

GÖTEBORGS UNIVERSITET

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# Translational and clinical aspects of pancreatic cancer

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## Abstract

Pancreatic cancer is a disease with dismal prognosis due to late detection and ineffective treatments. The majority of the patients already have disseminated disease at the time of diagnosis. The only potential curative treatment, surgery, is extensive with high morbidity and non-ignorable mortality. One of the most feared complications is postpancreatectomy hemorrhage. Circulating tumor cells (CTC) and extracellular vesicles (EVs), both analyzed in this thesis, are potential biomarkers. CTC are important in metastasis and might have subclones with higher disseminating capacity. Patient-derived xenografts (PDX) mouse models can be used to receive information of tumors and their response to treatments.

The overall aim of this thesis was to establish a translational research platform for pancreatic cancer to improve diagnostics and treatment. The specific aims of the studies were to detect CTC in blood and EVs in tissue to try to identify biomarkers for early detection, determine a fractional uptake of CTC in the lung-liver compartment perioperatively, evolve a PDX model of pancreatic cancer to evaluate the effect of immunotherapy and to define predictive factors of postpancreatectomy hemorrhage.

In paper I blood samples from the portal vein and peripheral artery were collected perioperatively during pancreaticoduodenectomy to detect CTC. The difference in the number of CTC in portal and arterial blood was calculated. In paper II pancreatic tumor tissue were removed from the specimen perioperatively and implanted into immune compromised NOG mice. Tumor infiltrating lymphocytes (TILs) from the same tumor tissues were expanded. Growing tumors were serial transplanted into NOG mice expressing human interleukin 2 (hIL2-NOG mice). When the tumors gained a volume of 80-100 mm3, TILs were injected in the mice to evaluate the effect of adoptive T-cell transfer (ACT) therapy. The pancreatic tumor specimens were also used to extract EVs in Paper III. Both tumor tissue and non-tumor pancreatic tissue were utilized. The protein profiles of the pancreatic tumor and non-tumor derived EVs were analyzed with mass spectrometry and compared. In paper IV potential pre-, peri- and postoperative predictive factors of postpancreatectomy hemorrhage after pancreaticoduodenectomy was evaluated.

A difference in the number of CTC in portal and peripheral blood was detected, indicating a possibility of a perioperative fractional uptake of CTC with a metastatic profile in liver and lung tissues. In the PDX study, three out of six established tumors in the hIL2-NOG mice were reduced in the size after the ACT, which might imply an effect of the immunotherapy. In the EV project, isolation of EVs was successful and potential biomarkers and interesting upregulated proteins and their connected pathways could be identified. The protein contents were significantly different in the tumor EVs compared to the non-tumor. In the last clinical project, high postoperative CRP was identified as a predictive factor for PPH C development.

A translational platform for pancreatic cancer research, that enable studies of tumor biology, prognostic biomarkers, new therapies and detection of postoperative complications was established.

**Keywords:** circulating tumor cells, extracellular vesicles, immunotherapy, PDX model, pancreatic cancer, pancreaticoduodenectomy, postoperative complications

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