Final Publishable Summary.

Cancer is a disease of aging. It is generally assumed that genetic changes responsible for the common cancers occur during adult life. However, it is likely that mutations occurring during embryonic development may contribute to neoplastic diseases throughout our life.

With this project (PanClon), we have developed all the basic *in vivo* systems necessary to approach one very simple question, in a particular tumor (pancreatic cancer), but with enormous health implications: how does an embryonic pancreatic progenitor acquiring a mutant oncogene compete with adjacent progenitors colonizing the organ?

Description of the objectives.

In our proposal (IEF-2010 PanClon), we had set up four different goals:

1. Clonal analysis of the embryonic mouse pancreas
2. Clonal analysis of the adult mouse pancreas
3. Clonal analysis to study murine models of pancreatic cancer
4. 3D reconstruction of the embryonic pancreas

Main Results

Early multipotent pancreatic progenitors are precursors to acinar, ductal and endocrine cells. On the other hand, second wave differentiation progenitors are already committed into pre-acinar and bi-potent ductal/endocrine progenitors. To understand better the behaviour of these progenitors I have used mouse models for *in vivo* cell fating (information on cell potential), models of clonal analysis (information about spatial distribution) and retrospective clonal analysis (targeting of one single progenitor).

In our results, we confirmed that multipotent and second wave of differentiation progenitors give raise to acinar cells. However, while multipotent progenitors form large clones in the prenatal pancreas, second wave progenitors give raise to small cluster of cells, the pancreatic chords they form being polyclonal, showing that these progenitors a low proliferation capacity. The situation is maintained in the adult pancreas, where we found small numbers of traced acinar cells intercalated among non-traced cells. Under these conditions, I am setting the necessary protocols to understand whether mutant oncogene acquisition by these progenitors favours their proliferation and, therefore, leads to an enriched number of pre-malignant cells in an adult pancreas.

Finally, I am approaching also the tridimensionality of the pancreas by whole mount immunofluorescence. Up to now I have applied this strategy only to the embryonic pancreas but in the future we plan to understand how progenitors acquiring oncogenes distribute in the whole pancreas.

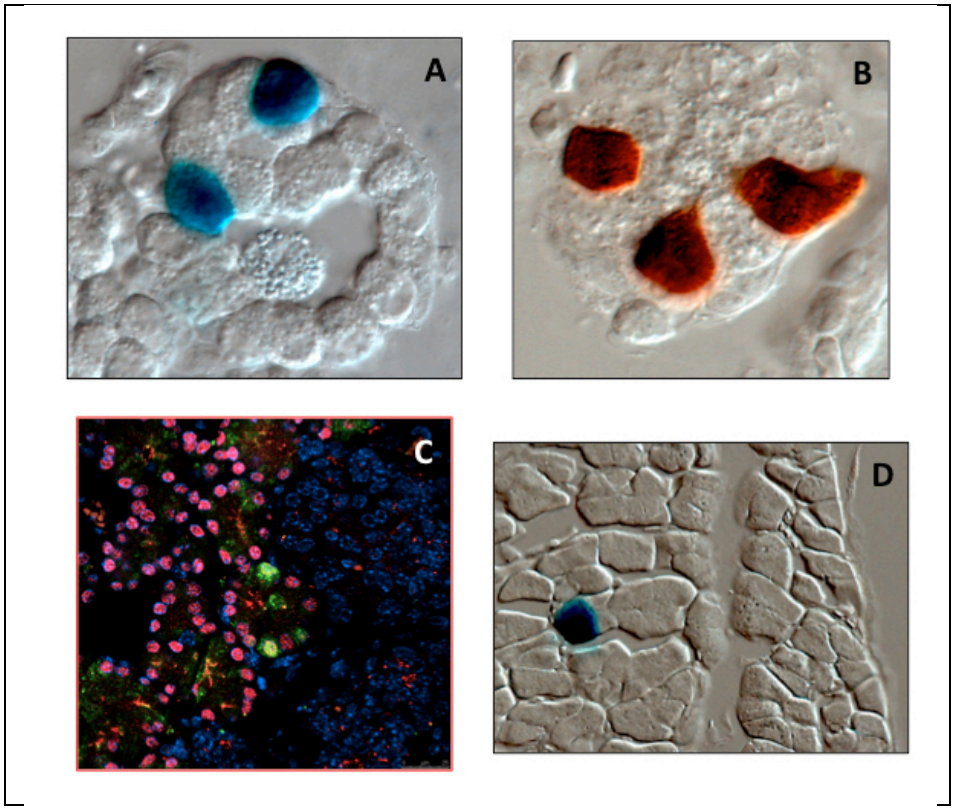

Figure 1: detail from an E17.5 pancreatic chord gelatin slide photo (A). Polyclonal E17.5 pancreatic chord (B). Double Immunofluorescence in a paraffin slide from an E17.5 embryo against GFP and Cpa1 (C). Stack from a whole mount Immunofluorescence against Pdx1 done in an E14.5 embryonic pancreas.

Potential impact of the results

Currently, several papers about clonal analysis of the embryonic progenitors of the pancreas are coming out. My results are first the basis of a good developmental paper implementing current knowledge about pancreas development. I expect these results to help me to become established as an independent researcher. Moreover, I have set up the basis to understand whether cancer is not only a consequence of somatic mutation accumulation but there is also an embryonic factor. This should be the basis of my future research plan as independent researcher: we are mosaic and cancer might be also an embryonic somatic illness.