multiple transcriptional regulators, using small molecules known to control pancreatic and intestinal development, and hormone production. We chose small molecules instead of gene editing tools to avoid the potential pitfall of off-target mutagenesis.

We found that inhibition of FoxO1 in our organoid culture led to an increase in EE cell differentiation as assessed by EE-specific gene expression, with a 5-10 fold upregulation in expression of *ChgA*, *NeuroD1*, and *Neurog3* compared to whole mucosal biopsies (P<0.01 for all targets, n=3 per group). Flow cytometry data showed 6-8% of cells produced CHGA, compared to 0.2% in undifferentiated organoids (P<0.0001, n=3 per group), and the 1% typically seen in the duodenum. We also noted a corresponding increase in the production of EE hormones, including glucose-dependent insulinotropic peptide (GIP), serotonin and somatostatin, by qPCR and immunofluorescence. Analysis of conditioned media using ELISA, compared to undifferentiated organoids, revealed increased serotonin (362.6±52.3 vs 167.5±5.1 ng/mL, P=.0037, n=3 per group) and GIP (5.76±1.31 pg/mL vs undetectable, n=3 per group). Independently, upregulation of GATA4-Nkx2.5 also induced EE cell differentiation and hormone production, although to a lesser extent than FoxO1 inhibition. The exception to this was GIP, which showed increased expression and production with GATA4-Nkx2.5 compared to FoxO1 inhibition (20.8±7.4 vs 5.8±1.3 pg/mL, n=3 per group), with a much larger increase when FoxO1 inhibition was followed by GATA4-Nkx2.5 activation (53.4±4.8 pg/mL, n=3). Of note, all experiments were performed in a minimum of three human lines.

Taken together, our data have identified multiple factors, including inhibition of FoxO1 and activation of GATA4-Nkx2.5, that can drive *ex vivo* human EE cell differentiation, with unique hormone production profiles, when targeted via small molecules. This is a critical first step towards understanding the role of enteroendocrine cells in disease and the development of EE cell-based therapies.

Neuroendocrinology and Pituitary

PITUITARY TUMORS I

Pituitary Stem Cells May Drive Adenomas Causing Cushing's Disease

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SAT-304

Introduction:Cell rests of self-renewing Sox2+ progenitor cells have been identified in the normal pituitary glands[1], however their role in human pituitary tumorigenesis is not understood. Adrenocorticotropic hormone (ACTH) producing microadenomas that cause Cushing's disease frequently (~70%) lack pathogenic genetic mutations.[2] In mice, targeted expression of oncogenic β-catenin in Sox2+ cells generate microadenomas. Interestingly, the Sox2+ cells reside within the adjacent normal gland and drive adenomas in a paracrine fashion.[3] We hypothesized that Sox2+ progenitors in human pituitary gland may drive the formation of microadenomas that cause Cushing's disease (CD).

Methods:Four ACTH producing adenomas and two non-functional adenomas (NFPA) with separately annotated adjacent normal tissue (henceforward called 'microenvironment') were procured for this study (NCT00060541). We performed RNA deep sequencing (RNAseq) and compared expression of lineage-specific markers and progenitor markers using two-sample T-tests after testing for variance equality and using Welch's approximation for degrees of freedom.

Results:We found expected overexpression of ACTH preprohormone POMC in CD adenomas compared to adjacent microenvironment (?-fold) and NFPA (?-fold). The microenvironment in Cushing's disease showed increased expression of progenitor markers including *SOX2, SOX9, CDH1, GRFA2,* and *KLF4* compared with microenviroment in NFPA. Likewise, the Cushing's disease microenvironment showed increased expression of*POMC* (26.98 - fold, P = 0.004) as well as PRLR (FC 17.39, P = 0.006) and GH1 (FC 29.91, P = 0.003) implying that increased Sox2+ progenitors contribute to terminally differentiated corticotrope, lactotroph and somatotroph lineages in-vivo.

Conclusions:We report increased expression of several progenitor markers and concomitant elevation in tissues-specific markers in the microenvironment of Cushing's disease patients. Our results indicate that increased pituitary progenitors in the microenvironment of human corticotropinomas may signal in paracrine fashion and may contribute to the pathogenesis of Cushing's disease.

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Adrenal

ADRENAL - TUMORS

Status at 10 Years: Long-Term Follow-Up for a Phase 2a Study of High-Specific-Activity (HSA) I 131 Iobenguane in Patients (Pts) with Relapsed/ Refractory High-Risk Neuroblastoma

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SAT-163

Background: Metaiodobenzylguanidine (MIBG; iobenguane), a guanethidine derivative, is a substrate for norepinephrine reuptake transporter which is highly expressed on the surface of neuroblastoma cells. AZEDRA® (HSA I-131 MIBG) has been approved by the FDA for the treatment of pheochromocytoma and paraganglioma, in pts 12 years and older with MIBG avid, unresectable, locally advanced or metastatic PPGL who require systemic

anticancer therapy. The aim of this study was to establish the maximum tolerated dose in children with neuroblastoma, with secondary aims of assessing overall response and tumor and organ dosimetry. Here we report current long-term survival and toxicity data. Methods: Eligible pts were 1-30 years old with resistant neuroblastoma. A diagnostic dose of HSA I-131 MIBG was followed by 3 dosimetry scans to assess radiation dose to critical organs and soft-tissue tumors. To prevent prolonged myelosuppression, autologous hematopoietic stem cells were infused 14 days after therapy. Response and toxicity were evaluated on day 60. Dose-limiting toxicity (DLT) was failure to reconstitute neutrophils to greater than 500/μL within 28 days, or platelets to greater than 20,000/μL within 56 days, or grade 3 or 4 nonhematologic toxicity by Common Terminology Criteria for Adverse Events (version 3.0) except for predefined exclusions. Results: First pt was enrolled in June 2008. 15 pts total were evaluable at 12 (n=5), 15 (n=3), and 18 (n=7) mCi/kg. Mean whole-body radiation was 0.23 mGy/MBq, and mean organ doses were 0.92, 0.82, and 1.2 mGy/MBq of MIBG for the liver, lung, and kidney, respectively. Eight pts had 13 soft-tissue lesions with tumor-absorbed doses of 26-378 Gy. MYC-N amplification was present in two of 11 pts with available results. Of the 15 treated pts, 1 had a complete response, 3 had a partial response, 1 had a mixed response and 6 had stable disease. The remaining 4 had progressive disease. Twelve of the 15 evaluable pts received non-protocol therapy after HSA I-131 MIBG, the remaining 3 died due to tumor without further therapy. At 3.6 years of follow-up the overall survival was 26.7% (95% CI, 8.3%-49.6%). As of March 2018, one remaining pt is in long term follow up with an overall survival of 8.4 years. This pt was previously reported to have a secondary malignancy of myelodysplastic syndrome which has been in remission since receiving an allogenic bone marrow transplant in March 2014. Conclusions: HSA I-131 MIBG contributed to long term median survival of two years and was well tolerated. Treatment showed promising activity in the absence of significant nonhematologic toxicity.

Diabetes Mellitus and Glucose Metabolism

TYPE 1 DIABETES MELLITUS

Autoimmune Hypoglycemia: A Treatment Challenge

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SAT-679

Background: Upon evaluation of patients with recurrent hypoglycemia, both exogenous and endogenous causes should be excluded. Among endogenous hyperinsulinemic hypoglycemia (EHH) pathologies, Insulin Autoimmune Syndrome (IAS), even though extremely rare, must be considered. Most cases of IAS have been reported in the Oriental population, mostly Japanese. No gold standard of care for this condition has been established. **Clinical Case:** This is the case of an 82 year-old obese female patient with dyslipidemia, obstructive sleep apnea, and osteoarthritis that comes to the Endocrinology clinics for evaluation due to recurrent episodes of hypoglycemia. She refers that for the last three years she had been presenting with multiple episodes of symptomatic hypoglycemia, even levels as low as 30 mg/dL, requiring multiple hospitalizations. Consequently, she refers a 15-pound weight gain because of multiple daily snacks. Home medications were simvastatin and diclofenac. She denies using insulin, sulfonylureas, other hypoglycemic agents, alcohol, or illicit substances. Abdominal MRI and PET CT scan were remarkable only for an atrophic pancreas without focal masses. Patient was hospitalized for a supervised 72-hour fast, resulting in severe hypoglycemia within 14 hours with elevated insulin levels at 46.3 uIU/mL (1.7-31.0 uIU/mL), elevated C-peptide levels at 5.79 ng/mL (0.9-4.3 ng/mL) and elevated insulin antibodies 53μU/mL (<5μU/mL). Patient showed sufficient hepatic reserve after glucagon administration as well as intact cortisol and growth hormone axis upon severe hypoglycemia. With these results, a diagnosis of IAS was made; not associated with other autoimmune diseases, or with medications with sulfhydryl groups, such as the cases already reported on literature. This condition represents a therapeutic challenge because there is no gold standard of care. Literature recognizes diverse treatment options that range from diet modification to more aggressive therapies, including plasmapheresis and immunosupressants. Our patient was managed with diet modification including frequent snacks and Diazoxide with the goal of decreasing insulin levels and inducing hyperglycemia. Diazoxide therapy achieved a steady euglycemic state and decreased insulin antibodies. Patient developed intolerable bilateral lower extremity edema and treatment was modified to complex carbohydrates, frequent snacks in the daytime and Diazoxide only at bedtime, which is the longer fasting period. Patient has remained without episodes of hypoglycemia and diabetes has not been diagnosed since starting treatment two years ago. **Conclusion:** Early recognition of IAS is essential in order to avoid unnecessary studies and procedures which could delay management. Although no gold standard therapy has been identified for this condition, our case report identifies Diazoxide as a compelling medical treatment.

Adrenal

PROGRESS IN ADRENAL CORTEX AND MEDULLA RESEARCH

Novel Lipidome Signature in Active Cushing Syndrome Revealed by UHPLC-MS Metabolomics

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