



Scientific Abstract

Pancreatic Cancer Collective Research Team:

“Computational Approaches to Identifying High-Risk Pancreatic Cancer Populations Identification of Genomic and Immune Factors in High-Risk Populations for Pancreatic Cancer”



[This abstract was provided by the scientists when their application was accepted.]

Pancreatic cancer is one of the deadliest tumors, with a five-year survival rate below nine percent and a rising incidence in developed countries, where risk is difficult to predict with current methods. Aside from age, several environmental factors have been only weakly associated with increased risk, including diabetes mellitus type 2, obesity, chronic pancreatitis, smoking, and heavy alcoholism. Inherited genetic variants such as mutations in *CDKN2A*, *BRCA2*, *PALB2*, *TP53*, and *STK11* also increase risk, but they explain just 20 percent of cases with a family history of pancreatic cancer. Additionally, GWAS studies have identified up to 40 susceptibility loci with low to modest effect sizes, mostly in non-coding regions. To date, known factors only explain a small fraction of the attributable risk of pancreatic cancer, highlighting the importance of novel markers and risk predictors.

There are some interesting hints suggesting that, in addition to cancer genetics, the tumor microenvironment plays an important role. Several studies have shown differential expression of human leukocyte antigen (HLA) genes in pancreatic cancer, suggestive of the critical roles of neoantigen presentation and immune suppression. Others have demonstrated increased risks due to bacterial (*H. pylori*, *P. gingivalis*) and viral (Hepatitis B and C) infections, as well as a reduced risk associated with certain allergies. Altogether, these findings underline the potential for new microenvironmental and immune-derived biomarkers for high-risk individuals.

We have assembled an interdisciplinary, multi-institutional, and international team that combines expertise in cancer genomics (Rabadan), genetic and molecular epidemiology (Malats and Molina-Montes), and the microbiome (Korem) with physicians and translational researchers specializing in pancreatic cancer (Manji and Olive). Here we will leverage the power of large datasets, including the UK Biobank, European Study on Digestive Illnesses and Genetics (PanGenEU), TCGA, and ICGC, to comprehensively assess the compounded risk of well-established clinical factors together with novel genomic and microenvironmental markers in pancreatic cancer.

Our specific aims are:

- (1) the identification of common and rare germline variants associated with pancreatic tumors;
- (2) the characterization of the tumor microenvironment including microbiome and HLA allele-specific expression; and
- (3) their validation using two cohorts from Europe and the US.

If successful, we will provide an integrated quantitative approach to studying genomic and immune components for the identification of populations at high risk of pancreatic cancer.

