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New strategy against HER2

HER2 is an oncogene that plays an important role in progression and metastasis of several malignancies including advanced gastric cancer. Several strategies have been devised to abrogate HER2 expression in cancer, including the use of monoclonal antibodies. In the present study, Zhang et al constructed a chimeric molecule (HER-PE-CP3) that includes an anti-HER2 monoclonal antibody and a constitutively active caspase-3. The latter is a key regulator of apoptosis and activation of its enzymatic activity leads to initiation of this process. They tested this fusion protein on a human gastric cancer cell line (SGC7901) that overexpresses HER2 and found that it reproducibly induced apoptosis. The fusion protein was also highly effective in reducing gastric cancer tumour volume and prolonging survival in nude mice bearing xenografts of human gastric cancer (see figure 1). This approach offers a novel HER2-directed treatment option for human gastric cancer and is worthy of further development. ***See page 292***

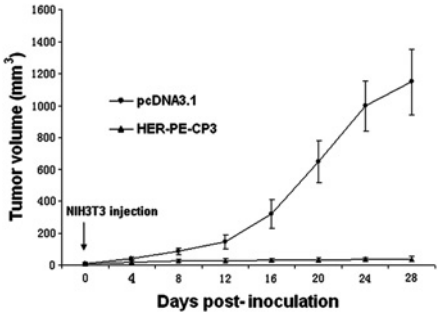

Figure 1 Suppression of human gastric cancer xenograft growth in nude mice receiving fusion protein (HER-PE-CP3) or control (pcDNA3.1).

Sacral nerve stimulation for intractable constipation

Many patients with severe idiopathic constipation are resistant to pharmacological and behavioural treatments. The traditional surgical procedures also have a variable outcome and carry a substantial morbidity. In this prospective European study, the authors evaluated the response and effect of 21-days sacral nerve stimulation (SNS) on the defecation frequency and quality of life in patients with constipation failing conservative treatment. A total of 62 patients underwent test stimulation, of whom 45 (73%) proceeded to chronic stimulation. Response was observed in no less than 39 (87%) of patients and defecation frequency increased from 2.3 to 6.6 evacuations per week ($p<0.001$). There was also a decrease in the perception of incomplete evacuation (71.5% to 46%, $p<0.001$) and in the subjective rating of abdominal pain and bloating ($p<0.001$). The Cleveland Clinic constipation score (0= no to 30= severe constipation) decreased from 18 to 10 ($p<0.001$) (see figure 2). Finally, the quality of life significantly improved and colonic transit normalised in half of those with baseline slow transit ($p=0.014$). Therefore, SNS is an effective therapy for idiopathic slow and normal transit constipation resistant to conservative treatment. ***See page 333***

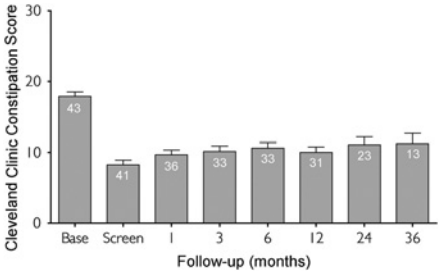

Figure 2 Mean (S.D.) Cleveland Clinic Constipation Score before and after chronic sacral nerve stimulation.

Visceral fat better predictor of outcome to Bevacizumab-based therapy in metastatic colorectal cancer

Obesity is an established risk factor for colon cancer and adipose tissue is now regarded as an endocrine and paracrine organ that releases angiogenic factors that may promote tumour growth. Recent work suggests that visceral rather than subcutaneous fat is more relevant to cancer risk. In the present study, Guiu *et al* determined whether body mass index (BMI), subcutaneous fat area (SFA) and visceral fat area (VFA) are associated with outcomes in patients given first-line bevacizumab-based treatment for metastatic colorectal cancer (MCC). SFA and VFA was measured by CT scan in 120 patients with MCC who received bevacizumab (n=80) or chemotherapy alone (n=40). Associations linking BMI, SFA and VFA to tumour response, time-to-progression (TTP) and overall survival (OS) were evaluated. High VFA was associated with shorter OS ($p<0.05$). By multivariate analysis, high VFA was independently associated with response, TTP and OS. This study provides the first evidence that high VFA independently predicts a poorer outcome in patients given first-line bevacizumab-based treatment for MCC. If the findings are validated in a different dataset, the measurement of VFA will have to be included in clinical trials for MCC, thereby taking into account tumour parameters and also host parameters. ***See page 341***

Cationic trypsinogen (*PRSS1*) p.A16V mutation in pancreatitis families

Hereditary pancreatitis (HP) is an autosomal dominant disorder characterised by recurrent episodes of acute pancreatitis and an increased risk of progression to chronic pancreatitis with endocrine and exocrine failure. Mutations in the cationic trypsinogen gene, *PRSS1*, have been associated with HP. In this study, the authors characterised the clinical significance of the third most common *PRSS1* mutation p.A16V. Patients were recruited on the basis of family history of pancreatitis or as a result of genetic testing. Families were categorised as having HP (≥2 cases in ≥2 generations), idiopathic disease or pancreatitis in a single generation. Ten families with p.A16V mutations including 22 affected individuals were identified: 6 HP families, 3 with idiopathic disease and one with only a single generation affected. The median age of onset was 10 years and there were 8 confirmed cases of exocrine failure and 3 pancreatic cancers. No significant differences were detected between patients with the p.A16V

mutation as compared to other *PRSS1* mutations. The authors conclude that p. A16V contributes to the multigenic aetiology of HP (figure 3). ***See page 357***

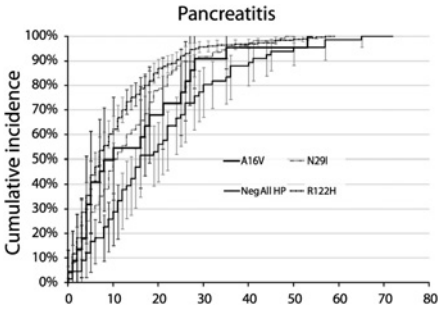

Figure 3 Kaplan-Meier curves comparing p. A16V to other mutation groups for onset of pancreatitis.

No help from MARS

Type 1 hepatorenal syndrome (HRS) still has a detrimental prognosis unless liver transplantation is available. Renal failure in HRS is of functional nature and due to reduced renal perfusion upon systemic arterial vasodilation and renal vasoconstriction in advanced cirrhosis. Therefore, targeting these hemodynamic changes might reverse HRS, as recently shown for treatment with terlipressin in combination with albumin infusion. MARS dialysis removes some albumin-bound substances from the circulation and has been advertised as a liver-assist device. It has been suggested, but not convincingly demonstrated, that MARS affects hemodynamics and improves renal function and moreover survival in patients with HRS. The present work by Wong et al excels previous investigations by determining renal blood flow and glomerular filtration rate (GFR) in HRS before and after 5 days of MARS treatment. While serum creatinine decreased significantly (see figure 4), GFR and renal perfusion were unchanged. Thus, MARS affected laboratory parameters but unfortunately could not improve renal function. This important study should help resolve a long-lasting debate about the usefulness of albumin dialysis for HRS. ***See page 381***

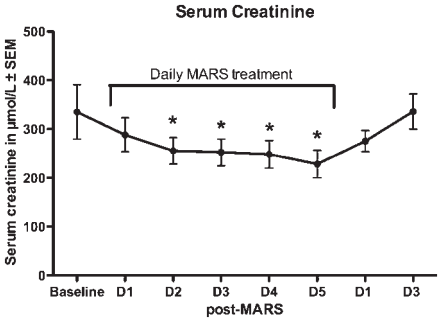

Figure 4 Serum creatinine in patients with type 1 hepatorenal syndrome treated with MARS. *p<0.05 versus baseline.

Obesity increases hepatic cytokine and chemokine expression in HCV patients

Obesity and fatty liver are frequently observed in patients with chronic HCV infection. In such patients liver disease seems to progress more rapidly. The underlying mechanisms, however, remain to be elucidated. In the present study, Palmer et al elegantly show that obesity modifies intrahepatic cytokine and chemokine expression by comparing obese and lean HCV patients with a NASH group to correct for inflammation caused by fatty liver only. In obese HCV patients, TNFalpha and IFNgamma were markedly increased in the liver (see figure 5). Furthermore, enhanced expression of the chemokines MCP-1 and IP-10 was observed. This may account for the augmented inflammatory infiltrate observed in the portal tract of obese HCV patients and could contribute to rapidly progressing fibrosis. ***See page 397***

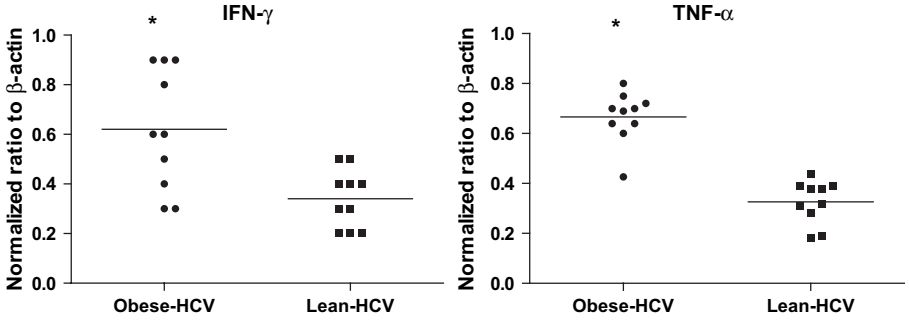

Figure 5 Cytokine mRNA expression in obese- versus lean-HCV subjects. Increased mRNA expression of the cytokines, IFN-γ (*p=0.004) and TNF-α (*p<0.001).