Abstract 410, Table 1

Cell type	β_1	α_1	α_2	α_3	α_4	α_5	α_6	α_V
Quiescent rat cells	±	+++	±	±	-	±	±	+
Transformed rat cells	+++	+++	++	+	±	+++	++	++
normal human quiescent	+	+	-	-	-	+	-	±
normal human transformed	+++	+++	++	±	±	++	+	+
primary biliary cirrhosis	+++	+++	+	±	±	++	+	+
alcoholic cirrhosis	+++	++	+	±	+	++	+	+
autoimmune cirrhosis	+++	+++	+	±	+	++	±	+
alcoholic hepatitis	+++	+++	+	±	±	++	+	+

The results are summarised in the table above. In rat stellate cells, β_1 , α_2 , α_3 , α_5 , and α_V are all weakly expressed by quiescent cells, and their expression is increased in activated cells. In contrast, α_1 is strongly expressed in both quiescent and activated rat stellate cells. The repertoire of integrins expressed by human stellate cells resembles that of rat stellate cells. As human stellate cells transform, they upregulate the expression of α_1 , α_3 and α_V , with de novo expression of α_2 , α_3 , α_4 and α_6 . The integrin expression in stellate cells isolated from diseased human livers resembles activated rather than quiescent cells. In conclusion, chronic liver injury is associated not only with modifications to the components of the ECM, but also with changes in the expression of ECM receptors. Thus, manipulation of integrin expression or function may lead to new antifibrotic therapies.

The President's Plenary Session: 411-416

411 THE PREVENTION AND TREATMENT OF MURINE COLITIS USING GENE THERAPY WITH ADENOVIRAL VECTORS ENCODING INTERLEUKIN-10

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Background: Interleukin-10 knockout (IL-10 $-/-$) mice spontaneously develop Th1 T cell mediated colitis with many similarities to Crohn's disease. Daily injections of IL-10 are able to prevent disease onset but do not induce remission in established disease.

Aims: To investigate the therapeutic efficacy and mechanism of action of gene therapy using adenoviral vectors encoding IL-10 (AdvmuIL-10) in the IL-10 $-/-$ mouse model of colitis.

Results: A single systemic injection of AdvmuIL-10 was able to prevent the onset of colitis for at least 10 weeks, but was also sufficient to induce remission in IL-10 $-/-$ mice with established disease ($p < 0.001$ by ANOVA compared to saline or empty vector (Adv0) treated controls). Histological scores were significantly lower in AdvmuIL-10 treated mice than controls ($p < 0.05$). In addition, AdvmuIL-10 therapy reduced the elevated serum amyloid protein levels and stool IL-1 β concentrations characteristic of this disease ($p < 0.05$). IL-10 protein was present in colonic homogenates of AdvmuIL-10 treated IL-10 $-/-$ mice, and the effects of secreted IL-10 were detectable by a sensitive bioassay for at least 10 weeks after injection. The immunoregulatory effect of a single AdvmuIL-10 injection was manifest both by a reduction in TNF- α , IFN- γ and RANTES release from stimulated spleen cell cultures ($p < 0.005$ compared to saline treated controls) and also by a change in the proportion of CD45RB^{high/low} lymphocytes in the spleen compared to control mice ($p < 0.05$ compared to saline treated controls). The delivery of IL-10 appeared to diminish the host anti adenoviral response as serum from IL-10 $-/-$ mice treated with AdvmuIL-10 contained significantly lower titres of neutralising anti-adenoviral antibodies than mice that had received either empty vector or a virus encoding an irrelevant protein - Adv β gal ($p < 0.05$).

Conclusion: Gene therapy strategies using adenoviral vectors encoding immunoregulatory cytokines may prove to be a potent approach for the treatment of chronic inflammatory diseases such as Crohn's disease.

412 ACID 1 STUDY: RESULTS OF A RANDOMISED TRIAL OF *H. PYLORI* ERADICATION IN PATIENTS ON MAINTENANCE ACID SUPPRESSION IN THE COMMUNITY

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Objective: The assessment of community intervention in dyspepsia (ACID1) study investigates the effect of *H. pylori* (*Hp*) eradication in a large community based dyspeptic population irrespective of underlying diagnosis.

Patients/methods: 11,149 of 176,268 patients receiving H_2 RA or PPI from 40 general practices were identified. After exclusions those receiving maintenance therapy (≥ 3 scripts/year) were randomised to active (n=4003) or control (n=1707) groups. Active patients were divided according to diagnostic groups: investigated ulcer n=1143 (28.5%); investigated non-ulcer n=1772 (44.3%); and uninvestigated n=1088 (27.2%). Active patients were invited to a nurse led community dyspepsia clinic and received health information, ^{13}C Urea Breath Test (UBT) and, where positive, were prescribed *Hp* eradication. Glasgow Dyspepsia Severity Score (GDSS) and Digestive Disease Quality of Life (DDQol) data (0, 6 months) and prescription data (0, 6, 12 months) were collected. Patients receiving *Hp* eradication had repeat ^{13}C UBT at 6 months.

Results: 1213 of 2353 (51.6%) patients attending clinic were *Hp* positive. Per protocol eradication rate achieved was 766/937 (80.4%) patients. Mean changes in score for GDSS and DDQ are presented.

Abstract 412, Table 1

<i>Hp</i> Status	N	GDSS	DDQol	Off therapy for 1 year
Successful eradication	766	2.03*	0.27*	39.9%*
Failed eradication	171	1.26	0.14	23%
<i>Hp</i> Negative	898	1.77*	0.11	17.7%

* $p < 0.05$, ANOVA; * $P < 0.05$, χ^2 test versus both other groups.

Conclusions: *Hp* eradication irrespective of underlying diagnosis in a large dyspeptic population on maintenance acid suppression in general practice leads to a significant improvement in symptom and quality of life scores and a significant reduction in prescribing.

413 TGF- α INDUCES A β -CATENIN/TCF MEDIATED TRANSCRIPTION EVENT IN BARRETT'S OESOPHAGUS

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In Barrett's Oesophagus one of the earliest identified events is the up-regulation of the EGF-receptor, and its associated ligand TGF- α . Previous reports have identified a number of alterations in the expression and localisation of cell-cell adhesion molecules, such as E-cadherin and β -catenin of the adherens junction, in the transition from a normal stratified squamous to the metaplastic mucosa of Barrett's Oesophagus. Relocalisation of β -catenin from the membrane to the nucleus induces oncogene expression (a process termed β -catenin / TCF mediated transcription).

In this study we assessed whether the elevated levels of TGF- α could direct the metaplastic-remodeling event observed in the initiation of Barrett's Oesophagus.

Stimulation of both primary and established oesophageal cell cultures with TGF- α for 3 hr resulted in the transition of β -catenin from a membranous to nuclear localisation, as assessed by immunofluorescence. We further identified this transition was associated with tyrosine phosphorylation of β -catenin. Using the TOP-FLASH luciferase reporter construct, a measure of β -catenin / TCF mediated transcription, TGF- α stimulation induced a 5 fold increase in TCF- β -catenin mediated transcription. This could be inhibited by use of an EGF-receptor kinase inhibitor, tyrphostin.

This data has identified that TGF- α , which is up regulated in the majority of human epithelial cancers, may induce tyrosine phosphorylation of β -catenin by receptor-ligand activation. This results in its migration to the nucleus where it can participate in the activation of β -catenin / TCF mediated transcription, the target genes of which

include oncogenes such as Cyclin D1 and c-myc. Such changes in adhesion molecule localisation and oncogene expression may be important in the metaplastic-remodeling events observed in Barrett's Oesophagus.

414 SWITCHING ON SWALLOWING, SWITCHING ON THE BRAIN—A NEW APPROACH FOR THE TREATMENT OF DYSPHAGIA

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Background/aims: Animal studies demonstrate that stimulation of both the cerebral cortex and brainstem can provoke swallowing. Peripheral, sensory input is also important for normal swallowing, since altered sensation can affect swallowing performance. Our aim was to identify, in healthy adults, the physiologic changes in cortical and brainstem activity that occur during normal swallowing, and then examine the effect of altered sensation (either sensory stimulation or topical anaesthesia of the swallowing musculature) on this activity. We then show that sensory stimulation can be applied to stroke patients with dysphagia (difficulty swallowing) and produce a quantifiable improvement in swallowing performance.

Methods: Techniques involved water swallowing; electrical, sensory stimulation of swallowing musculature by intraluminal catheter with ring electrodes; topical anaesthesia by lidocaine spray; transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI) and videofluoroscopy (VFS).

Results: Normal subjects (as recorded with TMS): (i) An increase in both cortical and brainstem activity occurred during water swallowing. (ii) Sensory stimulation, depending on the stimulus parameters, provoked either long-lasting suppression, or enhancement of activity within cortex but not brainstem. (iii) Topical anaesthesia suppressed cortical activity. Normal subjects (as recorded with fMRI): (iv) Sensory stimulation at the optimal parameters leading to enhancement of cortical activity, prior to swallowing, resulted in stronger, bilateral, hemispheric activation compared to swallowing alone. Dysphagic stroke patients: (v) Sensory stimulation both enhanced cortical activity within the undamaged (but not damaged) hemisphere and at the same time produced a clear improvement in swallowing performance compared to sham.

Conclusions: Normal swallowing leads to activation within brainstem and cortex. Altered sensation may suppress or enhance this activity. "Beneficial" sensory stimulation at the optimal parameters, leads to greater activation of areas of brain functionally important for swallowing. When this is applied to dysphagic stroke patients, cortical activity is also enhanced, predominantly in the undamaged hemisphere, and a clear improvement in swallowing performance is produced. Sensory stimulation therefore provides us with a new and exciting, physiologic technique for managing dysphagia, particularly after stroke.

415 ADMISSION BLOOD LACTATE IS PREDICTIVE OF OUTCOME IN PARACETAMOL INDUCED ACUTE LIVER FAILURE

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Background: The Kings College (KCH) criteria select patients with paracetamol induced acute liver failure (ALF) for transplantation (OLT) but have limited sensitivity and may identify patients too late for successful OLT. In a large cohort of ALF patients we have determined threshold values of blood lactate to best identify non-survivors and have applied these to a second prospective sample of patients, comparing prognostic accuracy and speed of identification with the KCH criteria.

Patients and Methods: L-lactate was determined in whole arterial blood using an automated analyser. In the initial sample of 103 patients (35 non-survivors, 10 OLT) threshold values of blood lactate 4 and 12 hours after admission were determined by ROC techniques and logistic regression. These were applied to the

validation sample of 107 consecutive patients (21 non-survivors, 8 OLT) and diagnostic performance compared to the KCH criteria. Assessment of prognostic accuracy of utilised standard measures and likelihood ratios (LR).

Results: Initial sample blood lactate was higher in non-surviving patients at 4 hours (8.5 mMol/l (range 1.7–21) vs. 1.4 mMol/l (0.53–7.9), $p < 0.0001$) and 12 hours (5.5 (1.3–18.6) vs. 1.3 mMol/l (0.26–3.2), $p < 0.0001$). 4 hour level with maximal sensitivity and specificity was 3.5 mMol/l, and 12 hour 3.0 mMol/l. Application to the validation sample identified non-surviving patients earlier (4 versus 12 hrs $p < 0.001$) and with equivalent accuracy to the KCH criteria. The addition of 12 hour lactate of > 3 mMol/l to KCH criteria raised sensitivity from 76% to 91%.

Abstract 415, Table 1

Indicator	n	died	Sensitivity	Specificity	Accuracy	PLR	NLR
A. 4 hr Lactate > 3.5	18	14	67	95	89	13	0.35
B. 12 hr lactate > 3	18	16	76	97	93	30	0.24
C. Either A or B	21	17	81	95	92	16	0.21
King's Criteria	20	16	76	95	91	15	0.25
Kings and B	24	19	91	94	93	14	0.1

PLR: positive likelihood ratio, NLR: negative likelihood ratio.

Conclusions: Blood lactate levels rapidly and accurately identify non survivors of ALF, and their measurement is likely to improve the speed and accuracy of selection of appropriate candidates for transplantation.

416 THE PREVALENCE OF COELIAC DISEASE IN PATIENTS FULFILLING THE ROME 2 CRITERIA FOR IRRITABLE BOWEL SYNDROME: A CASE CONTROL STUDY

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Background: European studies suggest that up to 20% of the population suffer with irritable bowel syndrome (IBS). The diagnosis is made by fulfilling symptom based criteria and the exclusion of organic pathology. Coeliac disease (CD) is thought to affect 1 in 2–300 individuals. CD can present with GI symptoms but alternative manifestations are increasingly recognised. No published studies have assessed the prevalence of CD in IBS.

Aim: To determine the prevalence of CD in patients fulfilling the ROME 2 criteria for IBS.

Methods: Data was collected prospectively from a single university centre from January 99 to October 2000. 300 patients who fulfilled the Rome 2 criteria had their IgG/IgA antigliadin and antiendomysial (EMA) antibodies checked. Patients with any positive antibody were offered duodenal biopsy. 300 healthy volunteers without IBS served as age and sex matched controls (C). In this cohort individuals positive for IgA gliadin or EMA were biopsied.

Results: IBS group: n=300 (214 female. Mean age 45.4 Median 56. Range 18–87). Controls (214 female. Mean age 45.4 Median 56).

Abstract 416, Table 1

	-ve ab	IgG only	IgA only	IgA/IgG	EMA	EMA/IgG	EMA/IgA	All 3 abs
IBS	234	49	4	1	6	4	1	1
C	256	41	1	0	0	2	0	0

Of the 66 IBS patients with positive antibodies. There were 14 cases of CD (11/12 EMA positive, 1 EMA positive patient declined a biopsy). 3 patients with CD were lost to follow-up/declined biopsy and 43 had normal duodenal mucosa. There were 2 EMA positive cases of CD from the controls ($p = 0.004$, Odds ratio 7.3 [95CI 1.6–32.4] chi-squared test for independence).

Conclusion: This is the first study to assess the prevalence of CD in patients with IBS (4.7%). Patients with IBS should be routinely screened for CD. Using only EMA 20% of cases would have been missed.