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MicroRNA Signatures as Novel Biomarkers in Small Intestine Neuroendocrine Tumors

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Background: Small intestinal neuroendocrine tumors (SI-NETs) arise from serotonin-producing enterochromaffin cells. SI-NETs are often well-differentiated tumors and most patients have regional or distant metastases at initial presentation. MicroRNAs (miRs) are post-transcriptional regulators which are important in diverse biological processes and can function as tumor suppressor genes or oncogenes. This study aims to identify an exclusive SI-NETs miR profile that may have a critical role in development, diagnosis, prognosis and progression of these malignancies.

Methods: Fifteen SI-NET specimens at different stage of malignancy, five primary tumors, five mesentery metastases and five liver metastases, were included in this study. Total RNA was hybridized onto Affymetrix GeneChip® miR arrays for genome-wide profiling. Array data summarization, normalization, and quality control were performed using *miRNA QC Tool software.* Differentially expressed miRs were then validated by quantitative real time PCR and Northern blot analyses on the initial specimens as well as on microdissected SI-NET cells. In addition a list of potential miR target genes was generated using TargetScan (www.targetscan.org).

Results: Array results show that the expression of nine miRs is significantly altered between primary tumors and metastases. Five of them (miR-96, -182, -183, -196a and -200a) are upregulated while the other four (miR-31, -129-

5p, -133a and -215) are downregulated during tumor progression. All of them are specifically expressed by microdissected SI-NET cells and therefore may be potential novel biomarkers of tumor progression. In addition we address three bioinformatically selected potential target genes for each significant miR.

Conclusion: To date, little evidence of miRNA expression/ deregulation in SI-NETs has been reported. Our genome-wide SI-NET-miR expression profiling provides information about potential pivotal miRs, their involvement in tumor progression and their possible role as novel targets for therapy. Further analyses to clarify which genes are directly controlled by the selected miRs are ongoing.