

# Using unsupervised clustering of multiomic data to define molecular and transcriptional subtypes of pancreatic neuroendocrine tumours

**Joan Miguel Romero, MSc**

MD-PhD Candidate, Division of Experimental Medicine, Rosalind and Morris Goodman Cancer Institute and Research Institute of the McGill University Health Centre (RI-MUHC), McGill University

Abstract:

**Background and rationale:** Personalized oncogenomics has revolutionized cancer treatment for patients. By deep profiling of individual tumours, new subtypes can guide treatment selection and generate novel hypotheses to help identify mechanism of targeting cancers. Pancreatic neuroendocrine tumours (pNETs) are rare tumors arising from neuroendocrine cells in the pancreas. Their clinical behaviour and prognosis are variable and durable responses are often difficult to achieve with conventional therapies. Recent studies of the pNET tumour microenvironment suggest that immunotherapy approaches may be efficacious in subsets of pNETs.

**Objective:** We are focusing on 1) correlating pNET molecular subgroups with clinical outcomes and 2) examining immune-related gene expression patterns across these subgroups to explore a role for immunotherapies. These investigations include evaluation of a 4-chemokine expression signature (c-Score: *CCL4*, *CCL5*, *CXCL9*, *CXCL10*), which we have shown to be a predictive biomarker of tumour inflammation and immune checkpoint treatment outcomes across cancer types.

**Methods and Results:** A multiomic dataset with clinical treatment and outcome annotations of rare pNETs was generated as part of a regional Marathon of Hope cohort (n=30). Unsupervised machine learning techniques are being used to help evaluate pNET clustering patterns and identify gene expression patterns predictive of clinical outcomes and treatment responses. Early data suggest that pNETs segregate into distinct molecular groups, which we are evaluating in a larger WGTS dataset with clinical correlations to identify predictive clinical outcome and immunotherapy biomarkers. Further, we discuss a patient with a germline *BRCA2* mutation, highlighting the orthogonal outcomes generated from these data that can help navigate patient treatment.

**Conclusions:** pNETs cluster into distinct subgroups with different gene expression profiles, with implications for treatment management.

**Anticipated Impact:** Deep profiling of rare pNETs can identify novel subtypes and help stratify patients into different treatment cohorts to improve outcomes.

Plain language summary:

**Background and rationale:** Profiling of individual patient tumours has helped physicians identify specific patterns that can make some tumours more receptive to treatments. In this project, we aim to apply these profiling techniques to help understand a rare subtype of pancreatic cancer called neuroendocrine tumours. Patients with these tumours have differing outcomes, and good responses are rare with common treatments. Recent work from scientists has suggested that pNETs may respond to a type of treatment called immunotherapy.

**Objective:** We aim to 1) find links between subtypes of pNETs and the corresponding clinical outcomes of these same patients and 2) examine specific patterns that may predict which tumours will respond to immunotherapy, including a biomarker we have investigated previously, called the c-Score.

**Methods and Results:** We have used a rich dataset with DNA and RNA profiles of tumours, and clinical outcomes, for 30 rare pNET tumours. Machine learning techniques are being used to help separate patients into groups, based on their DNA and RNA profiles. Early results on a small subset of patients show that pNETs can separate into different groups, and we are expanding these results on the full dataset. Further, we are seeing how these outcomes associate with clinical data. We will also discuss a patient with a specific genetic mutation, which, in addition to other data obtained from profiling their tumour, helped guide treatment management.

**Conclusions:** These rare pNETs separate into different subgroups, with different patterns of RNA expression, and this can have an impact of treatment selection for these patients.

**Anticipated Impact:** Understanding rare pNETs can help identify new subgroups and help guide treatment selection for these patients.