PROJECT 1

DoS: **Vanesa Gregorc**

Title: **Role of autophagy inhibition in Immune System response in patients with Head and Neck Cancer and Non Smal Cell Lung Cancer**

Curriculum: Experimental and Clinical Medicine

Residency Program: Otorhinolaryngology

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

Tumour Immunotherapy is a promising treatment strategy against several solid neoplasms. Immune checkpoint blockers (ICBs, such as anti-CTLA-4, anti-PD-1, anti-PD-L1 mAbs) unleashing antitumor T cell activity, have increased the overall survival of patients affected by different histologic malignancies, including Head and Neck Squamous Cell Carcinoma (HNSCC) and Non Small Cell Lung Cancer (NSCLC). [1] Nevertheless, there are still many patients relapsing after an initial response or progressing under treatment, indicating the presence of immunosuppressive mechanisms operating within the tumor microenvironment and affecting tumor-specific T cells. For this reason, an in-depth investigation of the molecular and cellular mechanisms regulating the interactions between tumour cells and immune cell populations has vital importance to predict antitumor responses and reach clinical success.

During the last decades, experimental oncologists have pointed out the key role played by a highly conserved intracellular degradative mechanism, namely autophagy, in tumorigenesis. This catabolic pathway acts as a "double edged sword" since it prevents cancer development in premalignant cells, but favours tumour cells survival and growth once tumor has been established. Recent findings have demonstrated the involvement of autophagy in the regulation of immune responses, both innate and adaptive. In preclinical studies, the inhibition of autophagy, both genetically and pharmacologically, has shown the possibility to endow the immune cells with reinvigorated antitumor activity.[2] Indeed, autophagic inhibitors, such as hydroxychloroquine (HCQ), have been shown to skew the polarization of tumour-associated macrophages (TAMs) from pro-tumoral M2 subsets to M1 tumour-killing cells. Moreover, the inhibition of autophagy restores tumour surface levels of MHC-I and leads to improved antigen presentation, enhancing anti-tumour T cell responses.[3] Therefore, autophagy has shown to be a powerful target for oncological therapy, not only for its own role in tumorigenesis, but also for its potential implication in immune-based antitumor responses.

Clinical experience at our institution has uncovered an unexpected antitumoral activity of HCQ in monotherapy in patients affected by NSCLC. Despite HCQ already represents a promising agent

in cancer treatment strategy, phase I/II studies evaluating its safety and efficacy in combination with chemotherapeutic agents have shown controversial results.

Aim of this project is to carefully dissect the role of autophagy inhibition in both direct and immune system-mediated antitumor response. A multidisciplinary approach will be used with preclinical in vitro and ex vivo studies using different HNSCC and NSCLC models, such as immortalized cell lines and primary tumour organoids established from patients' biopsies; analysis of clinical, molecular and immunological phenotype and clinical outcome of patients with HNSCC and NSCLC.

Skills to be acquired by the student:

The student will be directly involved in most of the tasks of the project:

- Obtainment of HNSCC and NSCLC biopsies and establishment of in vitro models
- Clinical data collection and analysis
- Assessment of gene and protein expression of tumor cells and tumor biopsies
- Functional characterization of homeostatic, stress adaptive pathways of tumour cells
- Genetic and pharmacologic manipulation of cellular responses
- Statistical analysis SPSS data set

The student will be adequately trained to acquire molecular and cellular biology skills/techniques to carry out the experiments reported above (i.e. establishment of in vitro cell cultures, HNSCC and NSCLC organoid establishment, in vitro and ex vivo assays, etc.). Moreover, the student will have the unique opportunity to interact with surgeons, pathologists and oncologists in order to get tumour tissues as well as collect, analyse and integrate pre-clinical and clinical data.

References (max. 3)

1. Zolkind P, Uppaluri R. Checkpoint immunotherapy in head and neck cancers. *Cancer Metastasis Rev*. 2017;36(3):475-489. doi:10.1007/s10555-017-9694-9

2. Amaravadi RK, Kimmelman AC, Debnath J. Targeting autophagy in cancer: Recent advances and future directions. *Cancer Discov*. 2019;9(9):1167-1181. doi:10.1158/2159-8290.CD-19-0292

3. Yamamoto K, Venida A, Yano J, et al. Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. *Nature*. 2020. doi:10.1038/s41586-020-2229-5