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.

Reference

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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

analysis set. Placebo data are shown only for proportion of ERs/ENRs.

Results: Of those with W16 data, for liraglutide 3.0 mg ($n = 1302$) 68.0% were ERs and 32.0% ENRs; for placebo ($n = 640$), 22.3% were ERs and 77.7% ENRs. At W160, greater WL (−8.6% and −9.1 kg change in ER body-weight versus −2.9% and −3.1 kg for ENRs), reduced proportions of subjects developing T2D (0.5% ERs, 3.2% ENRs) and greater regression to normoglycaemia (69.8% in ERs, 55.4% in ENRs) were observed in ERs to liraglutide 3.0 mg vs ENRs. ERs showed greater clinical improvements (FPG, HbA_{1c}, SBP levels) and patient-reported improvements compared with ENRs (SF-36 score +3.68 vs +1.81 and IWQOL-Lite score +13.40 vs +9.53 for ERs and ENRs, respectively. Increase in score = improvement). Adverse events (AEs) and GI AEs were similar between groups (87.1% and 75.3% for ERs; 95% and 71.6% for ENRs) while serious AEs and gallbladder disorders were more frequent in ERs (17.7% and 6.3% vs 12.7% and 2.2% for ENRs).

Conclusions: Among those treated with liraglutide 3.0 mg for 160 weeks, greater benefits were seen in ERs vs ENRs; overall AE rates were similar.

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Liraglutide 3.0 mg reduces body weight and improves cardiometabolic risk factors in adults with obesity or overweight, but without diabetes: The SCALE Obesity and Prediabetes randomised, double-blind, placebo-controlled 3-year trial

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Aims/objectives: Obesity and prediabetes are risk factors for developing T2D. 5—10% weight-loss can reduce risk of developing T2D by >50%. This phase-3 trial investigated effects of liraglutide 3.0 mg, as adjunct to diet + exercise, on delaying onset of T2D over 3 years (primary endpoint), body-weight and cardiometabolic risk factors.

Methods: Individuals (BMI $\geq 30\,kg/m^2$, or $\geq 27\,kg/m^2$ with ≥ 1 comorbidity) were randomised 2:1 to once-daily subcutaneous liraglutide 3.0 mg ($n = 1505$) or placebo ($n = 749$) and advised on a 500-kcal/day deficit diet and 150-min/week exercise. Efficacy data are observed means, with last-observation-carried-forward (LOCF) imputation. Clinicaltrials.gov NCT01272219.

Results: Baseline characteristics were (mean ± SD): age 47.5 ± 11.7 years, 76.0% female, weight 107.6 ± 21.6 kg, BMI 38.8 ± 6.4 kg/m^2. With continued treatment over 160 weeks, time to T2D onset was 2.7-fold longer with liraglutide 3.0 mg than placebo [95%CI 1.9;3.9, $p < 0.0001$], corresponding to a hazard ratio of 0.2; 3% vs 11% of patients, respectively were diagnosed with T2D. More individuals on liraglutide (66%) than placebo (36%) regressed from prediabetes