925 LOVASTATIN IMPROVES SURVIVAL AND LIVER FUNCTION IN ACUTE LIVER INSUFFICIENCY INDUCED BY 90% PARTIAL HEPATECTOMY IN RAT OR TYLENOL OVERDOSE IN MICE. SC Ga, K Motokama, SC Kennedy. MD, F. Kennedy, and KP Pender. 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 increased 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. 17% in controls that received 90% PH without drug), increased the mean of glycine to 87 mg/dl (vs. 57 in controls), and decreased the peak aspartate levels to 427 μl (vs. 846 in controls). The full survival and metabolic benefits were 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 PH had a survival rate of 10%. Administration of lovastatin p.o. at 30 min after tylenol improved survival to 50%. The rate of glycine was 114 mg/dl for lovastatin-treated animals (vs. 68 in controls that received tylenol without lovastatin), and the peak aspartate levels were 319 μl (vs. 918 in controls). Lovastatin decreased hepatic 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 the effect is due simply to decreased hepatocellular necrosis.

926 ADMINISTRATION OF GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF) CAN REVERSE THE FULMINANT LIVER FAILURE PHENOTYPE REVERSES NEUTROPENIC DEFECTS. Roland N, Clappenber, M, Institute of Liver Studies and, King's 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 (Hu 1). This study evaluates the in vivo effects of G-CSF on neutrophil function in patients with ALF due to acetaminophen overdose. Eight ALP patients who did not receive G-CSF were compared to four groups of ALP patients (w/ or w/o) who received G-CSF (Lenograma $81$) as a daily infusion at doses of $25, 50$, or $150$ mg/kg. Neutrophil phagocytosis and killing of Staphylococcus aureus and FML-stimulated superoxide release were measured on admission and at 94 hours in all patients. Results are expressed as mean ± standard error.

Results:

- **G-CSF mg/kg**
  - n= 25, 50, 100

- **Phagocytosis % adn
  - Day 4 38±8
  - Day 7 84±4
  - Day 10 75±9

- **Total kill %
  - Day 7 35±6
  - Day 10 23±6
  - Day 14 18±6
  - Day 21 10±6

Supersoxide adn
  - 36±8 22±8 15±8 11±8

- **p=0.05 compared to baseline value**

927 BIDIFATURAL LIVER TREATMENT OF ACETAMINOPHEN- INDUCED FULMINANT HEPATIC FAILURE. E. Win, O. O. Deery, N. Adams, F. C. Michael, AA Demetrio. Liver Support Unit, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, Circa 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 performed 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 biobifaturation liver (BAL) utilizing perfusion through a bioreactor loaded with 5 billion of porcine hepatocytes and a column with calfshing-coated activated charcoal. BAL liver used in 4 patients admitted to our hospital with acetaminophen-induced FHF (7 female and 1 male patient, age: 15-50 years), all fulfilling King's College criteria for emergent OLT (Table).

<table>
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<tr>
<th>pH</th>
<th>INR</th>
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<th>Urine</th>
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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, lasting 6 hours. Results: In patients with intracranial hypertension, the ICP was lowered (20±2±1.1 at the start of BAL treatment vs. 15.5±2.8 at the end, p=0.04). All patients enjoyed neurological improvement, as judged by the comprehensive level of consciousness score (28±0.5±2 vs. 32±0.5±6; p<0.0006). After BAL treatment, 2 patients received without OLT and were successfully "bridged" to OLT and 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 BIDIFATURAL LIVER: PRELIMINARY RESULTS. U. Murer, E. Horsman, M. Vitek, J. Roga, and AA Demetrio. Dept 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 rat 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 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 was observed between the two groups. At the end of the treatment, in 5 patients hyperoxocholic 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, -35.9% in ACLD). After BAL in FHF patients a significant reduction of lithocholate (p<0.001), deoxycholate (p<0.05), chenodeoxycholate (p=0.05) and cholic (p=0.05) levels was observed. The ratio of dihydroxy to trihydroxy BAs was significantly reduced after BAL (from 2.4±0.2 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 lithocholate (p<0.05). All in all, in this group a reduction of the ratio of dihydroxy to trihydroxy BAs was observed (from 4.7±1.3 to 3.3±2.2, p<0.05). These results confirm the ability of the BAL to clear BAs from the circulation in vivo. In BAL treatment, reducing the ratio of dihydroxy to trihydroxy BAs, decreases the hydrophilicity, and thus reduces also the cytotoxicity, of the BA pool. These properties could contribute to the beneficial effects previously reported in patients with AHF supported with the BAL.