Concluding statement: IC7Fc is an effective and potent therapy in *db/db* mice with a functional pancreas. Thus, IC7Fc may be a viable new treatment for T2D, provided patients still maintain β-cell function.

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Cognitive control of reward neurocircuitry in the activity-based anorexia rat model

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Anorexia nervosa (AN) has the highest mortality rate of any psychiatric disease, yet available treatments are largely ineffective, in part due to a lack of insight into the neurobiological drivers that underpin the condition. Functional neuroimaging in AN patients suggests that the interplay between underactive reward and overactive cognitive neurocircuits may underscore pathological body weight loss. Utilising the activity-based anorexia (ABA) rodent model, we have previously shown that chemogenetic activation of the ventral reward circuitry prevents and rescues precipitous body weight loss by increasing food intake. Here, we hypothesised that reducing activity in neurons of the prefrontal cortex with direct projections to ventral reward circuits would similarly improve body weight maintenance in ABA.

Female Sprague-Dawley rats ($N = 36$) underwent bilateral stereotaxic injections of a retrogradely-transporting Cre (AAV-pmSyn1-EBFP-Cre) into the nucleus accumbens (NAc) and coincident injections of either inhibiting [AAV-hSyn-DIO-hM4D(Gi)-mCherry] or activating [AAV-hSyn-DIO-hM3D(Gq)-mCherry] DREADD viruses into the prefrontal cortex (PFC). This dual viral strategy allows for precise modulation of only those PFC neurons that project to the NAc. Rats injected with the blank viral construct (AAV-hSyn-DIO-mCherry) were used as controls. During exposure to the ABA paradigm, which involves unhindered access to a running wheel and time-limited (90 min/day) access to food, all rats were administered CNO daily (0.3–3 mg/kg i.p.) at the onset of the dark phase for a maximum of 10 days.

Contrary to our hypothesis, chemogenetic inhibition of PFC-NAc projection neurons increased susceptibility to body weight loss in ABA ($\chi^1 = 6.33$, $p = 0.012$), by exacerbating running wheel activity compared to controls ($F = 10.16$, $p = 0.009$), with no effect on food intake ($t = 0.47$, $p = 0.65$). Taken together, our data indicate that both ventral reward and executive control circuits respectively impact on food intake and running activity, both essential elements of the ABA phenotype and the AN condition that contribute to pathological body weight loss.

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The role of amyloid beta$_{42}$ in heart disease

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Background: Heart failure is a major cause of mortality in obesity and can occur in the absence of other established risk factors such as hypertension. This is known as obese cardiomyopathy and an alteration in cardiac metabolism is thought to be one of the key drivers of the disease, however, little is known on the contributing factors. Serum levels of the Alzheimer's disease protein amyloid beta 42 ($A\beta_{42}$) increase in obesity and our research group has recently found that mice administered $A\beta_{42}$, to increase levels to those seen in obesity, develop cardiac dysfunction.

Purpose/aims: The aim of our research is to determine the mechanisms of action of $A\beta_{42}$ on cardiomyocytes in order to better understand the pathogenesis of the disease and potentially uncover therapeutical targets to prevent and treat it.

Methods: Hearts from mice administered $A\beta_{42}$ or scrambled peptide were examined using RNA sequencing, western blotting and qPCR. H9C2 cardiomyocytes were used to screen for receptors and signalling pathways mediating the effects of $A\beta_{42}$.

Results/conclusion: Analysis of RNA sequencing data revealed a number of signalling pathways that may be important in $A\beta_{42}$ mediated changes including the nerve growth factor and fibroblast growth factor signalling pathways. Furthermore, mice administered $A\beta_{42}$ and $A\beta_{42}$ treated cardiomyocytes showed evidence of inflammatory and ER stress responses. Inhibition of protein kinase D (PKD) in $A\beta_{42}$ treated cardiomyocytes impaired these responses, suggesting it may be an important signalling molecule.

To further understand these findings, the importance of PKD in $A\beta_{42}$-mediated cardiomyopathy will be examined in mice with a cardiac specific loss of PKD activity. In addition, the effectiveness of drugs developed for the treatment of Alzheimer's disease to preventing obese cardiomyopathy in a mouse model of obesity will be examined.

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Why do some mice resist weight gain on a high caloric diet? An omics approach

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Background: It's known that laboratory mouse strains respond differently to high caloric feeding in terms of their adiposity and glucose tolerance. However, significant inter-individual variability also occurs within strains. What drives this difference given background genetics is controlled is unknown, but may reveal insights regarding maintenance of leanness.

Methods: We screened 30 C57BL6/J mice fed a high fat/high sucrose diet (HFHS) for 8-weeks and identified three mice discordant for adiposity (i.e. they remained lean) compared to their

littermate cage-mates. Lipidomic and proteomic analysis was then conducted on metabolic tissues.

Results: After 8 weeks of the HFHS diet, the lean mice had an average of 6.69 gms less adipose tissue than their matched controls ($p \leq 0.001$) with a body fat percentage of 17.63% compared to 31.32% ($p \leq 0.01$). Lipidomic analysis identified that the lean mice had a decrease in multiple lysophosphatidylcholine (LPC) and an increase in ceramide (CER) sphingomyelin (SM) and triacylglycerol (TG) species in the adipose. LPC and SM species were elevated in the muscle of the lean mice. In the liver, diacylglycerols (DG) and TG species were decreased, while SM species were elevated in the lean group. Plasma analysis indicated a decrease in cholesterol esters (CE) and SM species. Proteomic analysis in the muscle and adipose revealed no differences between groups after catering for multiple hypotheses. In the liver Gene Ontology enrichment analysis indicated an overrepresentation of genes/proteins associated with fatty acid transport and metabolic processes in the lean animals.

Conclusion: Despite the same genetics and environment, discordance for adiposity in HFHS-fed mice is associated with specific changes in the tissue lipidomic signature. Further studies into the potential processes behind these alterations such as epigenetic or post-translational modifications are warranted.

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Fatty acid binding protein 4 inhibitor corrects metabolic disturbance in MKR mouse of Type 2 diabetes

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Fatty acid binding protein 4 (FABP4) is one of the key adipokines that can serve as an important biomarker predicting the risk of developing metabolic syndrome, type 2 diabetes (T2DM) and atherosclerosis (1). Genetic deficiency of FABP4 improves glucose homeostasis and reduces atherosclerosis in mouse models (2). The associated underlying mechanisms seem to be pleiotropic and request further characterization.

Here we reported that inhibition of FABP4 by a small molecule compound, BMS309403, corrected metabolic disturbance in a lean Type 2 diabetic MKR mouse model. Oral application of BMS309403 (15 mg/kg) in MKR mice for 10 weeks improved insulin sensitivity and glucose tolerance (ITT AUC 896.3 ± 107.3 mmol/l·min vs 688 ± 115.1 mmol/l·min and GTT 1741 ± 250.4 mmol/l·min vs 1459 ± 239.6 mmol/l·min, vehicle vs BMS309403) regardless of an increase in adipose fat mass (gonadal fat 0.28 ± 0.02 g vs 0.41 ± 0.04; inguinal fat 0.28 ± 0.01 vs 0.39 ± 0.04 g and brown fat 0.12 ± 0.01 vs 0.22 ± 0.02). These changes correlate well with an increase in genes responsible for lipogenesis (*ppar gamma*) and glucose transport (*glu4*) in adipose tissue, and a reduction of gluconeogenesis gene in muscle and liver (*g6pases*). In addition, treatment of BMS309403 significantly increased heat production alongside an increase in genes responsible for transcriptional activation of brown adipocytes (*ucp-1* and *pgc1-alpha*). Furthermore, inhibition of FABP4 tends to alleviate age-associated decline of pulsatile growth hormone (GH) secretion in MKR mice (total GH 358.1 ± 36.18 ng/ml·min vs 181.4 ± 54.46 ng/ml·min, vehicle mice, pre vs post treatment; and 469.1 ± 61.94 ng/ml·min vs 392.6 ± 32.94 ng/ml·min, BMS309403 treated mice, pre vs post treatment).

To conclude, inhibition of FABP4 improves glucose homeostasis in MKR mice, possibly by re-balancing fat/glucose metabolism and promoting adipose browning. The corresponding improvement in metabolism in diabetic MKR mice may also contribute to the relief of age-associated decline in GH secretion.

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Metabolic effects of mirabegron in primary adipocytes in vitro, and on metabolic parameters in vivo

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Introduction: The β_3-adrenoceptor was initially a target for obesity and diabetes treatment, but several β_3-adrenoceptor agonists failed in clinical trials due to their lack of efficacy at the human b_3-adrenoceptor. Recently, the β_3-adrenoceptor agonist mirabegron has been approved for use in humans for overactive bladder, but there is very limited knowledge of any effects mirabegron has on metabolic parameters in model systems.

Methods: We have investigated the actions of mirabegron in brown, white and brite adipocytes from mice, using cAMP assays, qPCR for Ucp1 mRNA content, glucose uptake using ^{3}H-2-deoxyglucose, Seahorse xF96 analysis for in vitro oxygen consumption and glycolysis measurements. We have assessed whether the effects of mirabegron *in vivo* (glucose uptake, oxygen consumption, glucose tolerance tests) are due to activation of the β_3-adrenoceptor with the use of β_3-adrenoceptor knockout mice.

Results: Mirabegron increases cyclic AMP levels, Ucp1 mRNA content, glucose uptake and cellular glycolysis in brown adipocytes, and this effect is significantly absent/reduced in white adipocytes. In brite adipocytes, mirabegron increases cyclic AMP levels, Ucp1 mRNA content leading to increased UCP1 mediated oxygen consumption, glucose uptake and cellular glycolysis. Mirabegron *in vivo*increases whole body oxygen consumption rates, glucose uptake into brown and inguinal white adipose tissue, and improves glucose tolerance, which are dependent upon the presence of the β_3-adrenoceptor.

Conclusion: Mirabegron has the potential to be used for further studies examining its effects in metabolic disease, specifically in humans.

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