doi:10.1136/gut.2011.238311

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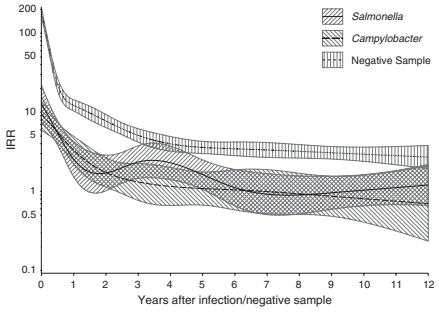
## Enteric infections and risk of IBD

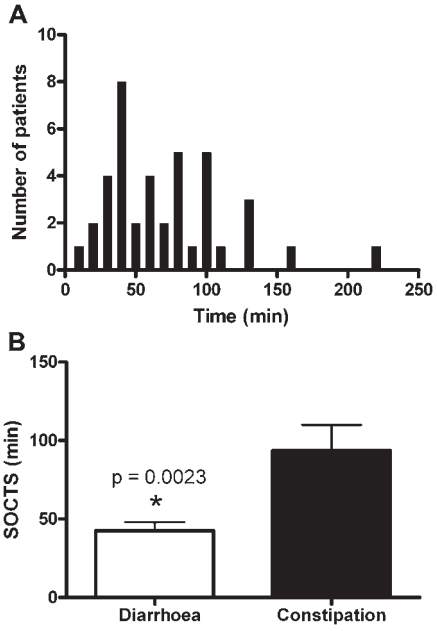
Enteric infections with Salmonella and Campylobacter have been suggested to play an aetiological role in IBD. However, the risk of detection bias in relation to this observation has not been studied. In this issue of *Gut*, Jess *et al* attempt to answer this important question. They followed the entire Danish population during the period from 1 January 1992 to 31 December 2008 with notice of dates for occurrence of first infection with *Salmonella* or *Campylobacter*, first negative stool test or a diagnosis of IBD, and until occurrence of the outcome of interest, emigration, death or the end of the study (31 December 2008). The study covered >94 million person-years of observation and revealed that the risk of both CD and UC is markedly increased not only following an enteric infection with Salmonella or Campylobacter but even more so, following a negative stool test. The findings strongly suggest that the risk previously ascribed to acute bacterial gastroenteritis reflects detection bias related to increase stool testing rather than causality. ***See page 318***.




Incidence rate ratios (IRRs) with 95% CIs for Crohn's disease as a function of time since the first positive stool test for Salmonella or Campylobacter or the first negative stool test relative to the background population, Denmark, 1992–2008.

## Lactulose hydrogen breath test measures oro-caecal transit, not SIBO

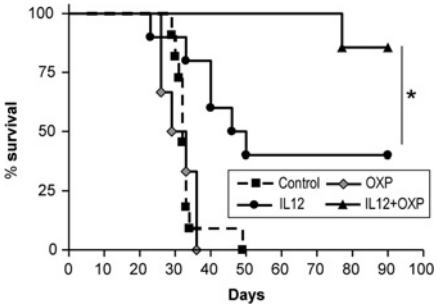
Some studies have suggested that the majority of patients with IBS have small intestinal bacterial overgrowth (SIBO) and have even advocated the use of antibiotics as treatment. SIBO was assessed in these studies by the lactulose hydrogen breath test (LHBT). However, there is significant doubt as to whether this test truly reflects SIBO, or simply changes in oro-caecal transit. In this issue of *Gut*, Yu *et al* combined oro-caecal scintigraphy with LHBT in 40 patients who were Rome II positive for IBS to determine if the increase in hydrogen is due to the test meal reaching the caecum. The oro-caecal transit time based on scintigraphic scanning ranged from 10 to 220 min and correlated with IBS sub-type, for example it was approximately twice as long in constipation-predominant IBS patients as diarrhoea-predominant patients (see figure). These findings demonstrate that an abnormal rise in $H_2$ measured in the LHBT can be explained by variations in oro-caecal transit time in patients with IBS and therefore do not support the diagnosis of SIBO, or the use of antibiotics in these patients. ***See page 334***.




Comparison of oro-caecal transit time in constipation-predominant and diarrhoea-predominant patients with IBS measured by $^{99m}$Tc scintigraphy.

## New therapeutic strategies for metastatic colorectal cancer

New therapeutic strategies are needed that can cure advanced colorectal cancer, especially metastatic disease. Tumour immunotherapy has that potential but the results to date of this form of therapy have been disappointing. In this issue of *Gut*, Gonzalez-Aparicio *et al* demonstrate that an immunostimulatory cytokine, interleukin 12 (IL-12), in combination with conventional chemotherapy, oxaliplatin, can effectively treat metastatic colorectal cancer in a pre-clinical model system. This is particularly striking in light of the lack of curative effect of either oxaliplatin or IL-12 as single agent therapy. These authors used a viral vector that expresses IL-12 in combination with oxaliplatin to eradicate metastatic colon cancer in a standard metastasis model. These effects were associated with a shift in the tumour microenvironment towards a more pro-immunogenic phenotype, with an increase in the CD8+/T regulatory cell ratio and a reduction in myeloid-derived suppressor cells. Furthermore, they were only seen with oxaliplatin and not with other conventional agents. These studies demonstrate the potential for combined immunotherapy with conventional chemotherapy to substantially advance the clinical care of patients with metastatic colorectal cancer. ***See page 341***.

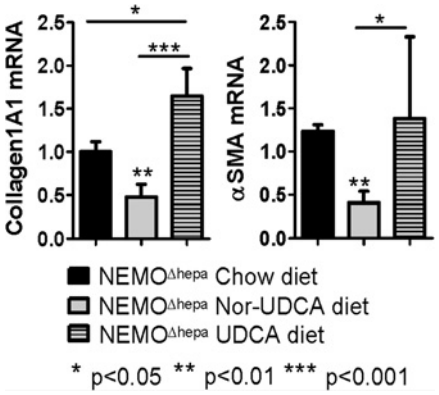



Survival of animals treated with different combinations of oxaliplatin and IL-12 showing synergistic effect of combination of oxaliplatin and IL-12 on treatment of colorectal metastases.

## Sulindac and experimental colon cancer

NSAIDs, including aspirin and sulindac, can prevent and induce the regression of colon adenomas in the average risk population and in individuals with

familial adenomatous polyposis. However, it is less clear if they are also effective in other cancer family syndromes, such as Lynch syndrome. In fact, results of a recent clinical trial demonstrated no effect of aspirin on colon adenoma formation in individuals with Lynch syndrome. In this issue of *Gut*, Mladenova *et al* used mouse models of Lynch syndrome and of Li Fraumeni syndrome to provide new insights into the basis of these results. They assessed the anti-tumour effect of sulindac in mice lacking the *MSH2* gene, one of the genes responsible for Lynch syndrome, and in mice lacking the *TP53*, the gene that is mutated in Li Fraumeni syndrome. Strikingly, they found that sulindac prevented azoxymethane (AOM)-induced distal colon tumours in all mice, but in the proximal colon sulindac induced inflammatory lesions and cancer. This is particularly relevant for Lynch syndrome because of the predisposition for right-sided colon cancer in these individuals. Clinical trials in humans are clearly needed before these drugs are considered for clinical care in such cancer family syndromes. ***See page 350***.




NorUDCA, but not UDCA, attenuates hepatic expression of collagen and of alphaSMA.

## Hepatology

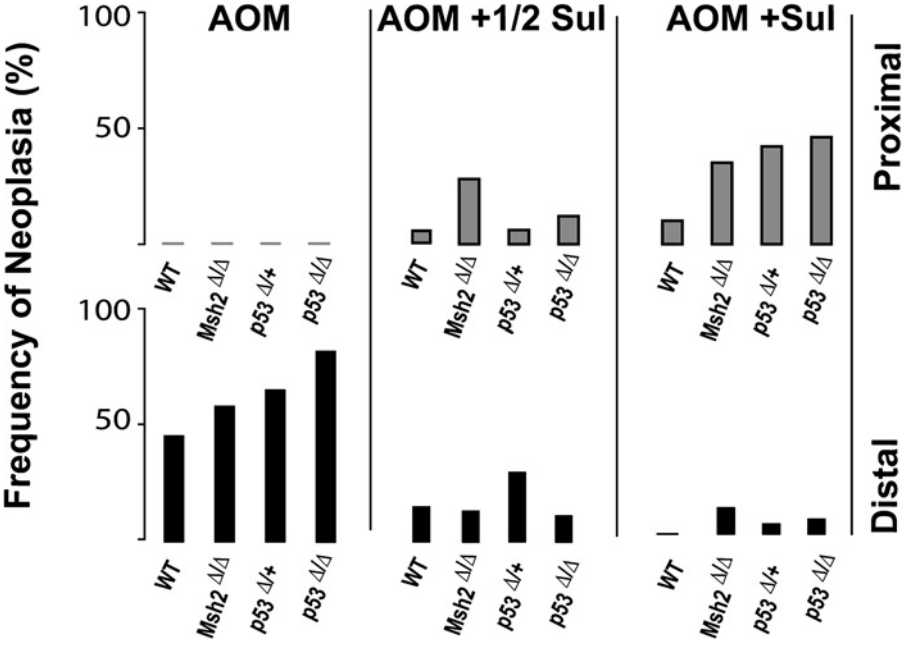
### Novel insight into mechanisms of liver diseases

*Nor-Ursodeoxycholic acid (NorUDCA) can attenuate the progression of NASH*

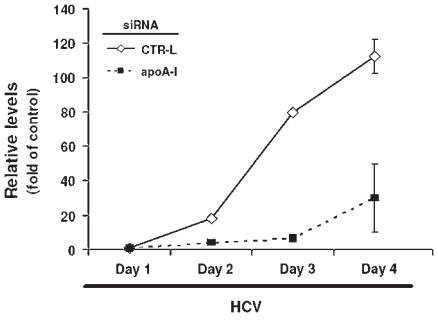
Novel approaches to treat non-alcoholic steatohepatitis (NASH) are urgently needed. Christian Trautwein and co-workers from his and Michael Trauner's group in this issue of *Gut* present interesting data obtained in their mouse model with hepatocyte-specific lack of NEMO/$NF_kB$ signalling. These mice develop NASH, fibrosis and ultimately hepatocellular carcinoma. The authors elegantly used a number of molecular techniques to characterise the effects of therapeutic intervention with UDCA and NorUDCA, and to elucidate the underlying mechanisms. Remarkably, they demonstrate that NorUDCA, but not UDCA, attenuates liver damage and fibrosis (see figure). These results are most interesting as they suggest a potential new therapeutic strategy to inhibit the progression of NASH with a compound that is available for clinical use. ***See page 387***.

*Apolipoprotein A-I (Apo A-I) is essential for Hepatitis C virus (HCV) replication*

HCV uses the lipoprotein metabolism of its host for several important steps of its life cycle. This study from Italy in this issue of *Gut* elucidates important novel details of the interaction between lipoproteins and HCV. Using sophisticated techniques, samples from patients with chronic HCV infection and cell systems, the authors found a decreased Apo A-I /LDL association. Specific down regulation of Apo A-I by siRNA clearly attenuated HCV replication (see figure). Among other very interesting findings, this study demonstrates an influence of Apo A-I on HCV replication and virion production. Thus, Apo A-I may become a novel target for antiviral strategies. ***See page 378***.




Frequency of colon neoplasia in p53Δ/Δ, p53Δ/+, Msh2Δ/Δ and corresponding wild-type (WT) siblings. Sulindac diet decreased the frequency of distal colon neoplasia in AOM treated mice, while increasing the frequency of neoplasia in the proximal colon.




HCV RNA in the culture medium of Huh7 cells transfected with control or with apo A-I siRNA and infected with HCV.