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Somatostatin Receptor Imaging and Therapy in MENɪ-Driven Murine Pancreatic Neuroendocrine Tumors

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BACKGROUND: Somatostatin receptor ligands are used for the detection and treatment of neuroendocrine tumors. Mutations of MEN1 are frequently observed in human pancreatic neuroendocrine tumors (PanNETs). We utilized a previously described murine model of PanNET that harbors a floxed Men1 allele to study the feasibility of somatostatin receptor type 2 (SSTR2) imaging and therapy in mice.

METHODS: Mice with pancreatic-specific expression of Cre recombinase and floxed Men1 (Pdx1-cre, Men1f/f) were aged to 9-12 months to allow for the development of PanNETs. Mice were injected with either the SSTR2 agonist 68Ga-DOTA-TATE or antagonist 177Lu-DOTA-JR11 via tail vein. Imaging with 68Ga-DOTA-TATE was performed using PET/CT. 177Lu-DOTA-JR11 binding was visualized with autoradiography. Immunofluorescence (IF) detected SSTR2 expression and a marker of DNA damage (γ-H2AX).

RESULTS: IF staining for SSTR2 showed membranous localization of the receptor limited to areas of neoplasia with high and low levels of SSTR2 expression variable by individual animal and tumor. Tumors were successfully detected in mice injected with 68Ga-DOTA-TATE using PET/CT. Injection of 177Lu-DOTA-JR11 and subsequent autoradiography confirmed localization of radionuclide to areas of histology-confirmed neoplasia. Treatment effect (DNA damage) was

observed with co-localization of γ-H2AX and SSTR2 staining in neoplastic areas as compared to hyperplastic islets and normal pancreatic parenchyma that were both SSTR2 and γ-H2AX negative.

CONCLUSION: PanNETs from Pdx1-cre, Men1f/f mice can be successfully imaged and treated using somatostatin-based radionuclides. This genetically accurate model can be employed to study peptide receptor radionuclide therapy efficacy and toxicity either alone or in combination with other treatment strategies.