Evaluation of NOTCH1 and NOTCH3-dependent anticancer drug resistance in a 2D and 3D model of Head and Neck Squamous Cell Carcinoma (HNSCC)

The aim of the project is to determine the role of NOTCH1 and NOTCH3 signalling interplay in drug resistance in head and neck squamous cell carcinoma (HNSCC).

The Head and Neck Squamous Cell Carcinoma (HNSCC) is one of the most common cancers in the world, yet, the prognosis for patients with this type of cancer remains poor. The 5-year survival rate of patients with HNSCC remains at around 65%, despite a better understanding of the mechanisms of progression of this cancer and the development of new therapeutic targets. The HNSCC are characterized by a high index of proliferation and invasion, often accompanied by chemoresistance. Therefore, the HNSCC is a significant global health problem with high mortality and morbidity, with only a handful of drugs, often together with surgery and radiotherapy, as treatment options. The search for key signalling pathways associated with proliferation, invasion and the reduction of drug resistance is one of the goals of personalized treatment strategies that can improve the survival of patients with HNSCC.

The Notch signalling pathways play key roles in the development of primary tumours and their metastasis in many types of cancer. At a first glimpse, NOTCH-3 signalling is apparently similar to that of NOTCH1, nevertheless, some studies have shown that these 2 receptors may have opposite cellular responses. Additionally, both activity of NOTCH1 and NOTCH3 also influence to sensitivity to chemotherapeutic agents. Despite that, it is still unclear what the functional impact of these changes on cancer progression and invasion might be, and what implication this might have for therapy and the development of personalized medicine.

We are going to use the optogenetic system developed in our laboratory, for control specific NOTCH activity in HNSCC cells. This optogenetic system allows us to control NOTCH activity by using pulses of blue light. Using this molecular biology tool, we will study the influence of NOTCH1 and NOTCH3 activity on the tumorigenic process, proliferation, migration, invasion and chemoresistance of cancer cells. Despite their advantages, classical 2D cell cultures have many limitations, the most important being that their response to anticancer drugs is non-predictive for patients' tumours, which consequently lowers their clinical value. Thus, there is need to mimic cultures with conditions closer to the natural tumour microenvironment (TME). Advances in 3D culture technologies such as spheroids and organoids have brought more predictive tumour models. For this reason, the planned research will be carried out in 2D (monolayer) and 3D (organoid) cultures to bring the natural environment of the tumour as close as possible. Additionally, 3D cultures will be carried out in the company of cells such as cancer associated fibroblasts (CAFs), tumour associate macrophages (TAMs) as well as endothelial cells. Moreover, all cells will be grown in human tumour matrix (Myogel).

We believe that our research will contribute to deepening the knowledge of head and neck cancer development. Thus, establishing the connection between the activity of NOTCH1 and NOTCH3 signalling interplay and drug resistance in HNSCC will contribute to the development of a new therapeutic strategies.