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Clinical Utility of Genomic Profiling of Pancreatic Neuroendocrine Tumors

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Background: Rare cancers pose particular difficulties for therapeutic development. We assessed the manner in which genomic information gained from novel technologies could be used clinically to improve the care of patients with pancreatic neuroendocrine tumors (PNETs).

Methods: We applied a novel technique using flow-cytometry to sort clonal populations of tumors cell for genomic profiling with array-based comparative genomic hybridization. We profiled the copy number aberrations present in the genomes of tumor cell populations from 7 PNETs.

Results: Of the 3 insulinomas studied, 2 had very simple genomes lacking significant aberrations at the genomic level predicting a benign phenotype. A third 8 mm low-grade insulinoma harbored numerous aberrations predicting malignant behavior including a focal amplicon within chromosome 11 containing *GAB2*, a known activator of the *AKT* pathway. A second PNET harbored a homozygous deletion of *DISC1* at 1q42.1 that would also predict for activation of *AKT*. These tumors could be targeted with an AKT/PI3K inhibitor. In one PNET, we detected a focal deletion in 11p targeting 3 genes: *IMMP1L* an activator of the proapoptotic *DIABLO*, *ELP4* a component of histone acetyltransferase, and *PAX6*, a key regulator of pancreatic islet hormone gene transcription necessary for normal islet cell development and an activator of *c-MET*, an oncogene. A glucagonoma harbored a deletion in *CDX2*. The *CDX2* and *CDX3*complex with P*AX6* and binds to the glucagon promoter. The same tumor harbored a deletion in *CDKN2*, a tumor suppressor gene that enhances *p53*-dependent apoptosis.

Conclusions: We have identified 3 potential ways in which clonal genomic profiling of PNETs by array CGH can assist in the clinical care of patients: 1) better definition of histopathology and determination of malignant phenotype, 2) provide insight into pathophysiology of excess hormone production, 3) expose therapeutic targets to guide decisions regarding selection of chemotherapy in patients with unresectable malignant PNETs.