which have been engineered to improve protein stability and solubility in solutions containing preservatives, are currently in human clinical trials. In addition, in vivo FGF21 gene therapy using viral vector is being explored as an alternative therapeutic approach. In this study, we present a simpler method of in vivo FGF21 gene therapy, in which liver-specific delivery of an unpackaged plasmid construct expressing an HA-tagged FGF21 protein increases de novo hepatic FGF21 production and secretion in mice. Our data show that FGF21 protein expression can be successfully restored into the livers of FGF21 conditional knockout mice for at least two weeks after a single tail vein injection with the expression plasmid, and that the HA-tagged protein is secreted and readily detectable in serum. In wild-type C57BL6/J mice, in vivo plasmid delivery significantly increased hepatic FGF21 protein 2.3-fold after two weeks, and was associated with reduced body mass and a 14% reduction in fasting serum glucose. In addition, elevated hepatic FGF21 levels correlated with a 27% decrease in the ratio of fat to body mass, visibly smaller subcutaneous and visceral white fat adipocytes, and a 3.3-fold increase in uncoupling protein 1-dependent mitochondrial respiration in the white fat. Together, these data suggest that in vivo plasmid delivery may potentially be an effective strategy for promoting hepatic FGF21 expression in models of obesity. We are currently testing this hypothesis with experiments in high-fat diet-challenged mice.

# Neuroendocrinology and Pituitary

## PITUITARY TUMORS: TRIALS AND STUDIES

### *Post-Operative Day One Morning Cortisol Value as a Biomarker to Predict the Recurrence of Cushing Disease*

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**OR23-03**

Tumor removal by transsphenoidal surgery (TSS) is the first line treatment for Cushing disease (CD). However, recurrence is relatively common. A one week post-operative (post-op) nadir cortisol has been used as a biomarker to predict recurrence[1]. We identified 299 CD patients from our longitudinal multidisciplinary clinic or our institutional RPDR search tool who met biochemical diagnostic criteria[1] and had undergone TSS between May 2008 and May 2018, to evaluate post-op cortisol levels as biomarkers to predict long-term remission and to characterize clinical features of Cushing syndrome. Predictors of recurrence were identified with logistic regression, using recurrence as the dependent variable, and a Kaplan-Meier survival curve analysis was performed to compare long-term remission after TSS among the 202 patients who reached initial remission and had at least 1 year of follow-up. The post-op day 1 morning (AM) cortisol had significant association with CD recurrence (OR=1.025, 95%CI:1.002-1.048, p=0.032). The time to recurrence was significantly longer in patients with post-op day 1 AM cortisol <5 μg/dL. In contrast, one week post-op nadir cortisol (OR=1.081, 95%CI: 0.989-1.181, p=0.086), urinary free cortisol (OR=1.032,95%CI: 0.994-1.07, p=0.098), or late night salivary cortisol (OR=1.383, 95%CI:0.841-2.274, p=0.201) had no significant correlation with recurrence. There were no significant differences in time to recurrence for post-op day 2 AM cortisol <5 μg/dL. Among patients who developed post-op adrenal insufficiency, recurrence was significantly lower if glucocorticoid replacement continued for more than one year. In addition, tumor proliferative index (MIB-1) had a significant correlation with recurrence (OR=1.287, 95%CI:1.106-1.498, p=0.001). The most common symptoms and signs of initial presentation of CD were weight gain (91.6%), central obesity (79.6%), menstrual disorders (77.9%), round face (65.9%), hypertension (63.2%), mood disorders (60.2%), dorsocervical fat deposition (59.9%), supraclavicular fat deposition (59.9%), osteoporosis (58.9%), fatigue (58.2%), bruising (55.9%) and facial hirsutism (54.2%). Most of the best discriminating CD features did not have high sensitivity, such as purple striae (31.4%), facial plethora (33.4%) and proximal muscle weakness (30.8%). Our data show that post-op day one morning cortisol level above 5 μg/dL had significant association with recurrence. In contrast, the one week post-op nadir cortisol level had no significant value to predict recurrence. Our data also suggest that nonspecific symptoms and signs of CD are more common than stereotypical signs. **Reference:** Nieman LK, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:2807-2831

# Thyroid

## BENIGN THYROID DISEASE AND HEALTH DISPARITIES IN THYROID I

### *Pharmacokinetics (PK) and Exposure-Response Relationship of Teprotumumab, an Insulin-Like Growth Factor-1 Receptor (IGF-1R) Blocking Antibody, in Active Thyroid Eye Disease (TED)*

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**SAT-432**

**Introduction:** Teprotumumab treatment resulted in statistically and clinically meaningful improvements across multiple facets of active TED and was generally well-tolerated in Phase 2 and 3 trials.[1,2] An initial intravenous infusion of 10 mg/kg followed by 20 mg/kg every 3 weeks was selected based on in vitro activity and clinical PK profile, to maintain pharmacologically active exposures and >90% saturation of IGF-1R over dosing intervals and to achieve efficacy at a well-tolerated dose for this vision-threatening disease.

**Methods:** Population PK analysis were performed on data from a Phase 1 oncology study (n=60)[3] and Phase 2 and 3 trials in active TED (N=83)[2,3] and covariate effect