**PROJECT 1**

**DoS**: Irene Franco

Title: "Somatic mutation mechanisms in pre-malignant kidney and their role in tumor initiation"

Curriculum: BAIO

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/genetics-and-cell-biology/cystic-kidney-disorders/irene-franco.html

**Project description** (*Number of characters*, *including spaces*: 2.000 - 3.000):

Exposure to exogenous and endogenous mutagens results in the daily accumulation of somatic mutations. The consequent loss of genome integrity is recognized as the leading force of malignant transformation. Despite this important role, our information about ongoing mutagenic processes in different healthy tissues and cell types is sparse. The recent expansion of next-generation sequencing applications has finally enabled the analysis of non-cancer genomes and provided extraordinary tools to identify, directly in human samples and at single-cell resolution, the mutagenic forces that drive tumor initiation (Kakiuchi and Ogawa, 2021).

In the aging kidney, a particular subpopulation of proximal tubule cells that responds to damage display an excessive accumulation of somatic mutations compared to other kidney and non-kidney cells (Franco et al., 2019). The origin of these mutations is unknown, but the unique mutation profile observed in these cells indicates cellular metabolism as the likely source. In support of this hypothesis, metabolic regulation is a major difference between the PT and other segments of the tubule. In fact, while other kidney cell types primarily depend on glucose to drive their energy needs, PT cells rely on oxidative metabolism. This metabolic setting increases oxygen demand and renders PT cells exceptionally sensitive to hypoxia episodes that commonly accompany kidney overload. Meaningfully, metabolic changes and adaptation to hypoxia are major features of kidney carcinoma (Linehan et al., 2019).

The project will explore in details the interplay between hypoxic damage, metabolic changes and somatic mutagenesis in different kidney tubule cell subpopulations, with the aim of identifying the chain of events that leads to selection of malignant clones. The candidate will work with both animal models and cells derived from human biopsies. Biopsies from patients affected by an inherited syndrome that predisposes to kidney carcinoma by altering the cellular response to hypoxia (Von Hippel Lindau syndrome) will be obtained in collaboration with the Urological Research Institute of San Raffaele. The candidate will also interact with the Center for OMICS Sciences of San Raffaele and produce and analyze genomics and metabolomics data. Understanding the mechanisms of kidney tumor initiation will possibly have a translational outcome and help defining means of tumor prevention.

**Skills to be acquired by the student** (*Number of characters*, *including spaces*: max 600):

Cell culture, culture of primary cells from human urine, cellular treatments including transfection, silencing and drug-treatments, RNA and DNA extraction from cultured cells and other biological samples, gene expression analyses, sequencing, analysis of whole genome sequencing data, handling of genetically modified mouse strains, cell sorting of fluorescent cells from murine tissues, histological procedures and analyses.

**References** (max. 15)

Franco, I., Helgadottir, H.T., Moggio, A., Larsson, M., Vrtacnik, P., Johansson, A., Norgren, N., Lundin, P., Mas-Ponte, D., Nordstrom, J.*, et al.* (2019). Whole genome DNA sequencing provides an atlas of somatic mutagenesis in healthy human cells and identifies a tumor-prone cell type. Genome Biol *20*, 285.

Kakiuchi, N., and Ogawa, S. (2021). Clonal expansion in non-cancer tissues. Nat Rev Cancer *21*, 239-256.

Linehan, W.M., Schmidt, L.S., Crooks, D.R., Wei, D., Srinivasan, R., Lang, M., and Ricketts, C.J. (2019). The Metabolic Basis of Kidney Cancer. Cancer Discov *9*, 1006-1021.