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Coupled Diagnostic-Therapeutic Regimen for Neuroendocrine Cancer

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BACKGROUND: Cyclin-dependent kinase 5 (Cdk5) is the regulator of an important tumorigenic signaling network in medullary thyroid carcinoma, one type of NE cancer. Therefore, we asked 1) if Cdk5 plays a role in other types of NE cancers, 2) if biomarkers of Cdk5 driven tumors can be identified, and 3) if inhibitors targeting Cdk5 are effective as therapeutics in vivo.

METHODS: FFPE human NETs were analyzed by H&E and immunohistochemistry. Cell lines treated with inhibitors and SIPs were monitored for effects on growth. Phosphoproteomic analysis was conducted on growing and arrested mouse tumors. Phosphorylation state-specific antibodies were generated to a set of candidate biomarker phosphoproteins. Cell lines, mouse tumors, and human tumors were evaluated for these phosphoproteins by western blot. Transgenic and human xenograft mouse models of NE cancers were treated with Cdk5 inhibitors and monitored for effects on tumor growth.

RESULTS: Cdk5 pathway components are present in multiple types of human NETs and growth of human NE cell lines is dependent on Cdk5 activity. Using phosphoproteomic analysis and cell-based growth screens a set of potential downstream targets of Cdk5 was identified. Phosphorylation state-specific antibodies were generated to interrogate these targets in vivo. Phosphorylation of these proteins is dependent on Cdk5 activity in cell lines and elevated in mouse tumors generated by transgenic expression of Cdk5 activators, validating the phosphosites as biomarkers of Cdk5 activity. Additionally, these biomarkers

are present in a subset of tumors derived from human patients. Preclinical studies in three NE mouse models that contain biomarkers of aberrant Cdk5 activity demonstrate that treatment with Cdk5 inhibitors blocks tumor growth.

CONCLUSION: Aberrant activation of Cdk5 drives tumor growth in a subset of human NE patients. Biomarkers of Cdk5 activity, identified here, could potentially be utilized clinically to distinguish this group of patients as expected responders to Cdk5-targeted therapies.