

## PROJECT

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### 1) Project title

Development of innovative therapies for chemotherapy-treated prostate cancer

### 2) Abstract

**Prostate cancer** is the second commonest malignancy in men worldwide and the second commonest cause of male mortality. Patients with metastatic prostate cancer, specifically those with disease progression following primary androgen ablation therapy and addition or withdrawal of an anti-androgen, are generally considered to be refractory to hormonal therapy. The treatment of castration-resistant prostate cancer (CRPC) remains unsatisfactory. Unfortunately, chemotherapy can only marginally improve patient survival, providing a palliative benefit in this setting. Patients with hormone-refractory prostate cancer have, thus far, not been cured with either hormonal treatments or chemotherapy. It is hoped that the development of novel targeted therapies and immunotherapies will improve the outcome of patients with androgen refractory diseases.

PTEN is one of the most frequently altered tumor suppressor genes in prostate tumors and **PTEN loss** is often associated to both **chemo- and radiotherapy resistance** in prostate cancer patients. Despite the high incidence of PTEN mutations or deletions, a treatment that target prostate tumors harboring PTEN alterations still does not exist. **Major objective of this project is to identify novel treatment modalities for the therapy of PTEN deficient prostate cancer.**

**Cellular senescence** is a stable cell growth arrest that occurs in tumor cells subjected to different kinds of stress including treatment with chemo-/radiotherapy or targeted therapies. Several findings *in vivo* demonstrate that senescence limits tumor progression. Although arrested, senescent tumor cells remain metabolically active and secrete a variety of cytokines and inflammatory factors known as the **senescence-associated secretory phenotype (SASP)**. The SASP of tumor cells can activate the tumor immune response and promote the clearance of senescent tumor cells, a phenomenon referred as senescence surveillance. However, we have recently found that tumor infiltrating myeloid cells can hinder senescence surveillance by inhibiting the proliferation and function of T cells. In these tumors, remaining **senescent tumor cells through the SASP can support tumor growth** by increasing angiogenesis, cell migration, invasion and even metastasis. Thus, removal of senescent cells, hereafter referred as **senolytic therapy**, has been proposed as a strategy to improve the efficacy of

currently available treatments in tumors where immunosuppression hinders the clearance of senescent cells. Nowadays, there are few examples of effective senolytic compounds for cancer therapy. The majority of these compounds targets Bcl-2, a regulator of apoptosis that is found increased in senescent cells. However, the efficacy of Bcl-2 inhibitors is variable and it depends by the genetic background of the senescent tumor cells, being effective in certain type of senesce response but not in others. Thus, **the main objectives of our invertigations are:**

- 1) to identify pro-senescent compounds that trigger a positive anti-tumor immune response in PTEN null prostate tumors
- 2) to develop novel senolytic therapies for chemotherapy-treated prostate cancers
- 3) to combine pro-senescent compounds with checkpoint inhibitors.