Objectives/hypothesis:
The project aims to win one of the main challenges of innovative therapeutic strategies. When tumor mass grows, it lacks oxygen thus develops angiogenesis.
Tumor angiogenesis is abnormal and this appears as one hallmark of cancer.
Angiogenesis in tumors produces abnormal vessels which allow tumor escape and metastases.
The project is to normalize the vessels in tumors to avoid dissemination and restore the immune response in tumor bearing organism.
We have brought a strategy to increase the oxygen partial pressure in the tumor showing a deep effect on the ability to raise an immune response and reducing the selection of aggressive cancer stem like cells.
The issue is to stabilize the normalized vessel state to favor the accessibility of tumor cells to drug treatment and maintain an elevated oxygen level to enhance the radiotherapeutic effects.
The danger is to face the pre-established dysregulated factors which may compromise the efficacy of the vessel normalization based treatments.
The main modulatory factors are the microRNA, non coding short RNAs which deeply influence cancer progression, are very sensitive to hypoxic conditions and actively control angiogenesis.
In endothelial cells, forming angiogenesis the tumor suppressor factor PTEN is a decisive molecule which must be activated to control and maintain a normal type of vasculature. Its activation is induced by the molecule ITPP (*inositol tris pyrophosphate)*, that we have described and shown that it acts by a) helping the hemoglobin to deliver O2 in hypoxic site and b) binding and activating PTEN. To stabilize this effect we plan to restore a balance of microRNA in the tumor site. This will permit to stabilize the normalized vessels and counteract the action of hypoxia induced dysregulation of microRNA.
The strategy uses the ability of endothelial progenitor cells to specifically home into tumor site, where angiogenesis develops. The cells will be transfected by the compensatory microRNA and used to target the tumor site.
The methods will:
1. Define the profile of tumor cells micro RNAs modified upon compensation of hypoxia. Identify the microRNAs which remain dysregulated in the tumor cells, impair vessel normalization and PTEN activation. Identify their role in the immune response.
2. Investigate the specific miRNAs that can inhibit tumor-type angiogenesis, help PTEN activation and consequently restore immunity and immune checkpoint control inhibiting cancer cells' growth and aggressiveness.
3. Transfect endothelial progenitors with the identified miRNAs, follow their expression and properties towards cancer stem cells and anti-cancer immunity.
Impact: PTEN regulated vessel normalization is a new mean to maintain PO2 elevation in the tissues. It is the decisive effect to type the most effective miRNAs. Their action will produce a synergistic effect with conventional anti-cancer therapies and open to new anti-cancer drugs discoveries.
The new knowledge obtained from the realization of this project will help to design better strategies against cancers based on hypoxia compensation and efficient immune response. Moreover the identification of novel miRNAs profiles will open new diagnosis for cancer and follow up of treatment.