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