The ubiquitously expressed non-receptor protein tyrosine phosphatase SHP2, encoded by the PTPN11 gene, is involved in signal transduction downstream of multiple growth factor, cytokine and integrin receptors, where it is necessary for complete RAS-MAPK activation as well as for regulation of the JAK-STAT signaling. A novel potent allosteric SHP2 inhibitor was described to be efficient in receptor tyrosine kinase-driven cancers, but not in KRAS-mutant cancer cell lines \textit{in vitro}. Pancreatic cancer patients carry activating KRAS mutations in 95\% of cases, and therefore appear to be unsuitable for anti-SHP2 therapy. In accordance with that, the Team also observed little or no effect of SHP2 inhibition in KRAS-mutant tumor cells under normal cell culture conditions.

Nevertheless, they showed that SHP2 inhibition under growth factor-limiting conditions (low serum) \textit{in vitro}, or \textit{in vivo}, results in impaired tumor growth, mainly due to induction of cellular senescence. In particular, they demonstrated that genetic deletion of Ptpn11 profoundly inhibited tumor development in mutant KRAS-driven murine models of pancreatic ductal adenocarcinoma, although deletion or inhibition of Shp2 in established pancreatic tumors delayed tumor progression but was not sufficient to achieve tumor regression.

Therefore, they set up to identify rational treatment combination to enhance the anti-tumor activity of SHP2 inhibitors, and found that SHP2 depletion or pharmacological inactivation short-circuits a feedback mechanism that makes KRAS mutant cells unresponsive to MEK inhibitors through receptor tyrosine kinase (RTK) activation. In addition, evidence of efficient MEK and SHP2 combination treatment in KRAS amplified gastroesophageal tumors has also been reported, and further supports the hypothesis that combined SHP2 and MEK inhibition might be beneficial in KRAS mutant tumors, such as pancreatic cancer.

**Specific Aims**

The ultimate aim of the Team’s research proposal is to bring the SHP2 and MEK inhibitors combination to the clinic, by starting a phase I clinical trial with pancreatic cancer patients. Nevertheless, despite their extensive \textit{in vitro} and \textit{in vivo} validation, which provide a solid basis for the proposed drug combination, further pre-clinical studies need to be carried out in order to ensure optimal therapeutic efficacy with minimal toxicity.
Therefore, the specific aims of the proposed pre-clinical studies are:

- **Aim 1:** Evaluate the maximum tolerated dose of the SHP2 inhibitor and MEK inhibitor of choice in non-tumor bearing mice.
- **Aim 2:** Identify qualifying biomarkers for response that will allow the identification of patients most likely to respond to the proposed therapy.
- **Aim 3:** Test different treatment schedules in different mouse models of pancreatic cancer, in order to maximize the anti-tumor effect and to minimize toxicity.