the 2 arms: median age, 51 vs. 50.5 years; female, 73% vs. 67%; stage I, 20% vs. 26%; stage II, 67% vs. 63%, stage III, 13% vs. 11%; ACC secretion 44% vs. 36%; Weiss 5 vs. 5; respectively. In ADIUVO OBSERVATIONAL, 42 patients were treated with mitotane and 53 were untreated. Baseline characteristics of patients were matched between the 2 groups and with MIT and OBS groups in ADIUVO. Thus, the ADIUVO OBSERVATIONAL cohorts could be analyzed in parallel to those of ADIUVO.

Results: In the ADIUVO study, recurrences were 8 in the MIT and 11 in the OBS arm, while deaths were 2 and 5, respectively. RFS and overall survival (OS) did not significantly differ between the 2 arms. Tumor size was a predictor of RFS in multivariable analysis. In the OBS arm, the HR for recurrence was 1.321 (95%CI, 0.55–3.32, p=0.54) and HR for death 2.171 (95%CI, 0.52–12.12, p=0.29). The survival analysis in the ADIUVO OBSERVATIONAL study confirmed the findings of ADIUVO. Given the outcome of both studies, the NNT is 55.

Conclusions: ACC patients at low-intermediate risk of recurrence after surgery are a minority; however, they show a far better prognosis than expected (5-year RFS is about 75%) and do not benefit significantly from adjuvant mitotane. The results of the ADIUVO study do not support routine use of adjuvant mitotane in this subset of patients, who may thus avoid a potentially toxic treatment. This is an important step toward personalization of ACC care.

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Effects of CRN04894, a Nonpeptide Orally Bioavailable ACTH Antagonist, on Corticosterone in Rodent Models of ACTH Excess

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CRN04894 is an orally administered nonpeptide that is a potent and selective antagonist for adrenocorticotropic hormone (ACTH) acting at the melanocortin 2 receptor (MC2R) and is currently under development for the treatment of diseases of ACTH excess such as Cushing's disease, congenital adrenal hyperplasia, and ectopic ACTH-secreting tumors. Cushing's disease results from an adenoma derived from pituitary corticotropic cells that secrete excess ACTH, whereas ectopic ACTH syndrome arises from nonpituitary ACTH secreting tumors. Congenital adrenal hyperplasia is a genetic disease that results in cortisol deficiency leading to high levels of ACTH and adrenal androgens. Each of these indications is characterized by high ACTH levels that act on MC2R expressed in the adrenal cortex to drive pathological elevations of adrenally derived steroid hormones. CRN04894 blocks the action of ACTH at MC2R, providing a potential novel treatment for these diseases. Preclinical models of chronic hypercortisolemia include implantation of ACTH-secreting pituitary tumor cells in mice and continuous administration of ACTH via subcutaneously implanted osmotic pumps in rats. These models induce features consistent with human diseases of ACTH excess including hypercortisolemia and hypertrophy of the adrenal glands. We employed both rodent models to examine the pharmacodynamic effects of CRN04894 on corticosterone levels and adrenal gland morphology. In the mouse pituitary tumor model, subcutaneous inoculation of the ACTH-secreting mouse pituitary tumor cell line, AtT-20, into immunodeficient mice resulted in formation of tumors and increased plasma ACTH and corticosterone levels. Repeated daily oral administration of CRN04894 for 14 days dose-dependently and robustly suppressed plasma corticosterone levels in mice with AtT-20 tumors. In the rat model, subcutaneous implantation of osmotic pumps delivering ACTH resulted in increased corticosterone levels, reduction in body weight, and hypertrophy of the adrenal glands after 7 days. Daily oral administration of CRN04894 over 7 days dose-dependently suppressed corticosterone levels, mitigated the effect of ACTH excess on body weight, and rescued the adrenal gland hypertrophy. These findings provide evidence that CRN04894 functions as an effective ACTH antagonist at MC2R to suppress adrenal corticosterone secretion in both mouse and rat models of ACTH excess and hypercortisolemia, thus providing a strong rationale for its potential therapeutic utility in diseases of ACTH excess. *This work was supported in part by an SBIR grant from the NIH awarded to Dr. Struthers (R43- DK115245)*

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Genome-Wide Association Study Links Autoimmune Addison's Disease to Break of Central Tolerance

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Autoimmune Addison's disease is the predominant cause of primary adrenal failure, and is highly heritable. The genetic background has remained poorly understood due to the low prevalence and complex inheritance of the disease. We performed a genome-wide association study, which identified nine independent risk loci ($P < 5 \times 10^{-8}$). In addition to novel and previous risk loci involved in lymphocyte functionality, we further associated autoimmune Addison's disease with two independent protein-coding alterations in the gene *Autoimmune Regulator* (*AIRE*). The most striking is the amino-acid substitution p.R471C (rs74203920, OR = 3.4 (2.7–4.3), P = 9.0×10^{-25}), which introduces an additional cysteine residue in the zinc-finger motif of the PHD2 domain of AIRE. This unbiased elucidation of the genetic contribution to development of autoimmune Addison's disease points to the importance of central immunological tolerance, and explains 35–41 percent of heritability.

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Insights From Targeted Genetic Analysis of 364 Adrenocortical Carcinomas

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Adrenocortical carcinoma (ACC) is a rare endocrine malignancy affecting individuals across a broad age spectrum. Disease rarity, scarcity of pre-clinical models, lack of effective targeted therapy and limited clinical trials have contributed to poor prognosis for patients with ACC. Identifying targetable genetic drivers and pathways to guide precision medicine approaches is therefore critical to improve outcomes. The purpose of this study was to analyze the genomic profile of a large cohort of ACC to identify potential therapeutic targets. FoundationOne (Foundation Medicine Inc.; FMI, Cambridge, MA) is a next-generation sequencing-based platform for somatic genetic testing in solid tumors. The FoundationOne genomic data and limited demographic data through 2018 for 364 unique ACC specimens were analyzed. The cohort of 364 tumors were from 222 females and 141 males (1 gender unknown). The mean age (SD) was 48.6 (13.6) for females and 50.6 (12.20) for males with overall median age of 52 years. A total of 3117 genomic alterations were identified impacting 457 genes. The median number of genomic alterations per tumor was 7 (range 1–56), with single nucleotide variants and indels being the most common alterations (median=4), followed by copy number alterations (median=1) and rearrangements (median=0). The most frequently altered genes were *TP53* (38%), *CTNNB1* (28%), *ZNRF3* (17%), *CDKN2A* (13%), *ATRX* (11%), *TERT* promoter (10%). Several novel recurrent alterations were identified including *IL7R* (6%), *LRP1B* (8%), *FRS2* (4%), *PTCH1* (4%) and *KRAS* (3%). Pathway enrichment analysis confirmed that tumor suppressor genes (51%) and Wnt signaling pathways (51%) are the most commonly dysregulated in ACC tumors. Epigenetic alterations, including histone modification (38%), SWI/SNF (21%) and DNA methylation (8%), affected upwards of one third of ACC tumors. Mutation signature analysis identified tumors with signatures 6, 15 and 26 associated with defective DNA mismatch repair (MMR), which was not reported previously. In addition, fifty ACCs (13.7%) exhibited 60 genomic alterations in MMR genes, *MLH1, MSH2, MSH6* and *PMS2*, which included 49 SNVs/indels, 10 CNAs and one truncating rearrangement. In addition to MMR gene alterations, potentially actionable (www.oncokb.org) genomic alterations were found in 46 genes in 213 (58.5%) ACCs. In summary, this study represents the largest to date genomic analysis of ACC that showed that over 50% of ACC tumors had potentially actionable genomic alterations. Approximately 13% of tumors had an alteration in MMR pathway, suggesting that immunotherapy is a relevant therapeutic modality in a significant subset of patients with ACC.

Adrenal

WIDE SPECTRUM OF TRANSLATIONAL ADRENAL RESEARCH

Novel Germline SUCLG2 Mutations in Patients With Pheochromocytoma and Paraganglioma

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Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors derived from neural crest cells