HPG80 (Progastrin), a novel blood-based biomarker for detection of neuroendocrine neoplasms.

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Background:
Neuroendocrine neoplasms (NENs) are heterogeneous tumors which originate from various organs and are of variable aggressiveness based on grade and morphology. Current biomarkers for NENs lack sensitivity and specificity, especially for high-grade NENs (small and large cell neuroendocrine carcinomas). hPG80, progastrin, is a novel bio-marker which is easily measured in plasma using an ELISA test. Physiologically, hPG80, an 80 amino acid protein, is the precursor of the gastrointestinal hormone gastrin. It is synthetized by gastric antrum G cells, and then processed into gastrin by multiple enzymatic processes. In pathological conditions, the GAST gene, which encodes hPG80, was shown to be over-expressed in human solid tumors from various primary sites. hPG80 is unprocessed and released from the tumor cells and becomes detectable in the blood. This study is the first to explore hPG80 in NENs.

Methods:
hPG80 was quantified in the plasma from 31 NEN patients using DxPG80 technology (ECS-Progastrin, Switzerland). Progastrin concentrations in 18-70 YO (n = 557) and 18-25 YO (n = 137) healthy blood donors were compared to 31 stage IV NENs patients. The study was IRB approved.

Results:
Mean age of study cohort at the time of blood collection was 60.9 years. 21 patients had grade 1 and 2 well differentiated NET. 10 patients had high grade NEN (Small cell, large cell and poorly differentiated
NEC). High grade sub cohort also included two well differentiated grade 3 NET patients. Mean hPG80 in NENs was 14.17 pM as compared to 2.04 pM and 0.99 pM in 18-70 and 18-25 YO control groups ($p < 0.0001$), respectively. Subgroup analysis of NENs revealed mean hPG80 of 24.61 pM in high-grade NENs ($n = 10$) vs 10.88 pM in G1/2 NETs ($n = 21$).

**Conclusions:**
This first-ever study of plasma hPG80 in NENs suggests hPG80 may be a diagnostic and/prognostic blood-based biomarker in both low and high-grade NENs and further study is warranted. A prospective trial is ongoing in high-grade NEN to evaluate its role in monitoring of disease (NCT03958045) and further studies in low-grade NETs are underway. This research was supported by Cancer Center Support Grant (CCSG) from the National Cancer Institute (P30 CA177558) and ECS Progastrin.