components of body weight loss in cachectic patients. We hypothesized that there is a correlation between the marked increase in activin A production in PDAC patients and the remodeling of adipose tissue and consequent cancer-associated cachectic state. **Experimental Design:** We measured serum activin A levels of a cohort of PDAC patients and analyzed the expression of activin A in tumor-derived cell lines and biopsies of both humans and mice. We further investigated the effect of activin A on remodeling of adipose tissue secondary to tumor progression in PDAC patients and an orthotopic murine model. **Results:** We observed that PDAC cell lines express and secrete activin A. We recognized a loss of adipose tissue mass and adipocyte diameter in PDAC patients and our orthotopic PDAC mouse model in relation to increased circulating activin A. We also noted that both exogenous activin A and conditioned medium from pancreatic tumor-derived cell lines dampened adipocyte differentiation and lipid droplet formation via reduction of PPARγ expression in mouse mesenchymal stem cells. These treatment conditions also reduced lipid droplet size without upregulating traditional markers of adipose tissue browning and lipolysis such as UCP-1 and ATGL in mature mouse adipocytes. PPARγ, UCP-1, and ATGL expression are also heavily downregulated in adipose tissue of PDAC patients. Furthermore, our studies revealed that the expression of extracellular matrix proteins such as collagen I and fibronectin is dramatically upregulated in adipose tissue of PDAC patients and our orthotopic PDAC mouse model. Thus, we found that there is a clear correlation between elevated levels of activin A and the progression of cancer-associated cachexia in PDAC. **Discussion:** Our results reveal an imperative role of activin A in relation to the loss and remodeling of adipose tissue in the progression of cachexia in PDAC patients.

Adipose Tissue, Appetite, and Obesity
NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Preclinical Weight Loss Efficacy of AM833 in Combination With Semaglutide in Rodent Models of Obesity

Linu M. John, PhD, Thomas Kruse, PhD, Kirsten Raun, DVM.
Novo Nordisk A/S, Maaloev, Denmark.

Weight management pharmacotherapies seldom induce body weight loss that is comparable to that produced by bariatric surgery. In this regard, combination therapies targeting multiple signaling pathways that regulate energy balance may provide a means to achieve greater weight loss efficacy while also allowing the use of lower doses of each drug, and thus mitigating potential gastrointestinal tolerability issues commonly observed with current therapeutics for weight management. Amylin and GLP-1 are peptide hormones that regulate appetite. Upon ingestion of a meal, amylin is co-secreted with insulin from pancreatic beta-cells, while GLP-1 is secreted from enteroendocrine cells in the intestine. Both native peptides have a short half-life and reduce food intake, delay gastric emptying and decrease glucagon levels. Amylin and GLP-1 analogues have been developed for the treatment of diabetes, as well as weight management. The long-acting once-weekly GLP-1 analogue, semaglutide is approved for the treatment of type 2 diabetes and is in clinical development for weight management. AM833 (NNC0174-0833) is a long-acting, once-weekly human amylin analogue that is also in clinical development for weight management. Here, we present the combined effect of AM833 and semaglutide on weight loss in rodent models of obesity. Diet-induced obese (DIO) rats and mice on a high energy diet were dosed subcutaneously once-daily for 24 or 28 days with sub-maximal doses of AM833, semaglutide or two modes of combination treatments. The first combination mode consisted of concurrent co-dosing of both drugs, while the second entailed add-on of AM833 after one week of treatment with semaglutide. Body weight and food intake were measured daily. Body composition was assessed by magnetic resonance scan pre- and post-treatment. In the DIO rat, both concurrent (-13.1% ± 0.7%) and add-on (-12.8% ± 1.2%) treatment modes induced equivalent weight loss that was greater than each monotherapy (-6.3% ± 0.7%, 2 nmol/kg semaglutide and -5.8% ± 0.9%, 2 nmol/kg AM833) relative to initial body weights. Both combination groups achieved normalization of body weight to that of lean age-matched control rats. Reductions in cumulative food intake corresponded with the extent of weight loss. In the DIO mouse, weight loss in the combination groups was not significantly different (-9.6% ± 1.5%, concurrent vs. -11.5% ± 1.2%, add-on) but was greater than that observed in each monotherapy group (-1.9% ±1.2%, 1 nmol/kg semaglutide and +1.5% ± 2.2%, 10 nmol/kg AM833). In the DIO mouse, body weight did not normalize to match that of lean controls with combination treatment. In both rodent models, combination therapy at submaximal doses of AM833 and semaglutide achieved significantly greater weight loss compared to the monotherapy groups highlighting the potential of this combination for further clinical development.

Adipose Tissue, Appetite, and Obesity
NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Pro-Opiomelanocortin Neural Activation and Sexual Interest in Male Mice

Mitchell T. Harberson, B.S.[1], Jennifer W. Hill, PhD[2].
[1]UNIVERSITY OF TOLEDO, Toledo, OH, USA, [2]University of Toledo, Toledo, OH, USA.

Pro-opiomelanocortin (POMC) neurons in the hypothalamus play a role in both the control of metabolic state and sexual behavior. Along with the fast neurotransmitters glutamate and/or GABA, POMC neurons secrete cocaine- and amphetamine-regulated transcript (CART) and products of the POMC gene, including β-endorphin and α-melanocortin stimulating hormone (α-MSH). Published data from our lab demonstrate a lack of sexual interest in male mice when both the leptin receptor and insulin receptor are deleted from POMC neurons. Furthermore, this absence of interest correlates with a decrease in the POMC product α-MSH. However, it is not known whether these effects correspond to an increase in POMC neural activation. We hypothesized that activation of POMC neurons in male mice would lead to improved sexual interest. We have crossed mice with cre-dependent expression of the