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### ► To cite this version:

Flora Clement, Monika Hospodiuk-Karwowski, Vincent Haguet, Amandine Pitaval, Anastasia Papoz, et al.. Development of an amphicine pancreas-on-a-chip to study tumor initiation in a diabetic microenvironment. Pancreatic Cancer Symposium - 3e International Pancreatic Cancer Symposium, Oct 2023, Bordeaux, France. hal-04399625

**HAL Id: hal-04399625**

**<https://hal.science/hal-04399625>**

Submitted on 17 Jan 2024

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# Development of an amphicine pancreas-on-a-chip to study tumor initiation in a diabetic microenvironment

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## Purpose

In 2021, 537 million of the global adult population worldwide were living with diabetes [1]. Type 2 diabetes, which accounts for more than 95% of diabetes mellitus, is associated with an increased risk of pancreatic ductal adenocarcinoma (PDAC) [2]. PDAC is a destructive disease with an unoptimistic prognosis. It ranks 9<sup>th</sup> in the incidence of solid cancers but 4<sup>th</sup> for cancer-related deaths [3]. While several studies described potential molecular links between diabetes mellitus and PDAC, there is a lack of pertinent biological models to better elucidate the molecular mechanisms involved [2]. Three-dimensional cell cultures emerge as more relevant models towards organ-emulating constructs superseding the traditional two-dimensional format. Here, we created a perfusable microtissue-laden device using 3D printing technology to investigate the molecular links between diabetic microenvironment and PDAC initiation.

## Methods

We use a 3D-printed device in which fugitive ink has been extruded to form a pancreatic duct. The duct is lined with a hydrogel from healthy or diabetic origin that also contain islets of Langerhans. The duct-mimicking channel is then filled with human pancreatic epithelial cells either healthy or harboring preneoplastic abnormalities.

## Results

We developed an amphicine pancreas-on-a-chip model that recapitulate diabetic condition and allow immunostaining labelling in 3D, as confirmed by ELISA quantification of insulin secretion in response to glucose stimulation, and light-sheet microscopy. We have also developed a decellularized extracellular matrix of healthy tissue that allows perfusion and good cell survival, a necessary first step towards the preparation of matrix from diabetic tissue. We maintain the perfused devices over several weeks, enabling the study of tumor initiation over long periods. We will further analyze the link between the diabetic environment and the cell activity (proliferation, migration) in cells harboring preneoplastic abnormalities (such as genetic mutations, inflammatory/hyperglycemia exposition) to study the link between cells abnormalities in diabetic patients and the risk for development of pancreatic cancer.

## Conclusion and significance

Our approach allows the fabrication of semi-automatized and standardized devices that can be used for multiple organ models. The advantages of hydrogel-based devices are the possibility of cell self-arrangement in the relatively large bulk of hydrogel. The self-organized cells will then synthesize their own extracellular matrix, and will mature over time. The results are promising to generate glucose-responsive, functional Langerhans islet-based device for a breakthrough research in the early stages of pancreatic adenocarcinoma in diabetic patients, to identify new early diagnostic biomarkers.

[1] IDF Diabetes Atlas 2021, International Diabetes Federation (2021)

[2] D. Li, "Diabetes and Pancreatic Cancer" *Mol Carcinog.* 2012 Jan; 51(1): 64–74 (2013)

[3] A. Jemal et al, "Cancer statistics" *CA Cancer J. Clin.* 56 106-30 (2006)