Role of circular RNAs in pancreatic cancer

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Background

***Background*:**
In the pancreas research group at the Dept. of Pathology, OUH, we are currently offering a research project focusing on the role of circular RNAs (**circRNAs**) in pancreatic cancer. The candidate should be either a Biomedicine student (**bachelor project, ISA / kandidatspeciale**, Naturvidenskabeligt Fakultet) or a Medicine student ("**prægraduat forskningsår**").

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer. Around 1.000 new cases of PDAC are diagnosed in Denmark each year. Median overall survival is only 8 months. Surgical resection is the only option for long-term survival, but can be offered to only 20%, and even after surgery the median survival is 24 months. Subtyping of PDAC is currently not part of patient management. No cllinically relevant predictive biomarkers are in clinical use. A new method to separate PDAC into two major **microscopic subtypes**, called "gland-forming" and "non-gland forming" subtypes, have been published[1] **(Fig. 1)**. Findings from our group and others showed that the two microscopic subtypes of PDAC are related to median survival[1,2]. We recently found that immune related genes are upregulated in the gland-forming subtype of PDAC[2] **(Fig. 2)**.

In recent years, **circular RNAs (circRNAs)** have emerged as a class of non-coding transcripts generated by an alternative splicing event, which links a splice-donor site to an upstream splice-acceptor site. The circRNAs have diverse functions related to the binding of other molecules, including microRNAs (miRNAs) and proteins. The most studied circRNA is ciRS-7 which harbors 63 binding sites for miR-7 stimulated the idea that circRNAs, in general, may function as **competitive endogenous RNAs** by sponging miRNA molecules and thereby relieving the corresponding miRNA target genes from post-transcriptional repression (**Fig. 3**)[3]. Since then, there has been a strong interest in discovering differentially expressed circRNAs in cancer and most of these circRNAs were proposed to function as ceRNAs. Our knowledge regarding the role of circRNAs in PDAC this is still limited.

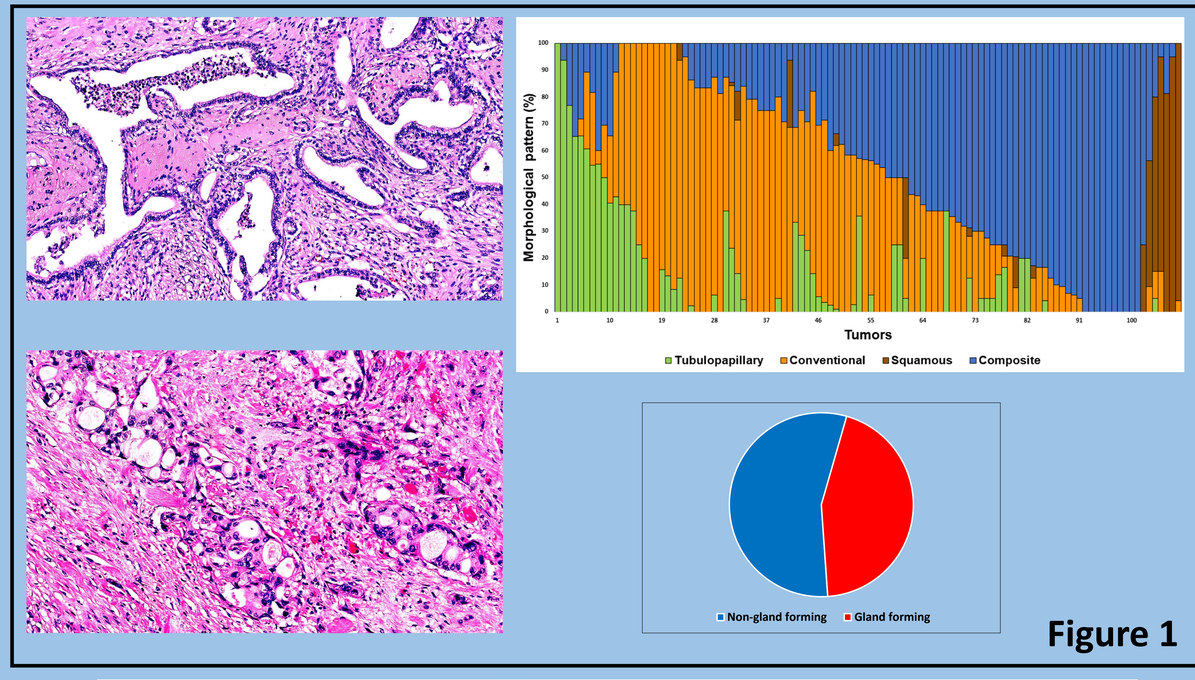
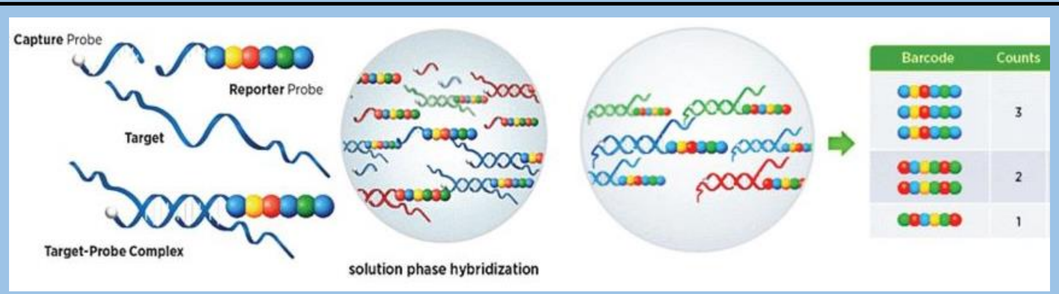


Figure 1



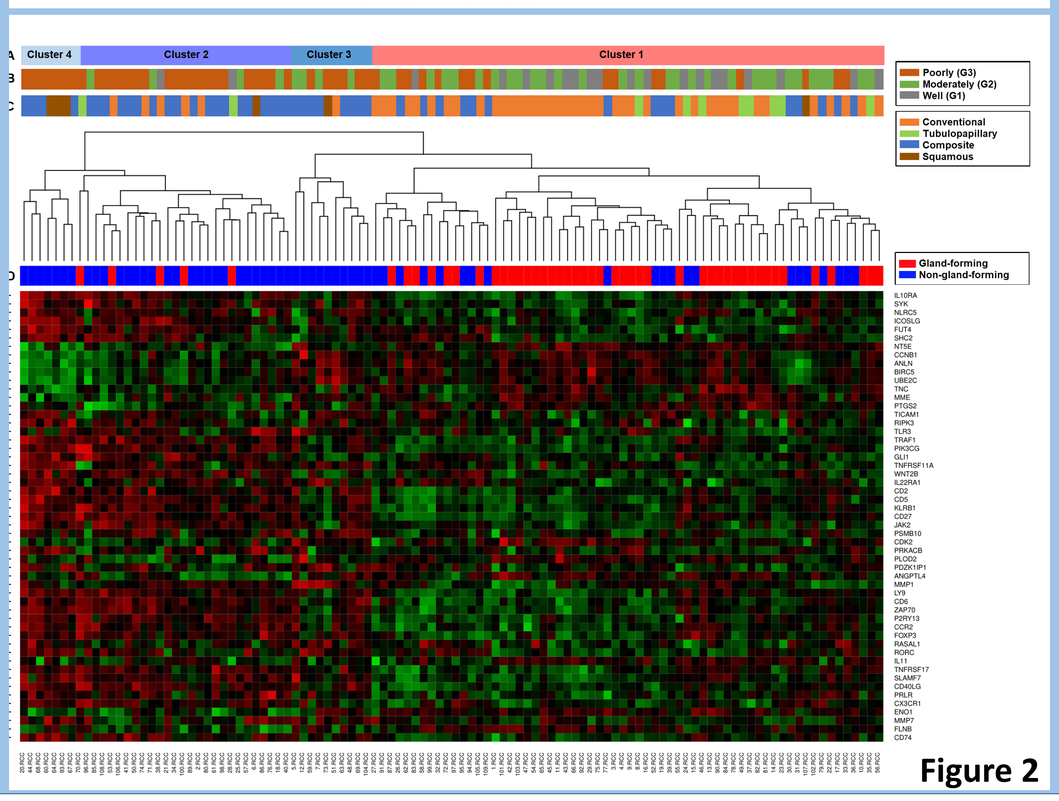


Figure 2

Planned research project

Aims:
With this project, we aim to answer the following questions regarding PDAC:

1) Which key circRNAs can be identified in PDAC?
2) How is the expression of circRNAs related to its microscopic subtypes?
3) In which cells (cancer celles vs. stromal cells) are key circRNAs expressed?
4) Which circRNAs hold prognostic value in PDAC?

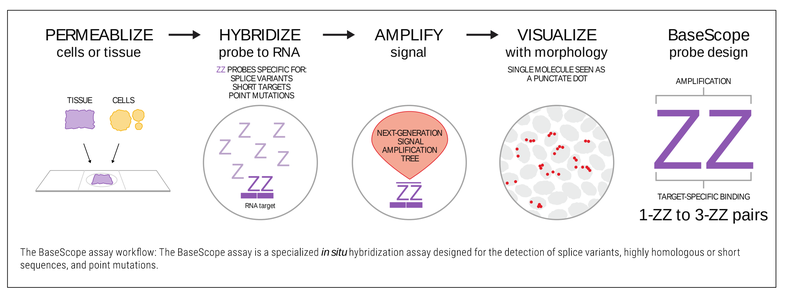
***Materials*:**
108 consecutive, chemotherapy-naïve surgical PDACs will be included. The cohort is well-characterized and has already been subtyped microscopically[2].

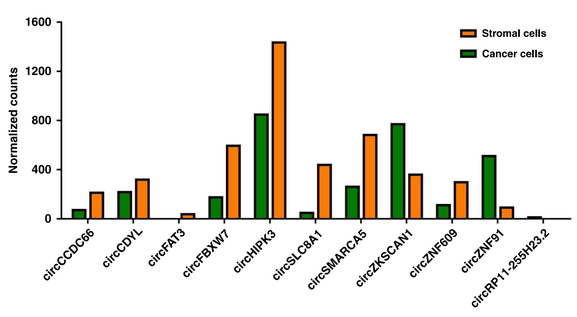
***Methods*:**

- PubMed search for identification of the **30 most interesting circRNAs**
- Design of a **customized panel** to detect relevant circRNAs
- **Digital expression profiling of circRNAs** in 108 PDACs
- BaseScope Chromogenic in-situ hybridization (**CISH**) to identify the cellular location of selected circRNAs
- Verification of the CISH results using **laser micro-dissection (LMD),** separating stromal and epithelial cells, and their analysis using digital circRNA expression profiling

Research Group:

- Professor Sönke Detlefsen, Dept. of Pathology, OUH (main supervisor)
- Assoc. professor Henrik Hager, Dept. of Pathology, Vejle Hospital (co-supervisor)
- Assoc. professor Lasse S. Kristensen, Dept. of Molecular Biology and Genetics, Aarhus University





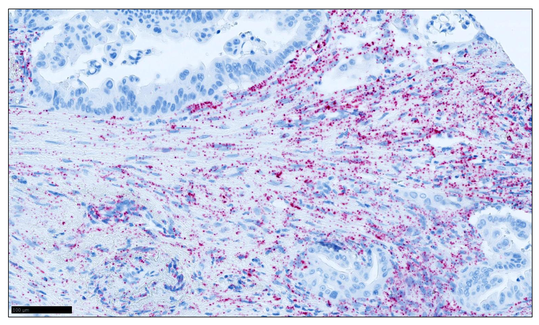


Figure 3

References:

1) Kalimuthu SN, Wilson GW, et al. Morphological classification of pancreatic ductal adenocarcinoma that predicts molecular subtypes and correlates with clinical outcome. *Gut* 2020;69:317-328
2) Rasmussen LG, Verbeke CS, et al. Gene expression profiling and histological subtyping of pancreatic ductal adenocarcinoma. Submitted. 2020.
3) Kristensen LS, Ebbesen KK, et. al. Spatial expression analyses of the putative oncogene ciRS-7 in cancer reshape the microRNA sponge theory. *Nature Communications*, in press

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