**Project title:** “Unraveling the genetics of neuroendocrine tumors by high throughput methods”

**ABSTRACT**

Gastroenteropancreatic tumors encompass a wide range of neoplasms arising from neuroendocrine cells of gastrointestinal mucosa and pancreas. Their pathobiology is stalled due to two main factors: the diversity of phenotypes that they can present and the relative rarity of each subtype that preclude the study of large series. Although the different subtypes have a low incidence, these tumors represent a significant clinical problem as they have diverse presentations and initial imaging studies to locate the tumor are normally inconclusive. Even more concerning is the inexistence of accurate means to assess tumor behaviour and disease prognosis. Another recurrent complication refers to the presence of metastasis at the time of diagnosis. For functional non-carcinoids NETs metastasis are found in 22% of the patients. Non-functioning gastropancreatic tumors typically manifest as a more advanced disease, which results in a greater frequency of metastasis at diagnosis (40%). Unfortunately, nearly all patients with metastatic disease have recurrence on 7-year follow-up, even after successful surgical treatment of metastatic disease, reflecting the lack of efficient therapeutic tools.

The knowledge of the genetic events underlying the ethiopathogenesis of these tumors is still very scarce. Multiple differences in chromosomal aberration patterns are noted between gastrointestinal carcinoids and pancreatic endocrine tumors detected by comparative genomic hybridization. These two groups of tumors also diverge in gene expression pattern, where specific genetic alterations are rare. A molecular elucidation for these tumors is highly needed to supply information that will allow differentiated diagnostic and therapeutic strategies as well as prognostic determination.

In order to fulfill this need we propose to characterize pathological, functional and clinically a series of collected cases of neuroendocrine tumors. Following its characterization, and based on each tumor profile we will separate them in subgroups. This separation represents an innovation when compared to previously studies, since GEP-NETs studies have almost always been studied as a single entity. Once we have these groups, previously defined known molecular alterations will be studied. Since only a few genetic hits and molecular mechanisms have been described most of the tumors will be investigated for new gene candidates. In order to achieve this aim we intend to perform high throughput molecular analysis. These will include genome-wide arrays for fine mapping and gene expression profiling. We believe these tools will help us to facilitate the delineation of the molecular pathology of neuroendocrine tumors and provide new insights into the cellular mechanisms. From our genome-wide studies we will be able to select candidate genes that will be evaluated and validated in our series both in vivo and in vitro. Due to the previous stated it is self-evident the need of a better comprehension of neuroendocrine tumors that can be translated to the clinical in terms of patient prognosis and/or in the identification of new therapeutic targets.