925 LOVASTATIN IMPROVES SURVIVAL AND LIVER FUNCTION IN ACUTE LIVER INSUFFICIENCY INDUCED BY 90% PARTIAL HEPATECTOMY IN RAT OR TYLENOL OVERDOSE IN MICE. SR Cai, K Motoyama, SC Kennedy, MW Flye, and KP Ponder. Dept. of Internal Medicine, and Surgery, Washington University School of Medicine, MO.

Liver insufficiency occurs when the liver cannot perform critical functions such as gluconeogenesis or ammonia metabolism. It was shown previously that activated p21-Ras inhibits several liver-specific functions in hepatocytes *in vivo*. p21-Ras is probably activated during liver regeneration, as both upstream and downstream signal transduction proteins are activated. The hypothesis of this study is that drugs might improve the function of surviving hepatocytes in fulminant hepatic failure by inhibiting p21-Ras-mediated signal transduction. Lovastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor that inhibits the synthesis of lipid molecules that are added posttranslationally to p21-Ras and are required for signal transduction. After 90% partial hepatectomy (90% PH) in rats, 20 mg/kg/day of lovastatin increased survival to 58% (*vs.* 6% in controls that received 90% PH without drug), increased the nadir of glucose to 87 mg/dl (*vs.* 57 in controls), and decreased the peak ammonia levels to 427 μM (*vs.* 846 in controls). The full survival and metabolic benefit was observed when the first dose of lovastatin was given at 30 minutes after 90% PH, although starting lovastatin at 2 hours or later had less or no benefit. We also tested the effect of lovastatin in tylenol-induced liver failure in mice. Mice that received 1,000 mg/kg of tylenol I.P. had a survival rate of 10%. Administration of lovastatin p.o. at 30 min after tylenol improved survival to 50%. The nadir of glucose was 114 mg/dl for lovastatin-treated animals (*vs.* 68 in controls that received tylenol without lovastatin), and the peak ammonia levels were 319 μM (*vs.* 918 in controls). Lovastatin decreased hepatocellular necrosis induced by tylenol, as demonstrated by liver pathology and SGPT levels. We conclude that lovastatin might be used to improve the function of existing hepatocytes in humans who undergo resection of large amounts of their liver. Although lovastatin also improves liver function and survival in mice after tylenol overdose, it is currently unclear if the function of existing hepatocytes is improved, or if this effect is due simply to decreased hepatocellular necrosis.

926 **ADMINISTRATION OF GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF) TO ACUTE LIVER FAILURE PATIENTS REVERTS NEUTROPHIL DEFECTS.** **Rolando N, Clapperton M. Institute of Liver Studies and, Kings' College School of Medicine and Dentistry , London, UK.**

Neutrophil function is defective in acute liver failure (ALF), and the *in vitro* ability of G-CSF to reverse these defects has been demonstrated (Ref 1). This study evaluates the *in vivo* effects of G-CSF on neutrophil function in patients with ALF due to acetaminophen overdose. Eight ALF patients who did not receive G-CSF were compared to four groups of ALF patients (n=6) who received G-CSF (Lenograstim ®) as a daily infusion at dosages of 25, 50, 100 or 150 mcg/m^2. Neutrophil phagocytosis and killing of *Staphylococcus aureus* and fMLP-stimulated superoxide release were measured on admission and at 96 hours in all patients. Results are expressed as mean ± standard error.

Results:

G-CSF mcg/m^2		no G-CSF	25	50	100	150
Phagocytosis %	adm	45±10	78±6	43±10	38±7	48±10
	day 4	38±8	85±4	73±9*	77±9*	80±2*
Total kill %	adm	35±9	69±5	35±9	24±6	35±8
	day 4	34±7	77±6	63±7*	60±11*	68±4*
Superoxide	adm	363±83	221±58	308±17	231±65	209±31
nmol/10^{6}cells	day 4	198±26	383±41*	592±99*	318±82*	329±45*

***p<0.05 compared to baseline value**

When no G-CSF was given, and in the group who received G-CSF at 25 mcg/m^2, phagocytosis and killing was unchanged at 96 hours. However G-CSF at doses of 50, 100 and 150 mcg/m^2, significantly increased phagocytosis, killing, and superoxide production at 96 hours. These results encourage studies to determine the value of G-CSF in the prevention and treatment of infection in ALF patients.

Ref: Effect of granulocyte colony stimulating factor (G-CSF) on neutrophil function in patients with acute liver failure. Rolando N et al. J Hepatol 1996;25:100.

927 BIOARTIFICIAL LIVER TREATMENT OF ACETAMINOPHEN-INDUCED FULMINANT HEPATIC FAILURE. P Ting, O Detry, N Arkadopoulos, E Kahaku, FD Watanabe, J Rozga, C J-P Mullon, AA Demetriou. Liver Support Unit, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, Circe Biomedical, Inc., Lexington, MA.

Acetaminophen overdose can lead to fulminant hepatic failure (FHF). When the patient fulfills criteria established at King's College Hospital, the probability of patient death without orthotopic liver transplantation (OLT) is 90% despite optimal medical management. However, OLT is often not available because of organ shortage. There is thus a need to develop means of liver support to either "bridge" to OLT or allow recovery without transplantation. We have developed a bioartificial liver (BAL) utilizing plasma perfusion through a bioreactor loaded with 5 billion of porcine hepatocytes and a column with cellulose-coated activated charcoal. The BAL was used in 8 consecutive patients admitted to our hospital with acetaminophen-induced FHF (7 female and 1 male patient, age: 13-50 years), all fulfilling King's College criteria for emergent OLT (Table).

pH	INR	Creatinine (μM/L)	Encephalopathy (grade; Trey)	max. ICP (mm Hg)
7.07	11.3	115	4	32
7.13	7.0	212	4	52
7.10	4.8	476	4	12
6.96	9.3	229	4	49
7.05	12.9	238	3	N/A
7.23	5.1	88	4	51
7.13	4.0	273	3	N/A
7.15	15.7	203	4	45

Additionally, 5/8 patients had episodes of intracranial hypertension with intracranial pressure (ICP) in excess of 30 mmHg. The patients received 2-4 BAL treatments, each lasting 6 hours. Results: In patients with intracranial hypertension, the ICP was lowered (20.5±3.1 at the start of BAL treatment vs. 15.5±1.8 at the end; p<0.04). All patients enjoyed neurological improvement, as judged by the comprehensive level of consciousness score (28.0±2.2 vs. 32.6±2.0; p<0.0006). After BAL treatments, 5 patients recovered without OLT and 3 patients were successfully "bridged" to OLT and were discharged from the hospital.
In conclusion: BAL therapy has a potential as a definitive therapeutic modality in patients with acetaminophen-induced FHF.

928 **SERUM BILE ACIDS IN PATIENTS WITH ACUTE HEPATIC FAILURE SUPPORTED WITH A BIOARTIFICIAL LIVER** P Pazzi, M Muraca°, E Morsiani^, MT Vilei°, J Rozga* and AA Demetriou*, Depts of Gastroenterology and ^Surgery, St. Anna Hospital, Ferrara, Italy, °Dept of Internal Medicine, University of Padua, Italy and *Dept of Surgery and Liver Support Unit, Cedars-Sinai Medical Center, Los Angeles, CA, U.S.A.

Acute hepatic failure (AHF) is associated with elevated serum bile acid (BA) levels and with increased ratio of dihydroxy to trihydroxy BAs, which means a more hydrophobic BA pool (more hepatotoxic and harmful for cell membranes). A bioartificial liver (BAL), consisting of a hollow-fiber cartridge filled with microcarrier-attached porcine hepatocytes and a charcoal column, has recently been shown to efficiently handle bile acids *in vitro*, but information about the effect of the BAL on individual BAs *in vivo* is still lacking. We evaluated serum BA levels, by gas-chromatography mass-spectrometry, in 18 patients with AHF before and after 6 hours of BAL treatment: 13 patients with fulminant hepatic failure (FHF) and 5 patients with acute exacerbation of chronic liver disease (ACLD). Pre-BAL total serum BA levels were higher in ACLD than in FHF patients (452.8± *vs* 182.1 μmol/L, p<0.05), but no significant differences in the composition of BAs pool were observed between the two groups. At the end of the treatment, in 5 patients hyodeoxycholic acid was found in trace amounts. After BAL treatment total serum BA levels were significantly (p<0.01) reduced in both groups (mean decrease: -38.8% in FHF, -35.8% in ACLD). After BAL, in FHF patients a significant reduction of lithocholate (p<0.001), deoxycholate (p<0.05), chenodeoxycholate (p<0.05) and cholate (p<0.05) levels was observed. The ratio of dihydroxy to trihydroxy BAs was significantly reduced after BAL (from 4.8±0.8 to 3.1±0.4, p<0.05). In ACLD group, the levels of all individual BAs were reduced after BAL, but the reduction was significant only for lithocholic acid (p<0.01). Also in this group a reduction of the ratio of dihydroxy to trihydroxy BAs was observed (from 4.7±1.9 to 3.3±0.22, p NS). These results confirm the ability of the BAL to clear BAs from the circulation *in vivo*. BAL treatment, reducing the ratio of dihydroxy to trihydroxy BAs, decreases the hydrophobicity, and thus reduces also the citotoxicity, of the BAs pool. These properties could contribute to the beneficial clinical effects previously reported in patients with AHF supported with the BAL.