activity at discrete time periods. The contribution of energy expenditure to body weight maintenance during activation is unclear. These results will inform not only the neurobiological underpinnings of AN but also provide an insight into the mechanisms of reward pathways relevant to feeding and weight loss.

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Harnessing the sun to halt obesity: Vitamin D, nitric oxide and brown adipose tissue

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The role of vitamin D in curtailing the development of obesity and comorbidities like the metabolic syndrome (MetS) and type-2 diabetes has received much attention recently. However, clinical trials have failed to conclusively demonstrate the benefits of vitamin D supplementation. In most studies, serum 25-hydroxyvitamin D (25(OH)D) decreases with increasing BMI above normal weight. These low 25(OH)D levels may also be a proxy for reduced exposure to sunlight-derived ultraviolet radiation (UVR). We have found that frequent skin exposure to a low non-burning dose of UVR reduced weight gain in C57Bl/6 male mice fed a high fat diet. Ongoing exposure to UVR also significantly suppressed glucose intolerance, insulin resistance, signs of non-alcoholic fatty-liver disease and serum levels of fasting insulin and glucose. These findings were independent of circulating 25(OH)D, and most could not be mimicked by vitamin D supplementation. We are now starting to characterise the effects of biological mediators induced by exposure to UVR, such as nitric oxide, and their potential to prevent obesity in already 'overweight' mice, as well as the potential involvement of brown adipose tissue using the uncoupled protein-1 luciferase transgenic mouse (''Thermomouse''), in which thermogenesis in brown adipose tissue can be tracked *in vivo*. Our studies suggest that UVR (sunlight exposure) may be an effective means of suppressing the development of obesity and MetS through mechanisms that are partially dependent on nitric oxide, and other novel UVR-induced mediators.

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Investigating the molecular basis and therapeutic potential of the heme oxygenase-1 (HO-751) — Adiponectin axis

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Adiponectin is a beneficial hormone produced primarily by adipocytes. Paradoxically, circulating adiponectin levels are reduced in the context of obesity and associated diseases. This hypoadiponectinemia is implicated in the aetiology of obesity-related cardiometabolic diseases making therapeutic strategies to increase adiponectin attractive. An emerging body of literature suggests that increasing heme oxygenase 1 (HO-1) may increase adiponectin levels, prompting the proposal of an 'HO-1 — adiponectin axis'. We have performed a series of investigations to explore this possibility.

Using two *in vitro* models of human adipocytes, combined with a comprehensive array of pharmaceutical (cobalt protoporphyrin (CoPP) or hemin) and genetic modulators of HO-1, we found that neither acute[1] nor chronic induction of HO-1 results in increased adiponectin production. However, in a mouse model of diet-induced obesity we observed that systemic induction of HO-1 with CoPP increased circulating adiponectin levels and this was concurrent with decreased food intake, body weight gain and adipocyte size as well as enhanced insulin sensitivity and reduced liver steatosis. Importantly only the effect on adiponectin was blunted when mice were co-treated with an inhibitor of HO-1 activity (SnMP) [1].

Taken together, our *in vitro* and *in vivo* observations suggest that CoPP increases circulating adiponectin levels in an indirect manner that is, at least partly, dependent on HO-1 activity. Furthermore, our *in vivo* studies indicate that systemic treatment with CoPP results in reduced food intake and improvements in a range of metabolic

parameters in a manner that is independent of HO-1 activity. Further studies are warranted to identify the underlying mechanisms that may reveal new molecular targets for the treatment of obesity and associated diseases.

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Invited talk: Treating diabetes and obesity using the gut microbiome involves dietary diversity

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Background: A healthy gastrointestinal microbiome is a diverse microbiome and results from a diverse diet. During the past 50 years, 75% of the world's dietary diversity has been lost. One can look for gut dysbiosis in disease and give foods to correct the dysbiosis or use rare, heirloom foods to increase microbiome diversity as two strategies to treat disease by acting on the gastrointestinal (GI) microbiome.

Methods: The microbiome in diabetes is low in short chain fatty acid (SCFA) production, has increased GI inflammation and produces excess methane. NM-504 contains inulin, beta-glucan and blueberry pomace to address the SCFA, GI inflammation and methane abnormalities, respectively. Soy pod fiber can be stimulated to make glyceollin which increases microbiome diversity.

Results: NM-504 reduced blood sugar in a clinical trial to a similar degree as sitigliptin, a DPP-4 inhibitor. NM-504 protected the GI mucosal barrier from inflammation, reduced hsCRP, reduced appetite, and had no adverse events while increasing bowel regularity. NM-504 also reduced the GI side effects associated with metformin. Young soy pods activated to make glyceollin by cutting was fed to mice with dietary obesity. The mice ate more food, but lost weight and systemic inflammation was reduced. Faecal fat was increased, but there was no oil in faeces. The activated soy contains an FXR agonist, reduces inflammation, faecal bile acids, bile acid transport and decreases microbiota making antagonists of bile acids in the gut.

Conclusion: Increasing the diversity and correcting the dysbiosis of the GI microbiome in disease can be used in the treatment of diabetes, metformin intolerance, obesity and possibly non-alcoholic fatty liver disease.

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Early weight loss responders to liraglutide 3.0 mg had greater weight loss, regression to normoglycaemia, and reduced T2D development at 3 years vs early non-responders: SCALE Obesity and Prediabetes

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Background: The SCALE Obesity and Prediabetes (NCT01272219) trial randomised adults with prediabetes and obesity (BMI $\geq$ 30 kg/m^2) or overweight with comorbidities ($\geq$27 kg/m^2; dyslipidaemia/hypertension) to liraglutide 3.0 mg (N = 1505) or placebo (N = 749) as adjunct to diet and exercise for 3 years.

Methods: This *post-hoc* analysis compared liraglutide 3.0 mg early responders (ERs; $\geq$5% weight loss [WL] at Week [W] 16) and early non-responders (ENRs; <5% WL at W16), in keeping with EMA and Australian stopping-rule criteria. Efficacy outcomes are estimated means in ERs (n = 580) and ENRs (n = 210) who completed 160 weeks' treatment. Development of T2D/regression to normoglycaemia were analysed using the full analysis set with LOCF. Safety was analysed using the safety