Background

The classic functions of the tumour suppressor protein p53 in response to acute DNA-damage signals are cell cycle arrest and/or apoptosis. Despite the large volume of literature, however, experimental evidence has demonstrated that these mechanisms are dispensable for p53-mediated genomic integrity and tumour suppression. Mouse models selectively lacking p53-mediated cell cycle arrest and/or apoptosis (*Trp53*[25,26] mice *and p21*$^{-/-}$*; Puma*$^{-/-}$*; Noxa*$^{-/-}$ mice) display efficient suppression of tumour development, mediated by unidentified p53 downstream effectors. Thus, the mechanisms underlining p53-dependent maintenance of genome integrity remain fundamentally unclear.

Aim

The *GOAL* of my research is therefore to dissect how alterations of the tumour suppressor p53 reshape the epigenetic landscape of cancer cells. I aim to address this by determining whether p53 enforces maintenance of constitutive heterochromatin, thus contributing to genome integrity. Subsequently I aim to exploit the identified epigenetic deregulations to design innovative therapeutic approaches and combinations to treat uncurable diseases. Specifically I aim to:

- Determine the epigenetic mechanisms responsible to p53-mediated tumour suppression.
- Identify of epigenetic vulnerabilities in cancer cells associated with p53 mutational status
- Investigate development of innovative therapeutic strategies combining epigenetic drugs with blockade of immuno-checkpoint.

Expected Results and Impact on Cancer

The identification of a causative relationship between p53 status and epigenetic maintenance of constitutive heterochromatin will help in defining the evolution of cancer to a therapy-resistant and metastatic phenotype.

The expected result is that a significant contribution to p53-mediated maintenance of genomic integrity is associated to its ability to epigenetically preserve constitutive heterochromatin. This mechanism prevents genomic aberrations triggered by accumulation of high expression level of repetitive RNAs (satellite RNAs) that can enable genomic instability and evolution of cancer. The subsequent outcome will be the identification of potential strategies to therapeutically exploit the epigenetic deregulation associated to p53 status to treat cancer.

This study will therefore significantly impact cancer by providing a better understanding of the molecular basis of its evolution to an untreatable disease and indicating potential innovative strategies (i.e. drug combinations) to treat cancer at uncurable stages.