133 gene panel reported no germline mutations in menin, RET, CDKN1B, NF12, VHL, SDH and other genes tested but there were variants of uncertain significance (VUS) identified in CHEK2 c.14C>T (p.Ser5Leu) and PTCH2 c.2812G>A (p.Gly938Ser). Patient successfully underwent left adrenalectomy after alpha blockage. Paired tumor-normal sequencing of the resected tumor detected a pathogenic deletion frameshift mutation in NF1 with loss of heterozygosity (LOH) along with copy number alterations with losses in 1p34.1-p11.2, 11p11.2-15.4, 11q14.1-q25 and 17q11.2 (including NF1). VUSs were also detected including CDKN1A C117Y variant, and CHD2P80L. Since germline and tumor testing failed to reveal any known pathogenic variants, whole exome sequencing (pending) will be pursued.

The presentation with RCC, pheochromocytoma, pituitary adenoma and parathyroid adenoma is consistent with a MEN syndrome in this patient despite no known pathogenic MEN mutations detected. Somatic mutation in NF1 is a common finding in pheochromocytoma. The biochemical phenotype of pheochromocytoma (elevated metanephrines) is consistent with cluster 2 tumors of kinase signaling pathway as seen in tumors of MEN syndrome and neurofibromatosis. We hope to gain more insight via whole exome sequencing to evaluate for potential novel gene mutation(s).

Reproductive Endocrinology

CHALLENGES IN REPRODUCTIVE ENDOCRINOLOGY: LATE BREAKING INSIGHTS

NT-814, a Non-Hormonal Dual Neurokinin 1,3 Receptor Antagonist Markedly Improves Vasomotor Symptoms in Post-Menopausal Women; Results of a Randomised, Double-Blind, Placebo-Controlled, Dose-Finding Study (SWITCH-1)

James Simon, MD[1], Richard A. Anderson, MDPhD[2], Elizabeth Ballantyne, BSc[3], Hadine Joffe, MD[4], Mary Kerr, PhD[3], Susan Seymore, BSc[3], Mike Trower, PhD[5], Steve Pawsey, MB BS[3].
[1]George Washington University, Washington, DC, USA, [2]Univesity of Edinburgh, Edinburgh, United Kingdom, [3]NeRRe Therapeutics, Stevenage, United Kingdom, [4]Brigham and Women's Hospital, Boston, MA, USA, [5]KaNDyTherapeutics Ltd, Stevenage, United Kingdom.

OR11-03

Introduction: Vasomotor symptoms (VMS), caused by declining estrogen in menopausal women, are common and debilitating. Hormone therapy is effective in many women but carries risks and may be contraindicated. Biological and clinical evidence shows a modulatory role for neurokinin (NK) receptor antagonists acting primarily via hypothalamic KNDy (kisspeptin, NK, dynorphin) neurons on VMS. NT-814 is an oral non-hormonal dual NK1,3 receptor antagonist which has previously been shown to cause rapid and marked improvements in VMS in post-menopausal women. This Phase-2b trial (SWITCH-1) was undertaken to further evaluate efficacy and safety and to establish the optimum dose(s) for Phase 3 studies.

Methods: SWITCH-1 was a double-blind, placebo-controlled, adaptive-randomization, dose-finding trial in 199 post-menopausal women. After a 2-week single-blind placebo run-in to establish symptom stability, women (40 to 65 years) with ≥7 moderate and/or severe VMS per day at baseline were randomized to 12 weeks of once daily treatment with placebo or one of 4 doses of NT-814: 40 mg, 80 mg, 120 mg, 160 mg. Subjects recorded the frequency and severity of VMS in electronic diaries twice daily throughout the study. Patient-reported measures of quality-of-life, sleep and mood were collected periodically. Adverse events (AEs) were recorded at each clinic visit.

Results: VMS frequency was reduced in all treatment groups, including placebo. VMS reductions were significantly greater with the 2 higher NT-814 doses at most timepoints, as early as the first week of treatment. Least squares mean reductions from baseline in moderate/severe VMS per day at week 4 were: placebo, 2.7; 40 mg, 4.3 (p=0.161 vs placebo); 80 mg, 4.1 (p=0.326); 120 mg, 6.7 (p<0.0001); 160 mg, 5.5 (p=0.007). In week 12 the reductions were: placebo, 4.7; 40 mg, 6.5 (p=0.185); 80 mg, 5.6 (p=0.599); 120 mg, 7.8 (p=0.009); 160 mg, 6.6 (p=0.109). At the 160 mg dose the median reduction in week 12 was significantly greater than placebo (6.9 vs 4.4, p=0.0023), indicating an effect of high outliers on the mean. Average HF severity was also improved in a dose-related manner, with greater reductions compared to placebo with the 2 higher NT-814 doses. Improvements in HF were accompanied by statistically significant benefits on sleep (assessed using the Insomnia Severity Index and Pittsburgh Sleep Quality Index), mood (measured using the Beck Depression Inventory), and all four domains of the MenQoL menopause-specific quality-of-life instrument. NT-814 was well-tolerated; most AEs were mild or moderate and there were no serious AEs related to treatment.

Conclusions: NT-814, a once daily non-hormonal NK antagonist, at doses of 120 & 160 mg reduced the frequency and severity of VMS and significantly improved quality of life, mood and sleep, in postmenopausal women. NT-814 was well tolerated, with a safety profile that supports further evaluation in Phase 3 trials.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS III

Case of the Broken Hearted

Divya Namboodiri, MBBS[1], Lynne Khor, MD[2], Bernard Champion, MD FRACP[3], Grant Shalaby, MD FRACP[2], Veronica Angela Preda, BSc, MBBS, MPH FRACP PhD[2].
[1]Dr, Bella Vista, Australia, [2]Macquarie University, Macquarie Park, Australia, [3]Macquarie University, Burwood, Australia.

SAT-LB307

Phaeochromocytomas are rare neuroendocrine tumours which, usually present with headache, diaphoresis, episodic tachycardia and hypertension. Takotsubo-pattern cardiomyopathy is an unusual initial presentation of phaeochromocytomas, however has been reported[1]. Approximately 10% of phaeochromocytomas present with cardiomyopathy. It is associated with a high mortality risk and early intervention with surgery is the key to recovery. We report a case of a previously healthy, 68 year old man who presented with symptoms of left ventricular failure, and feeling anxious. Physical examination

revealed signs of left ventricular failure, with a normal blood pressure and heart rate. A transthoracic echocardiogram (TTE) revealed dilated left ventricle with severe global hypokinesis and a left ventricular ejection fraction (LVEF) of 15%. A CTPA performed to exclude pulmonary embolism revealed an incidental right sided adrenal lesion measuring 3.9 X 3.4 X 3.7 cm. Subsequently a dedicated abdominal CT confirmed the adrenal lesion. Biochemistry revealed elevated 24 hour urine catecholamines and metanephrines and an elevated plasma metanephrines. Subsequently he proceeded to have adrenalectomy. Preoperatively the patient was managed with alpha and beta blocking agents for 3 weeks prior to surgery. Postoperative course was uneventful and histopathology confirmed right sided phaeochromocytoma. TTE performed 12 months post-operatively showed a significant improvement in his LVEF to 40 % with subsequent TTE showing maintenance of LVEF. This case demonstrates highlights the unusual presentations of phaeochromocytomas and that early recognition and early intervention with surgery is the key to recovery to avoid catastrophic cardiac events.1. Chiang YL, Chen PC, Lee CC, et al. Adrenal pheochromocytoma presenting with Takotsubo-pattern cardiomyopathy and acute heart failure: A case report and literature review. *Medicine (Baltimore)*2016;95(36):e4846. doi: 10.1097/MD.0000000000004846 [published Online First: 2016/09/08]

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Obesity Is Associated With Reduced Expression of the Anorexigenic Neuropeptide Nucleobindin-2/Nesfatin-1 in the Human Nucleus of the Solitary Tract.

Aristea Psilopanagioti, MD, PhD, Internist, Maria Makrygianni, MSc, Sofia Nikou, MSc, Souzana Logotheti, MSc, Dionysios Chartoumpekis, MD, PhD, Helen Papadaki, Professor.
University of Patras, School of Medicine, Patras, Greece.

SAT-LB102

Introduction: Feeding is a complex behavior coordinated by interrelated forebrain, hypothalamic, and brainstem neuronal networks. Brainstem neurons constitute an important input for the neural circuitry integrating nutrient signals to control ingestive behavior. Orexigenic and anorexigenic neuropeptides act in concert to regulate energy balance. Data from animal models suggest that altered neuropeptidergic expression contributes to obesity. Nucleobindin-2/nesfatin-1, an appetite-suppressing neuropeptide and negative regulator of body weight, is reduced in the hypothalamus of mouse obesity models. In obese and overweight humans, we have recently reported decreased nucleobindin-2/nesfatin-1 immunoexpression in the lateral hypothalamic area, which is critically involved in appetite and metabolic regulation and has extensive connections with brainstem feeding circuits. **Objective**: The present study explored nucleobindin-2/nesfatin-1 localization pattern as well as the association between nucleobindin-2/nesfatin-1 protein expression and body weight in human brainstem nuclei. **Methods**: Sections of 20 human brainstems (13 males, 7 females; 8 normal weight, 6 overweight, 6 obese) were examined by means of immunohistochemistry and double immunofluorescence labeling. **Results**: Nucleobindin-2/nesfatin-1 widespread distribution was observed in various brainstem areas, including nuclei with well-defined roles in energy homeostasis and in autonomic and behavioral processes, such as the nucleus of the solitary tract, dorsal motor nucleus of vagus, area postrema, inferior olive, raphe nuclei, reticular formation, locus coeruleus, parabrachial nuclei, and pontine nuclei, and in Purkinje cells of the cerebellum. Interestingly, nucleobindin-2/nesfatin-1 immunofluorescence signal extensively localized in neuronal subpopulations expressing neuropeptide Y and cocaine- and amphetamine-regulated transcript (peptides known to exert potent actions on food intake and energy balance) in nucleus of the solitary tract, inferior olive, locus coeruleus, and dorsal raphe nucleus. Of note, nucleobindin-2/nesfatin-1 immunoexpression was significantly lower in obese than normal weight subjects in the nucleus of the solitary tract ($p<0.05$). **Conclusions**: These data provide for the first time neuroanatomical support for the potential role of nucleobindin-2/nesfatin-1 in human brainstem circuits controlling energy homeostasis. In nucleus of the solitary tract, a key integrator of nutrient state signals and a neural substrate of food reward-related processes, altered neurochemistry such as nucleobindin-2/nesfatin-1 deficiency may contribute to dysregulation of homeostatic and/or hedonic feeding behavior and ultimately to obesity.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

The Effectiveness of Computed Assessment Using GP and TW3 Hybrid System

Lindsey Yoojin Chung, MD[1], Kyu-chong Lee, MD[2], Kyung-Sik Ahn, MD, PhD[2], Jae Jun Lee, PhD[3], Chang Ho Kang, MD, PhD[2], Kee-Hyoung Lee, MD,PhD[1].
[1]Korea University Anam Hospital, Department of Pediatrics, Seoul, Korea, Republic of, [2]Korea University Anam Hospital, Department of Radiology, Seoul, Korea, Republic of, [3]Crescom Inc., Seoul, Korea, Republic of.

MON-LB017

Background: Bone age assessments (BAAs) is an important clinical modality to investigate endocrine, genetic and growth disorders in children. It is generally performed by radiological examination of the left hand by using either the Greulich-Pyle (GP) or the Tanner-Whitehouse (TW) method. However, both clinical procedures show several limitations, from significant intra- and inter-operator variability to examination effort of clinicians. To address these problems, several automated approaches have been proposed; nevertheless, some disparity still exists between automated BAAs and manual BAAs to be employed in clinical practice. To overcome this disparity, deep learning-based bone age assess software using GP and TW3 hybrid method has been developed. In this study, we evaluate the accuracy and efficiency of the new automated hybrid