IHPBA Kenneth Warren Fellowship Progress Report

San Francisco July 1st, 2021

Dear IHPBA Research Committee,

I would like to thank the IHPBA Kenneth Warren Fellowship for giving me the opportunity to spend a year working under prof. Maker supervision at UCSF. The relevance of this opportunity both from a professional and personal perspective cannot be understated. As you are aware, given the impact of the COVID-19 pandemic worldwide, we had to postpone the beginning of my fellowship. But thanks to the support of prof. Salvia and prof. Maker I was able to start my fellowship in February 2021.

My project concerns the identification of a molecular panel that identify pancreatic cystic neoplasms that have a high risk of harboring high-grade dysplasia or invasive cancer. Building on previously published work, the analysis of an independent cohort of pancreatic cyst fluid samples was conducted. The assay used is based on a custom made Taq-Man Low Density array that allow for the simultaneous analysis of multiple targets using a small amount of cyst fluid (50ul). The possibility to use a small amount of fluid is crucial to the actual use of this test in the clinical practice, as the volume of fluid obtained by pancreatic cysts if often very low. We were able to run all the samples in Chicago, and we are now analyzing the data, using machine learning algorithms to identify the combination of targets that better satisfy our clinical needs. The preliminary results report a 99% sensitivity with a 90% overall accuracy in differentiating benign lesions such as Serous Cystic Adenomas from all potentially malignant lesions (such as IPMN and MCN) and malignant lesions (such as cystic PDAC or solid pseudopapillary neoplasms). Furthermore, the test showed a high specificity (100%) for the identification of IPMN with HGD with an AUC of 0.89.

The analysis of this independent cohort of patients confirmed the association between IL-1β and PGE2 with IPMN with HGD. Therefore, we designed a set of experiment to start assessing the in-vitro effect of IL-1β stimulation on a set of patient-derived IPMN organoids that are already available in our lab. Thanks to a collaboration with dr. Shokat's lab here at UCSF, we are also planning in using a $KRAS^{G12C}$ inhibitor to assess the role of this early mutation in shaping the Immune microenvironment of IPMNs.

Furthermore, we are designing a first set of experiments to be performed in a mouse model of IPMN to assess the role of these targets in the development and progression of IPMNs. These experiments are intended to be performed in a syngeneic murine model of IPMN in which we will target pathways that we have identified in the dysplasia to carcinoma sequence.

I am grateful for the opportunity to work on this project granted by the Kenneth Warren Fellowship, and I am looking forward to presenting the results in the next IHPBA meeting in New York in 2022,

Best regards,

Tommaso Pollini