KTaV-3 and KtaR-1 cells were treated with a range of doses of E2 (5-100pM) and/or progesterone (20nM) for varying durations (4-96h), exposed to steroid hormones either constitutively or via modulating levels over time, approximating concentration changes found during the murine estrous cycle. Following RNA isolation, cDNAs were probed with primers for *gnrhr*. Preliminary results in KTaV-3 cells reveal the expression of *gnrhr* is induced only following elevated (50-100pM) E2 treatment for 18-24h. These same E2 exposure conditions were also found to increase expression of the homeobox protein *dlx3*, a transcription factor required for GnRHR expression in pituitary gonadotropes. In Arc-derived KTaR-1 cells, *gnrhr* expression was observed only following decreases in E2 concentration, while *dlx3* remained constitutively elevated in this cell line. While reciprocal GnRH-Kisspeptin connections have not yet been observed *in vivo*, these observations suggest the potential for Kisspeptin neurons to respond to GnRH secretory changes under particular E2 exposure conditions, by modulating receptivity to GnRH at the level of the AVPV and/or Arcuate nuclei. We are continuing to explore the temporal parameters of this induction of GnRHR in KP cells, and if exposure of immortalized KP neurons to GnRH *in vitro* elicits expression and signaling changes in a time- and E2-dependent manner. Results will provide a more complete understanding of positive and negative feedback mechanisms required for normal neuroendocrine regulation of reproduction.

Thyroid
THYROID HORMONE ACTION AND SIGNALING
Thyroid Receptor Alpha Interacts with COUP-TFII in the Regulation of Postnatal Skeletal Muscle Regeneration

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OR01-03

Myopathic changes, including muscular dystrophy and weakness, are commonly described in hypothyroid and hyperthyroid patients. Thyroid hormone signaling, via activation of thyroid nuclear receptors (TRs), plays an essential role in the maintenance of muscle mass, function, and regeneration. TRs are ligand-inducible transcription factors expressed in almost all tissues, including skeletal muscle. In a mouse model of Resistance to Thyroid Hormone carrying a frame-shift mutation in the TRα gene (TRα1PV)[1,2] we observed skeletal muscle loss with aging and impaired skeletal muscle regeneration after injury. We recently described that TRα interacts with the nuclear orphan receptor Chicken Ovalbumin Upstream Promoter-factor II (COUP-TFII, or NR2F2), which is known to regulate myogenesis negatively and has a role in Duchenne-like Muscular Dystrophies[3]. We showed that COUP-TFII expression declines with age in WT mice, while the skeletal

muscle of TRα1PV mice shows a sustained significantly higher expression of COUP-TFII. Our findings suggest that the TRα/COUP-TFII interaction might mediate the impaired skeletal muscle phenotype observed in TRα1PV mice. To better characterize this interaction, we isolated SC from 10 months old WT and TRα1PV mice and cultured them in vitro using novel methods established within our lab. Using siRNA probes, we next silenced COUP-TFII and characterized the cells via RNA-seq analysis. In vitro, we assessed myoblast differentiation and proliferation using differentiation assays and EdU incorporation. We observed that satellite cells from TRα1PV mice display impaired myoblast proliferation and in vitro myogenic differentiation compared to WT SCs. However, when COUP-TFII was silenced, the myogenic potential of TRα1PV satellite cells was restored, with a higher proliferation of myoblasts and a higher number of fully differentiated myotubes after 4 days of myogenic induction. RNAseq analysis on satellite cells from TRα1PV mice after COUP-TFII knockdown showed upregulation of genes involved in the myogenic pathway, such as Myod1 and Pax7, and of genes in the thyroid hormone signaling, such as Dio2. Ingenuity Pathway Analysis further showed activation of pathways regarding cell growth, differentiation, matrix remodeling along with muscle function, muscle contractility, and muscle contraction. These in vitro results suggest that by silencing COUP-TFII we promote the myogenic pathway and may further rescue the impaired phenotype of TRα1PV mice. These studies can help increase our knowledge of the mechanisms involved in thyroid hormone signaling in skeletal muscle regeneration, which will ultimately increase the possibility of designing more specific treatments for patients with thyroid hormone-induced myopathies. References: [1]Milanesi, A., et al, Endocrinology 2016; [2]Kaneshige, M. et al, Proc Natl Acad Sci U S 2001; [3]Lee HJ, et al, Sci Rep. 2017.

Bone and Mineral Metabolism
NEW FRONTIERS IN BONE AND MINERAL METABOLISM
Natural Language Processing of Radiology Reports Improves Identification of Patients with Fracture

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OR29-02

Fracture liaison services (FLS) address the treatment gap for those with osteoporosis (OP) who fracture and are not treated. Given the limited human resources in FLS, screening high volumes of radiology reports for fractures with Natural Language Processing (NLP) could identify patients that have not been recognized or treated. This study is an analytical and clinical validation of X-Ray Artificial Intelligence Tool software (XRAIT) at its development site (a tertiary hospital) and external validation in an adjudicated cohort from the Dubbo Osteoporosis Epidemiology Study (DOES).Methods: XRAIT uses NLP to perform a Boolean search of radiology reports for fracture and related terms.