Title: ROLES OF EXOSOMES AND LIQUID BIOPSY COMPONENTS IN PNET

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The main objective of this project is to demonstrate roles of exosomes and liquid biopsy components (miRNA, LongNon-coding RNA) in pancreatic neuroendocrine Tumors.

Neuroendocrine tumors (NETs) are diverse group of neoplasms, mainly found in the gastrointestinal tract, lung and pancreas.

Pancreatic neuroendocrine tumors (PNETs) are the second most common epithelial neoplasm of the pancreas. Primary therapy for localized PNET remains surgical excision. Our current understanding of the molecular pathology of PNETs is insufficient for their clinical management, where the challenge is to predict the aggressiveness of individual tumors in order to identify patients who will benefit

from early aggressive therapy and to minimize harm from the inadvertent overtreatment of patients with indolent disease. Therefore in order to bring a wider horizon to this issue we are taking part in a big project containing the genetic, pathologic and oncologic characteristics of this cancer.

Primarily we will focus on the creation of a data base for clinical data collection, preparation of inform consent and ethical committee approval, sample collection, training in exosomes analysis, miRNA and Long Non coding RNA isolation and detection.

Currently we are working on exosomes and liquid biopsy training. This includes our collaboration in a comprehensive project of pancreatic Neuroendocrine Tumors, devoting to investigate the role of tissue and liquid biopsy in the resistance to first line treatment with mTOR inhibitor (Everolimus). The focus of my project is the liquid biopsy role in this process.

The PhD project is designed into two main parts. The first part is a division of a project developed by the University of Antwerp in which, together with the Department of Genetics, we will analyze the circulating nucleotides and the exosomes cargo in liquid biopsy samples derived from pNET patients. Our groups will analyze the exosomes cargo, measuring the levels of the miRNA and long-non-

coding RNA differentially expressed in the tissue, inside the exosomes, and how they change along with the development of the resistance to mTOR inhibitors.

The second part will consist of a proof of concept for liquid biopsy, mainly, circulating miRNA and long-non-coding RNA, in which we will try to validate the results obtained in the first part, in an independent cohort of patients. In this part we will try to make a sicilian network of rare tumors in order to demonstrate the role of miRNA and long-non-coding RNA in the evolution of pNET and the resistance of mTOR inhibitors in 3 groups of basal (naïve treatment), during treatment with Everolimus and PD as well. In this network however, we will collect both blood samples and clinical data of individuals.

Additionally, for the exosome part, we will work on the creation of the database in collaboration with University of Antwerp.