IAP may represent a novel therapeutic strategy to prevent fructose-induced obesity and diabetes. The beneficial effects of IAP may derive from the preservation of normal flora homeostasis and gut epithelial barrier function. ...

Sa2071 Overexpression of Gastric Leptin Precedes Fat Leptin Up-Regulation During Diet-Induced Obesity and Is Concomitant to Increased Number of Enterochromaffin Cells
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Background. Numerous gut hormones, secreted by enteroendocrine cells, participate in food intake control. Gastric leptin controls CCK or GLP-1 secretion, two peptides known to induce satiety. Gastric leptin could also regulate enteroendocrine cells differentiation. In this report, we studied the temporal changes in gastric leptin expression, serotonin (5HT) production by enterochromaffin (EC) cells as well as expression of Peptx, a critical transcription factor for the specification of EC cells during the induction of obesity. Methods. Gastric and/or duodenal mucosal biopsies were obtained from morbidly obese or lean subjects as well as from mice fed a normal (ND) or high-fat diet (HFD) for 12 weeks and from leptin-deficient ob/ob mice. Protein and mRNA were measured from these biopsies to quantify leptin, TPH-1 (an enzyme responsible of 5HT synthesis) and Peptx levels in the oxyntic and duodenal mucosa. Data were analysed using non-parametric tests. Results. Obese subjects exhibited a significant increase in leptin mRNA and protein levels in oxyntic mucosa and in TPH-1 and PAX-4 mRNA levels in antrum mucosa (P<0.01 vs. lean subjects). One-week HFD led mice exhibited an elevated insulinemia with no change in leptinemia but an increase in gastric Ob mRNA (+4-fold, P<0.01 vs. ND) and leptin content (2-fold, P<0.05 vs ND). These modifications were stable during 12 weeks. By contrast leptinemia significantly rose up at the third week of the HFD and correlated with fat mass increase (+19%, P<0.05 vs ND). The number of EC cells, identified by 5HT staining and Peptx mRNA levels were increased after one week of HFD. Furthermore, in leptin-deficient ob/ob mice on HFD, 5HT administration of leptin significantly increased Peptx mRNA levels in antrum (1.6-fold, P<0.05 vs control and duodenum (3-fold; P<0.05 vs control). Conclusions. This is the first demonstration of gastric leptin upregulation in obese subjects concomitantly with an increased number of EC 5HT-secreting cells. Results obtained with HFD mice further suggest that these changes occur before the onset of obesity (i.e. before any fat mass expansion) and that a leptin-serotonin pathway exists also in the gut. Furthermore, the increase in Peptx levels in obese patients suggests a role for gastric leptin in enterochromaffin cell differentiation.

Sa2072 Simeprevir (TMC453) With Peginterferon/Ribavirin for Chronic HCV Genotype–1 Infection in Treatment-Naive Patients: Results From QUEST–1, a Phase III Trial
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Background and aims: Simeprevir (TMC453), an under investigation, is a potent, once-daily, oral, Investigational, HCV NS3/4A protease inhibitor. QUEST–1 is a Phase III, randomized, double-blind, placebo-controlled trial assessing simeprevir plus pegferferon–a–2b/ribavirin (PR) versus placebo plus PR in treatment-naive patients with genotype–1 infection. Safety and SVR results from a primary (Week 60) analysis are presented Methods: HCV genotype–1–infected patients with METAVIR score F0–F4 (n=394), stratified by HCV subtype and host IL28B genotype, were randomized 2:1 to receive simeprevir (150 mg QD) plus PR for 12 weeks followed by PR for an additional 36 weeks. Treatment duration was 24 or 48 weeks (simeprevir group) based on response-guided therapy (RGT) criteria (HCV RNA <25 IU/mL, Week 4 and undetectable Week 12) or 48 weeks (placebo group) Results: Patient disease characteristics: 18% METAVIR F3, 12% F4, 29% CC. IL28B genotype, 11% infected with HCV genotype–1a. Simeprevir/PR was superior to placebo/PR, with SVR24 rates of 80 vs 55%, respectively (P<0.001). The majority (85%) of patients in the simeprevir group met RGT criteria and completed treatment at Week 24. Overall, 80% of simeprevir- and 59% of placebo-treated patients achieved RVR. Treatment with simeprevir/PR led to a lower on-treatment failure rate, compared to placebo/PR (vs 34%), and a lower relapse rate (9 vs 21%). In the simeprevir group, AEs led to discontinuation of simeprevir in 5% of patients. The most common AEs were fatigue, pruritus and headache. The prevalence of anemia and rash was similar between the simeprevir and placebo groups.Conclusions: Simeprevir 150 mg QD with PR was generally well tolerated, leading to a high SVR24 rate of 80%. The majority of patients (85%) receiving simeprevir was able to shorten therapy to 24 weeks.

Sa2073 SVR4 Results of a Once Daily Regimen of Simeprevir (TMC453) Plus Sofosbuvir (GS–7977) With or Without Ribavirin (RBV) in HCV GT 1 Null Responders
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Background and aims: Simeprevir (TMC453), an HCV NS3/4A protease inhibitor, is being studied in combination with Sofosbuvir (GS–7977), an HCV nucleoside NS5B polymerase inhibitor, in COSMOS, an exploratory, Phase IIa, randomized, open-label study investigating the efficacy and safety of 12 or 24 weeks of simeprevir + sofosbuvir with or without ribavirin (RBV) in HCV genotype (GT) 1 null responders to prior pegferferon (PegIFN)/RBV therapy with Sa2069 Mechanisms of Preprandial Ghrelin Release From Mouse Gastric X/A-like Cells - Molecular Basis for Regulation by Insulin 
Michelle Giffin, Janusz Jawien, Andreas Stengel, Miriam Goebel-Stengel, Niki W. Lambrecht 
Background: Ghrelin is the only known peripheral product and centrally acting peptide hormone that stimulates food intake in animals and humans. Despite the fact that the changes of circulating ghrelin have been investigated under various metabolic conditions, the physiological signals causing preprandial ghrelin release into the circulation on the cellular level are not known. Studies have been hampered by the difficult purification of ghrelin cells which are expressed in low abundance and in small clusters. We generated a novel transgenic mouse model expressing the red fluorescent protein mCherry specifically under the control of the ghrelin promoter. This allows for the time the isolation and purification of ghrelin expressing X/A-like cells to homogeneity. Aims: To identify proteins highly and specifically expressed in mouse gastric X/A-like cells involved in preprandial ghrelin release. Methods: Gastric mucosal single cells suspensions from transgenic mice expressing mCherry as a X/A-like cell specific fluorophore were prepared and ghrelin expressing X/A-like cells isolated using FACS. RNA expression of homogenous X/A-like cell suspensions after FACS was compared to RNA expression of preprandial gastric epithelial cell suspensions before FACS using Affymetrix GeneChip Mouse Genome 430 2.0 Array followed by in-silico subtractive expression analysis. Results: mCherry red fluorescent protein was exclusively expressed in ghrelin-expressing X/A-like enteroendocrine cells of the gastric oxyntic mucosa. FACS of primary gastric mucosal cell suspensions resulted in purification to near-purity X/A-like cell suspensions. Subtractive expression analysis followed by quantitative RT-qPCR and immunobstostimulatory antibody staining showed that X/A-like cells uniquely express the insulin receptor binding protein IRS4 (Table). The cells also show high but not unique expression of all three forms of the insulin receptor. Conclusions: Our findings provide a molecular basis of the recently reported hypothesis that X/A-like cell ghrelin release is stimulated by the pre-prandial fall of insulin concentrations in the circulation (Endocrinology 2012, 153, 3646-56). Funding: Supported by a VA Merit 5101BX00309-03
META VIR stage either F0 F2 (cohort 1) or F3–F4 (cohort 2). Methods: The study aims to randomize 90 patients per cohort, stratified by IL28B status and GT1 subtype (1a vs non-1a), in a 2:1:2:1 fashion to 1 of 4 arms: simprevir 150 mg once daily (QD) plus sofosbuvir 400 mg QD for 24 weeks with or without RBV, or simprevir 150 mg QD plus sofosbuvir 400 mg QD for 12 weeks with or without RBV. For cohort 1, a safety and efficacy interim analysis was conducted when approximately 20% of the planned randomized patients reached the end of treatment (EOT) or permanently discontinued treatment early. Results: At the time of this interim analysis, 80 patients in cohort 1 have been randomized and treated; 19 patients have reached EOT and have post-treatment follow-up data available. Duration of treatment exposure ranges from 3 to 171 days, median is 63 days. One patient discontinued study drug secondary to an adverse event (AE). Two patients discontinued treatment early for non-safety reasons: RBV dose was reduced in 4/5 patients due to decline in hemoglobin. No serious AEs were attributed to study drugs. Baseline characteristics and efficacy results are summarized. At the time of the presentation, results of an additional interim analysis are expected to be presented, including SVR in approximately 50 patients.Conclusions: Once-daily simprevir plus sofosbuvir with or without RBV for 12 or 24 weeks was well tolerated and resulted in high SVR4 rates in this initial group of study patients with null response to prior PegIFN/RBV therapy.

Su1017
Mucosal Healing and Risk of Fracture in Celiac Disease
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Background: Celiac disease (CD) is associated with an increased risk of osteoporotic fracture, a risk increase that persists after diagnosis. Although the gluten-free diet results in an improvement of symptoms in the majority of patients, a significant proportion have persistent villous atrophy (VA) on follow-up biopsy. It is unknown whether persistent VA impacts long-term fracture risk in patients with CD. Methods: We identified all patients in Sweden with histologic evidence of CD in a population-based database who underwent a follow-up biopsy between six months and five years after initial CD diagnosis. We excluded patients with a history of fracture prior to their follow-up biopsy. We compared those patients with persistent VA to those with mucosal healing with regard to their risk of 1) any fracture; 2) likely osteoporotic fracture (defined as fractures of the hip, distal forearm, thoracic and lumbar vertebrae, and any proximal humerus) and 3) hip fracture. We used Cox proportional hazards, adjusting for patient age, gender, calendar period, education, and duration of celiac disease at the time of follow-up biopsy. Results: Of 7,648 patients with CD who had a follow-up biopsy in this time period, 502 had a fracture history preceding their follow-up biopsy, leaving 7,146 patients for analysis. The median age of CD diagnosis was 23, and 64% were female. The median follow-up was 10.3 years after CD diagnosis, and 8.6 years after follow-up biopsy, during which 975 patients (14%) experienced a fracture. Persistent VA was present on follow-up biopsy in 43% of the patients. There was no significant association between persistent VA and fractures as a whole (Hazard Ratio [HR] 0.93, 95% CI 0.82-1.06); and there was a non-significantly increased risk of likely osteoporotic fractures (HR 1.11 95% CI 0.84-1.46). In contrast, persistent VA was associated with an increased risk of hip fracture (HR 1.67 95% CI 1.05-2.66), a risk that increased over time (HR > 5 years after follow-up biopsy: 2.18 95% CI 1.37-4.05). Compared to those with mucosal healing, hip fracture risk increased depending on the degree of VA on follow-up biopsy (HR for partial VA 1.70 95% CI 0.82-1.49; HR for subtotal/total VA 2.16 95% CI 1.06-4.41): Conclusions: Persistent VA on follow-up biopsy is predictive of long-term hip fracture risk, and this relationship is stronger for more severe degrees of VA. The relationship between persistent VA and hip fractures in particular, and not with fractures overall, suggests that osteoporosis is the mechanism by which persistent VA confers an increased fracture risk.

Su2074
The mutational architecture of oesophageal adenocarcinoma
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Introduction: Esophageal adenocarcinoma (EAC) has one of the fastest rising incidences of any cancer in the western world yet currently little is understood about the genetic alterations that drive its development. Methods: We have performed whole genome sequencing over 22 cases. Targeted amplicon sequencing of 27 recurrently mutated genes was performed on a validation cohort of 100 further oesophageal adenocarcinomas. Results: In the discovery set assessed via magnetic-bead based multiplex assays utilizing Bio-Plex technology and compared to ICD9–CM codes recorded during medical encounters and grouped based on antecedent designs that preclude the assessment of biomarker levels prior to infectious exposure and allowed a systematic review of published literature and performed a systematic literature search using online electronic databases regardless of language. Eligible studies were population-based case-control or cohort studies of ESCC that assessed the individual and combined effects of tobacco and alcohol use. The quality of studies was assessed by the Newcastle-Ottawa Scale. Differences from multiplicative effects in each study was quantified by the Synergy Factor (SF), defined as the ratio of the odds ratio (OR) for both tobacco and alcohol combined versus neither, divided by the product of the ORs for either factor alone without the other vs. neither, SF > 1 indicates positive synergy. Meta-analyses were performed to estimate summary ORs for each stratum and the summary SF using random effect models. Heterogeneity was defined by Cochrane’s Q < 0.20 and the inconsistency index (I², <25% low, >50% high) Results: Systematic review identified 4,951 unique citations, of which 7 were eligible. 6 were case-control and 1 was a cohort study; the majority was high quality. 5 studies provided ORs comparing smokers and ever/never drinkers, adjusting for other factors. Either tobacco or alcohol use was associated with approximately an 8% increased risk for ESCC, but use of both was associated with an almost 10-fold risk for ESCC (Table). The summary estimate of the SF for ever/never of both tobacco and alcohol was 2.33 (95% CI = 0.78, 7.01). The SF for never/ever of tobacco was 3.63 (95% CI = 0.65, 19.36). The SF for ever/ever of alcohol was 1.44 (95% CI = 0.46, 3.13), suggesting a strong synergistic effect (Figure). 3 studies provided data categorizing patients into never, light/moderate, or heavy use for both tobacco and alcohol, but only provided data in a format for estimating ORs without adjustment for other factors. Light to moderate use of both alcohol and tobacco was associated with an approximate 3-fold risk of ESCC vs. use of neither, and heavy use of both was associated with approximately a 10-fold risk (Table). Conclusions: There is likely a positive synergistic effect of alcohol and tobacco use for the risk of ESCC, but with impression in the estimate of its strength. The observed combined effect of the two factors is numerically twice that predicted for a combined effect if there were no synergy. The results are limited somewhat by the small number of eligible studies and heterogeneity in some analyses. Efforts for controlling the burden of ESCC should focus on the high risk population of individuals who use both alcohol and tobacco heavily.