placebo or one of three doses of NT-814 once per day; 40mg, 80mg or 120mg (n=8 per group) for up to 21 days.
Results: Compared to placebo, NT-814 reduced LH, estradiol and progesterone concentrations in a dose-related manner. The median changes in average LH (IU/L) during cycle 2 compared to cycle 1 were: placebo, 0.16; 40mg, -0.13; 80mg, -0.46; 120mg, -0.58. Median change in average estradiol (pmol/L) in cycle 2 was: placebo, -16.5; 40mg, -9.3; 80mg, -92.1; 120mg, -141.4. The median changes in progesterone (nmol/L) on day 21/22 in cycle 2 compared to cycle 1 were: placebo, 3.2; 40mg, 8.0; 80mg, -5.7; 120mg, -19.4. The reductions in estradiol and progesterone with 120 mg NT-814 were significant (p=0.038 & p=0.046, respectively). There were no clear changes in FSH concentrations. Of note, in women treated with 120mg NT-814, the average estradiol level reduced from 310.8 pmol/L in cycle 1 to 179.8 pmol/L in cycle 2. Cycle length was extended by at least 6 days in 5 of 8 women receiving the 120 mg dose. NT-814 was well tolerated; no participant experienced hot flashes during treatment.
Conclusions: Once-daily administration of the non-hormonal NK1,3 receptor antagonist NT-814 reduced serum LH, estradiol and progesterone in healthy women in a dose-related manner without causing vasomotor symptoms. The 120 mg dose of NT-814 lowered estradiol levels to potentially ideal levels for UF and EM treatment. These preliminary data support further studies with NT-814 to establish its efficacy and safety in treating patients with these hormone driven disorders.
References: [1]Barbieri RL Am J Obstet Gynaecol 1992 166 740-5.

Cardiovascular Endocrinology
ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS II

The Arg16/Gln27 Polymorphism of the Beta2-Adrenergic Receptor Impacts Blood Pressure Levels in a Transgenic Mouse Model via Sex-Specific Mechanisms.

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SUN-LB91
Background: The β2-adrenergic receptor (β2-AR) has been implicated in blood pressure (BP) homeostasis via its effects on the sympathetic nervous system, cardiac function, peripheral vascular resistance, and renin release. We also have documented that a β2-AR diplotype (Arg16/Gln27), carried by 15% of hypertensives, have salt sensitive hypertension (SSBP) and increased aldosterone (ALDO).
Gap in knowledge: it has been reported that hypertensive men and women respond differently to beta blockers. However, information regarding sex differences in carriers of the β2-AR risk diplotype is limited.
Hypothesis: In mice, the phenotype in female carriers of the mutant β2-AR risk diplotype will differ from male carriers.
***Methods*:** The CRISPR/Cas9 approach was used to generate transgenic mice carrying 0, 1 or 2 Arg16/Gln27 variant alleles (i.e. wild-type (WT), heterozygous (Het) or mutant (Mut)). The experimental design included twelve weeks old mice divided into 6 genotype/gender groups (male and female; WT, Het and Mut) maintained on low (0.03% Na+, LS) and high sodium diets (1.6% Na+, HS) for a week each.
Results: 1) Both male and female mice displayed significantly increased BP on LS and HS with increasing number of mutated alleles.
2) Only Mut females displayed SSBP ($P<0.05$).
3) As compared to WT, urine and plasma ALDO levels were lower in male (but not female) carriers of the mutated allele ($P<0.05$).
4) As anticipated, urine K^+ excretion was significantly lower in the Mut male (but not female) mice ($P<0.05$).
5) Doppler ultrasound measurements of renovascular function shows that the resistive index was significantly lower in Mut vs WT males ($P<0.05$), consistent with an appropriate increase in renal blood flow (RBF) in the face of an elevated BP. However, in the Mut females the RBF was inappropriately decreased compared to the WT ($P<0.05$).
6) β2-AR expression was significantly lower in female vs. male WT mice; however, this difference was lost in the carriers of the mutated allele, as B2-AR expression levels were significantly higher in female carriers of the mutated allele, as compared to WT ($P<0.05$). Interestingly, the B2-AR genotype had no effect on the receptor expression levels in males.
Conclusion: Both male and female Mut animals have increased BP compared to WT mice, but the mechanisms underlying their increased BP differ by sex. Female Mut mice have SSBP, inappropriately non-suppressed ALDO and decreased RBF. Male Mut mice do not have SSBP and have appropriate ALDO and RBF response to the salt load.

Cardiovascular Endocrinology
VASCULAR DISEASE AND PATHOPHYSIOLOGY

Inflammation May Mediate Coronary Artery Disease in Women With Hypothalamic Hypoestrogenemia: Findings From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE)

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SAT-LB99
Inflammation may Mediate Coronary Artery Disease in Women with Hypothalamic Hypoestrogenemia: Findings

from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Background: Among premenopausal women presenting with ischemia, hypothalamic hypoestrogenemia (HHE) has been associated with angiographic coronary artery disease (CAD). Further, serum amyloid-alpha (SAA), a marker of systemic inflammation strongly predicts future adverse cardiovascular events. We sought to relate inflammatory markers to HHE and understand if inflammation mediates relations between HHE and CAD.

Methods: We assessed premenopausal women not on exogenous hormones undergoing coronary angiography for suspected ischemia. HHE was defined as estradiol<50 pg/ml, luteinizing hormone<10 IU/l and follicle stimulating hormone<10 IU/l. Serum inflammatory markers, reproductive hormones, and angiographic CAD were measured.

Results: Overall, 40 (31%) of the 127 women had HHE with similar age and body mass index compared to no HHE (p=0.48 and p=0.77, respectively). Women with HHE had lower estradiol compared to no HHE (30.4+11.7 vs 112.5+62.4 pg/ml, p<0.0001). There were no significant differences between high sensitivity C-reactive protein (hsCRP) (0.86 ± 1.45 vs 0.65 ± 1.17, p=0.5211) and interleukin 6 (IL-6) (4.95 ± 6.06 vs 3.90 ± 3.90, p=0.2358). However, HHE women had significantly higher SAA compared to no HHE (4.44+13.5 vs 0.94+2.37, p=0.0495).

Conclusion: Among premenopausal women undergoing coronary angiography for suspected myocardial ischemia, SAA levels were significantly elevated in women with HHE, suggesting that inflammation may serve as a mediator between HHE and CAD. Further investigation relative to inflammation as a treatment target in this cohort may be warranted.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Dynamic Structural Model of Testosterone Entry Into the Unliganded Androgen Receptor

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SUN-LB138

Background: Crystallographic structures of nuclear receptor ligand binding domains provide a static model of a receptor stably wrapped around an internalized ligand. Understanding the dynamics of a receptor at different stages of ligand binding has been hampered by the paucity of crystal structures for unliganded nuclear receptors. Molecular dynamic models have been constructed for some nuclear receptors to fill that void.

Methods: The molecular simulation docking program MORDOR (MOlecular Recognition with a Driven dynamics OptimizeR)(1) was used to study the structural dynamics of the androgen receptor ligand binding domain (AR LBD) modeled from the static structure of the AR LBD bound to testosterone (T) (PDB ID: 2AM9). The goals of the study were to understand a) the dynamic interaction of the T in its binding pocket, b) AR LBD structural flexibilities that permit T entry/exit from the binding pocket and c) a model of the unliganded AR LBD.

Results: Modeling AR LBD structure flexibility over time revealed possible alternative dynamic structures, including those without ligand, overlaid against the canonical nuclear receptor structure. The model dynamically tracks the structural changes as a ligand enters into the ligand binding domain and nestles into the ligand binding pocket. The model predicted the appearance of alpha helices within the AR LBD that transiently fold/unfold during the ligand entry phases. Once in the pocket, the ligand itself remains very dynamic in a still flexible pocket. The model predicted also AR LBD amino acids that sequentially interact with the ligand during its dynamic entry into the AR LBD. Intriguingly, those AR amino acids include those mutated in castration-resistant prostate tumors that continue to grow during androgen suppression therapy. Functional studies showed those mutant ARs had a primary consequence of enhancing response to lower level T, and other androgens, consistent with their role in creating a higher affinity AR that can scavenge low-level androgens in an androgen-suppressed patient.

Conclusions: The molecular model of T binding to the AR LBD suggests a degree of structural dynamism not evident in the crystallographic structures commonly associated with nuclear receptors. Some AR mutations activating prostate tumor growth may do so by impacting androgen entry/exit, rather than by altering androgen fit into the ligand binding pocket.

Reference: (1) Guilbert C, James TL (2008) J Chem Inf Model. 2008 48(6): 1257-1268. doi: 10.1021/ci8000327

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS III

From Urolithiasis to Genetic Testing: An Unusual Presentation of MEN-4 Syndrome

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SAT-LB302

Background: Germline mutations in the *CDKN1B* gene are responsible for Multiple Endocrine Neoplasia Type 4 (MEN 4) syndrome (Alrezk et al. 2017). Around 20 cases have been reported to date. Here, we report on a new MEN4 family which possibly extends the phenotypic spectrum attributable to germline mutations in *CDKN1B*.

Clinical Case: A 56-year-old female presented with urolithiasis & was found to have hypercalcemia (serum calcium of 2.76 mmol/l ref. 2.12-2.62 mmol/l). Workup was in keeping with primary hyperparathyroidism (PHPT) (PTH