NADPH/NADP ratio. We used FK866 to inhibit nicotinamide phospho-riboisomerase (NAMPT, rate-limiting enzyme in NAD+ biosynthesis) to deplete NAD(P)(H) in wild type mouse primary myotubes. FK866 treatment for 48h impaired cellular energetic status, reducing NAD+ (>90%), NADP+ (>50%) and ATP (>30%) without limiting cell viability. 11β-HSD1 reductase activity was decreased to 30% that of untreated cells (15±2 vs. 51±4 pmol/mg protein/h respectively, p<0.005). Employing H6PD knockout myotubes, NADP+-dependent 11β-HSD1 dehydrogenase activity was also impaired following NAMPT inhibition. The NAD+ precursor nicotinamide riboside (NR, 0.5mM), which bypasses NAMPT inhibition through the NR kinase pathway restored NAD+ levels and rapidly rescued 11β-HSD1 reductase activity in wild type and dehydrogenase activity in H6PD knockout myotubes. To assess this in vivo, we examined 11β-HSD1 reductase activity in muscle explants of inducible muscle-specific NAMPT knockout mice in which NAD+ levels are reduced by 90%, and show 40% lower activity compared to wild type explants (11±2±4 vs. 67±10 pmol/mg protein/h, p=0.04). These data suggest a novel level of redox-regulated 11β-HSD1-mediated glucocorticoid metabolism in skeletal muscle. These data also imply a pathway by which NAD+ status is communicated between the cytosol and the SR, which is contrary to the current belief that the pyridine nucleotide pool in these compartments is separate. NAMPT inhibition is being studied as a potential anti-cancer therapy and these data reveal hitherto unanticipated effects this therapy may have in a range of tissues.

### Bone and Mineral Metabolism

#### Osteoporosis: Diagnosis and Clinical Aspects

**Addressing the Burden of Hip Fracture in Older Men**

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**INTRODUCTION:** Men have a lower incidence of hip fracture compared to women. However, hip fractures comprise a greater proportion of overall fractures in men and result in greater morbidity and mortality. In 2015, a new high-risk fracture prevention program was implemented in our medical group, targeting men aged 70-85y with hip, pelvic, humerus, wrist or vertebral fracture for osteoporosis treatment within 6 months of the fracture event. In this study, we examined patient characteristics, site of hip fracture, treatment initiation and time to treatment initiation in men who experienced a hip fracture before and after implementation of this new fracture prevention program.

**METHODS:** This study examines data from 1114 men age 70-85y (81% white race) who experienced a hip fracture during 2013-2014 (N=527) and 2015-2016 (N = 587), based on a principal hospital discharge diagnosis, excluding men who had received osteoporosis treatment in the prior year. Initiation of osteoporosis treatment within 6 months following the hip fracture and time to initiation of osteoporosis treatment (bisphosphonate, teriparatide, denosumab) were examined. The following covariates were ascertained using data from electronic health records and databases: age, race/ethnicity, smoking status, body mass index (BMI), and history of diabetes mellitus with diabetes pharmacotherapy. A Charlson Comorbidity Index was derived using health record data form the prior year. The site of hip fracture was classified as femoral neck or pterochanter.

Subgroups were compared using the Chi-square test.

**RESULTS:** Among the 1114 men with hip fracture (mean age 79 ± 4 years), half (54%) experienced a fracture in the femoral neck and the remainder (46%) in the pterochanter. Nearly 1 in 5 (17%) men were current smokers, 13% were obese (BMI ≥30 kg/m2), 25% had diabetes mellitus, and 42% had a comorbidity index ≥3. One fourth (24%) had a clinical fracture diagnosed in the past 2 years. Osteoporosis treatment initiation post-hip fracture increased from 16% in 2013-2014 to 29% in 2015-2016 with implementation of the high-risk program targeting men (p<0.01). Time to treatment examination of 2013-2014 vs 2015-2016 revealed that the largest increase in treatment initiation was seen at 2-4 months (4% vs 12%, p<0.01) whereas non-significant differences were seen at ≤2 (7% vs 10%) and 4-6 (4% vs 7%) months following hip fracture.

**CONCLUSION:** Implementing targeted post-hip fracture intervention in men dramatically increased osteoporosis treatment following fracture, with the largest intervention seen 2-4 months after fracture. The high burden of prevalent fractures, smoking, and diabetes highlights the need for post-fracture intervention and counseling for modifiable risk factors.

#### Genetics and Development (including Gene Regulation)

**G Protein-Coupled Receptor Signaling in Endocrine Systems: Novel Mechanisms in Health and Disease**

**Mutational Study of the GPR119 Receptor Binding Site**

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The GPR119 receptor, a class A G-protein coupled receptor located in the pancreatic β cells, induces insulin production when activated. Due to its specific activity, the pharmaceutical industry has identified GPR119 as a target for the treatment for type 2 diabetes. The lack of a GRP119 crystal structure has hindered the study of the receptor so our laboratory developed GPR119 active and inactive homology models. Docking studies with the inactive receptor model indicated that two leucine residues facing the binding pocket, L5.43(169) and L6.52(242), may be involved in ligand activation. Additionally, a serine at the extracellular end of the pocket, S1.32(4), may help orient of the ligand in the binding pocket via hydrogen bonding. To gain further insight into the role of these residues and
the receptor activation mechanism, molecular dynamics (MD) simulations and in vitro cAMP assays of the wild type and mutant receptors were employed. The software NAMD employing the CHARMM force field was used to carry out MD simulations of the active receptor model bound with the agonist AR231453 embedded in a hydrated lipid bilayer. Preliminary results indicate that L6.52(242), located on transmembrane helix (TMH) 6, does not face directly into the binding site and does not interact with the ligand, while L5.43(169), located on TMH5, does face into the binding site, potentially interacting directly with the ligand. Also, S1.32(4), because of its extracellular location, is solvated instead of interacting with the ligand. The in vitro studies overall support the MD simulations. The mutations L6.52(242)M and L6.52(242)A appear to have minimal to no effect on agonist-induced cAMP production, compared to the wild type. In contrast, the L5.43(169)M and L5.43(169)A mutations decrease the potency of activation by AR231453, indicating that L5.43(169) changes the shape of the binding pocket, affecting ligand binding and activation. Finally, the cAMP assays show that the S1.32(4)A mutant also shows decreased activity compared to the wild type, implying that the ligand may be losing a hydrogen bonding interaction when S1.32(4) is mutated to alanine.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

Identification of Thyrotrope Signature Genes and Regulatory Elements

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Recent genome wide association studies have begun to identify loci that are risk factors for sporadic pituitary adenomas, but the genes associated with these loci are unknown. In general, ~90% of GWAS hits are in noncoding regions, making it difficult to transition from genetic mapping to a biological understanding of risk factors. Recent studies that identify enhancer regions by undertaking large scale functional genomic annotation of non-coding elements like Encyclopedia of DNA Elements (ENCODE) have begun to yield a better understanding of some complex diseases. Dense molecular profiling maps of the transcriptome and epigenome have been generated for more than 250 cell lines and 150 tissues, but pituitary cell lines or tissues were not included. Epigenetic and gene expression data are emerging for somatotropes, gonadotropes and corticotropes, but there is very little available data on thyrotropes. We identified the transcription factors and epigenetic changes in chromatin that are associated with differentiation of POOU1F1-expressing progenitors into thyrotropes using cell lines that represent an early, undifferentiated Pou1f1 lineage progenitor (GHF-T1) and a committed thyrotrone (ToT1). ToT1 is an excellent cell line for this purpose because it responds to TRH, retinoids, and secretes TSH in response to diurnal cues. We have also used genetic labeling and fluorescence activated cell sorting to purify thyrotropes from pituitaries of young mice and analyzed gene expression using single cell transcriptomics. We used the Assay for TransposaseAccessible Chromatin with sequencing (ATACseq) and Cleavage Under Target and Release Using Nuclease (CUT&T&RUN) to identify POOU1F1 binding sites and histone marks associated with active enhancers, H3K27Ac and H3K4Me1, or inactive regions, H3K27Me3, in GHFT-T1 and ToT1 cells. We integrated DNA accessibility, histone modification patterns, transcription factor binding and RNA expression data to identify regulatory elements and candidate transcriptional regulators. We identified POOU1F1 binding sites that were unique to each cell line. For example, POOU1F1 binds sites in and around Cga and Tshb only in ToT1 cells and Twist1 and Gli3 only in GHFT1 cells. POOU1F1 binding sites are commonly associated with bZIP factor consensus binding sites in GHFT1 cells and Helix-Turn-Helix or basic Helix-Loop-Helix in ToT1 cells, suggesting classes of transcription factors that may recruit POOU1F1 to unique sites. We validated enhancer function of novel elements we mapped near Tshb, Gata2, and Pitx1 by transfection in ToT1 cells. Finally, we confirmed that an enhancer element near Tshb can drive expression in thyrotropes of transgenic mice. These data extend the ENCODE analysis to an organ that is critical for growth and metabolism. This information could be valuable for understanding pituitary development and disease pathogenesis.

Reproductive Endocrinology

HYPERANDROGENISM

Obesity Severity and Polycystic Ovary Syndrome in an Ethnically Diverse Cohort of Adolescent Girls

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TITLE - Obesity Severity and Polycystic Ovary Syndrome in an Ethnically Diverse Cohort of Adolescent Girls.

INTRODUCTION: Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders affecting young women and may present as early as adolescence. Early recognition is important, as polycystic ovary syndrome (PCOS) is associated with increased cardiometabolic risk and type 2 diabetes mellitus. The risk of PCOS increases with obesity, but fewer studies have explored the burden of PCOS in children with obesity within healthcare settings. In this study, we examined the proportion of adolescent girls with obesity who also had diagnosed PCOS and the relationship between PCOS and obesity severity.

METHODS: From an existing cohort of nearly 8000 children age 3-17 with obesity (Body Mass Index, BMI ≥95th percentile) who were seen at pediatric well-child visits and identified for weight management based on BMI, we classified the subgroup of girls age 12-17 years who had moderate (BMI 100-119% of the 95th percentile) and severe