# HIGHLIGHTS FROM THE AASLD MEETING


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AASLD | American Association for the Study of Liver Diseases

# The Liver Meeting® 2006

## Boston

# What was on at the meeting?

1. Postgraduate Course
2. Oral Presentations
3. Poster Presentations
4. Research Workshops
5. State of the Art Lectures
6. Early Morning Workshops
7. Meet the Professor Lunches
8. Satellite Symposia

# What was on outside the meeting?

# Postgraduate Course 2006

## Mechanisms of Liver Injury In Emerging Therapies

# Genetics in Liver Disease: Hepatic Fibrosis

Brenner

# Overview

- Host genetic factors are more important then environmental factors in determining the severity of chronic liver diseases
- Association studies have identified many SNPs that correlate with the severity of fibrosis

# Environmental risks for advanced fibrosis in HCV

- **Associated:**

1. Males
2. Alcohol
3. Older age
4. Insulin resistance

- **Not associated:**

1. Viral load
2. Genotype

# Genetic risks for advanced fibrosis in HCV

- **Associated:**

1. HFE
2. TGF-Beta1
3. Angiotensin
4. C5
5. Factor-5 Leiden
6. Interleukin-10 receptor polymorphism

# HCV Fibrosis: Effect of HFE genotype on fibrosis

| Kowdley 2003 | **Bridging fibrosis or cirrhosis** (Odds ratios) | **p value** |
|---|---|---|
| **C282Y/WT** | 30 | 0.02 |
| **H63D/WT** | 22 | 0,02 |

# How hepatitis C injures the liver

Rosen

# Overview

- The virus inhibits apoptosis promoting chronic infection and increasing the risk of liver cell cancer
- Stellate cells can be directly effected by HCV proteins to become profibrotic
- Cytotoxic T kill infected hepatocytes but the cytokines released damages the liver
- NK cells also kill infected hepatocytes but also have protective as well as antifibrotic effects

# Apoptosis in HCV

1. Histology
2. Caspase cleavage epitope of CK-18
3. HCV core protein:  Found everywhere and does everything
4. NS3/4A: cleaves MAVS therefore inhibiting apoptosis
5. NS5A inhibits apoptosis
6. Fas  and FAS ligand levels increased
7. Trail  and fat leads to apoptosis

# Mechanisms of liver injury due to fat

Maher

# Mechanisms of liver injury due to fat

- Fat is a cytotoxic agent
- Fatty change triggers hepatic insulin resistance
- Fat  causes microcirulatory disorder
- Fat stimulates hepatic fibrosis

# Fat is a cytotoxic agent

- Fatty acids activate apoptosis pathways
- Fatty acids induce destabilization of lysosomes  and TNF
- Fatty acids induce activation of Jun-N terminal kinase
- Steatosis inhibits mitochondrial function
- Steatosis induced CYP2E1

# Fat stimulates hepatic fibrosis

- Oxidant stress
- Fat related cytokines (adipokines)

Leptin +++

Osteopontin +

Adiponectin ++/--

- Angiotensin II +++

# State of the Art Lectures

Hans Popper Basic Science Lecture

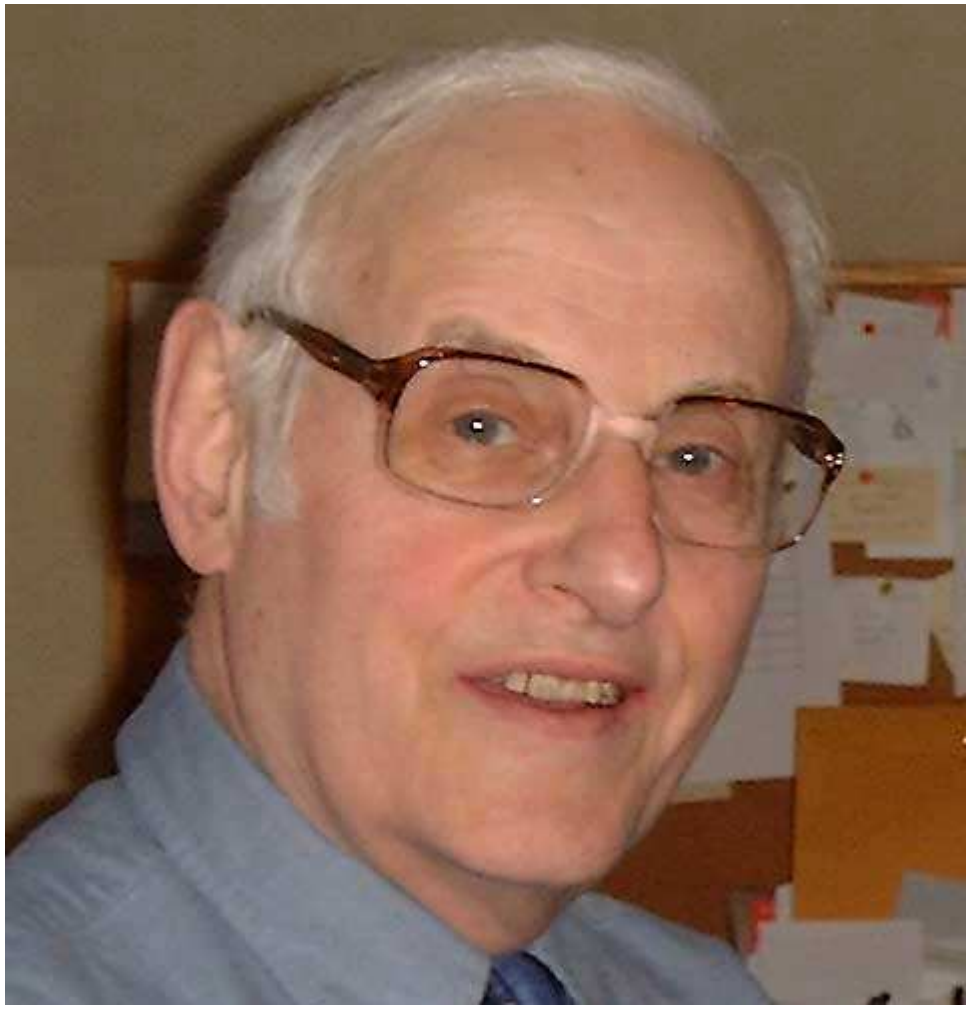
# Hepatic immune responses: Pathology and tolerance

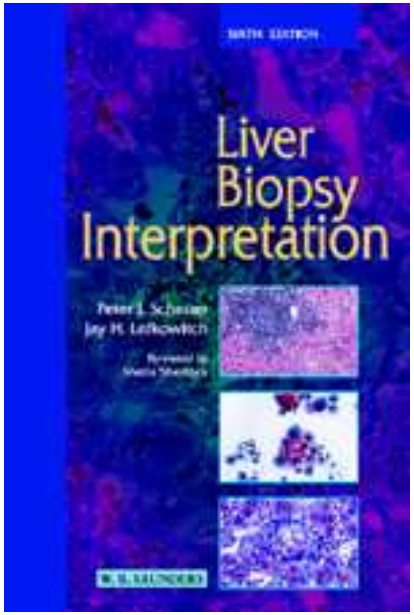
Crispe

# Why does the liver inhibit immune responses?

1. Direct activation of T cells by antigens expressed by hepatocytes leads to proliferation of CD8 positive T cells only
2. Low levels of endotoxin causes Kupffer cells to produce IL-10

# Peter Scheuer 1928-2006





Hyman J Zimmerman Lecture

# Drug-induced Liver Disease: **The Risk Profile of Statins**

Dr. Will Maddrey

# Statins and the liver

- HMG-CoA reductase inhibitors
- 14.5 million prescriptions per year
- Increased AST in 0.5%, no increased bilirubin
- Liver failure in $1/10^6$
- May be value in NASH
- Inhibits HCV replication!

# Abstracts

1346 !

# AI hepatitis

# #107

# IMPROVING THE END POINT OF CORTICOSTEROID THERAPY IN TYPE-1 AUTOIMMUNE HEPATITIS

# #107

- 122 patients with definite type 1 AIH were treated with conventional corticosteroid therapy until the liver biopsy showed:

1. Normal liver or
2. Portal hepatitis or
3. Inactive cirrhosis

#207

# PREVALENCE AND MANAGEMENT OF AUTOIMMUNE HEPATITIS IN THE SETTING OF CHRONIC HEPATITIS C

# #207

- The prevalence of AI hepatitis in patients with HCV is unknown
- ALT flare > 5xULN and/or histological features of AI hepatitis
- 6/704 patients, all female
- Positive ANA or SMA non-specific
- Treatment needs to be individually tailored in this group of patients

# #107

- Patients with normal AST, gamma-globulin or IgG had lower relapse rates than others
- Histological findings must be correlated with clinical ones in determining the optimal endpoint of treatment

# Fatty liver disease

# #697

- **FIBROSIS PROGRESSION OCCURS IN A PARTICULAR SUBGROUP OF HEAVY DRINKERS WITH TYPICAL HISTOLOGICAL FEATURES**

# #697

- 193 heavy drinkers with consecutive liver biopsies
- Mean follow up = 3.51 (+/-0.18) years

# #697

- In a multivariate analysis the following were the only independent predictors of fibrosis score in the second biopsy:

1. Steatosis (r=0.42)
2. Alcoholic hepatitis (r=0.74)
3. Stage of fibrosis in the first biopsy (r=0.69)

# #32

- **RELATIONSHIP BETWEEN SEVERITY OF STEATOSIS AND OTHER HISTOLOGICAL FEATURES OF STEATOHEPATITIS IN NAFLD**

# #32

- 331 liver biopsy specimens with fatty change
- Steatosis categorised as mild, moderate or severe
- The features of NASH were scored according to the NASH CRN standardized system

# #32

- **There was a significant association between the severity of fatty change and:**

1. lobular inflammation,
2. zone 3 fibrosis and
3. definite NASH

- This supports the 2 hit hypothesis

# #189

- **COMPARISON OF ADULT AND PAEDIATRIC NAFLD – CONFIRMATION OF A SECOND PATTERN OF PROGRESSIVE LIVER DISEASE IN CHILDREN**

# #189

- Alternative pattern of NAFLD in childen:

1. Marked steatosis
2. Portal-based fibrosis
3. Little or no ballooning Mallory's hyaline

- 288 adults and 76 children
- 10 hepatopathologists scored them according to the NASH CRN

# #189

- Confirmed that this pattern of liver disease is commoner in children ( only seen 1% of adults)
- Not explained by differences in sex or race/ethnicity
- Prospective studies are required

# #1238

- **SYSTEMATIC REVIEW OF FIBROSIS PROGRESSION IN NASH**

# #1238

1. Search of Medline etc.
2. No treatment of histological benefit
3. 2 liver biopsies at least a year apart

# #1238

- 9 studies
- 194 patients
- 34.4% had stage 3 / 4 fibrosis on initial biopsy
- Follow up: 3.2 - 8.1 years

# #1238

- Fibrosis progressed: 37.6%
- Fibrosis regressed : 20.6%
- Mean fibrosis progression 0.10 fibrosis units/year
- *Risk factors for fibrosis progression*:

1. BMI>25
2. Diabetes
3. Increased AST

# HIV

# #164

- **SIGNIFICANT LIVER DISEASE PROGRESSION AMONG HIV/HCV COINFECTED PERSONS WITH MINIMAL FIBROSIS ON THE INITIAL LIVER BIOPSY**

# #164

- In patients with HCV current guidelines suggest that treatment may be deferred when the biopsy shows minimal fibrosis
- 177 coinfected patients had sequential liver biopsies (median interval 2.91 years)
- Scored using the modified HAI system
- 10 patients with cirrhosis on the initial biopsy were excluded

# #164

- Fibrosis *increased* in 22%  of patients by 2/>
- Fibrosis *decreased* in 6.5% of patients by 1/>
- Suggests that coinfected patients with mild fibrosis should be actively considered for treatment
- No details provided as to the relationship to treatment

#898

# HEPATOPORTAL SCLEROSIS IN HIV INFECTED PATIENTS: POSSIBLE ROLE OF DIDANOSINE

# #898

- **Hepatoportal sclerosis:**

1. Portal hypertension
2. Patent portal vein
3. No morphological evidence of cirrhosis
4. No other cause for liver disease

# #898

- 7 patients
- 3 presented with evidence of portal hypertension
- All biopsies showed obliteration of central veins
- All had received Didanosine

# 688

**THROMBOPHILIA-ASSOCIATED NODULAR REGENERATIVE HYPERPLASIA:**

A NEW CAUSE OF NON-CIRRHOTIC PORTAL HYPERTENSION IN HIV INFECTED PATIENTS

# #688

- 7 patients with HIV (but not viral hepatitis)
- **Screened for thrombophilia**:

1. Protein C deficiency
2. Protein S deficiency
3. Factor V Leiden
4. II G20210A
5. Lupus anticoagulant
6. Antiphospholipid antibodies

# #688

- 6/7 biopsy proven nodular regenerative hyperplasia
- All were receiving HAART
- All patients had had least 1 clotting abnormality – Protein S deficiency is the commonest

# Hepatitis

# #430

- **STEATOSIS IS ASSOCIATED WITH INTRAHEPATIC HCV RNA LEVEL IN GENOTYPE 3 CHRONIC HEPATITIS**

#295

# THE ROLE OF HEPATITIS C GENOTYPE 3 CORE PROTEIN DOMAIN 3 IN INTRAHEPATIC STEATOSIS

# #295

- Amino acid polymorphisms at residues 182/186 within domain 3 of HCV core correlates with steatosis
- L and I / F and V: fat
- F and I: no fat

# #1250

- **IMPACT OF NON-ALCOHOLIC LIVER DISEASE ON CHRONIC HEPATITIS B**

# #1250

- The impact of NAFLD on chronic HCV has been established
- 63 biopsies from patients with chronic HBV (and with no excess alcoholic intake were studied)

# #1250

**Conclusions:**

1. The presence of NAFLD was associated with components of the metabolic syndrome
2. Fibrosis was no more advanced in patients with NAFLD than those without

# #633

- **THE DEVELOPMENT OF HEPATIC GRANULOMAS IN PATIENTS RECEIVING PEGYLATED INTEFERONS FOR RECURRENT HCV POST LIVER TRANSPLANTATION**

# #633

- 10,225 biopsies were examined
- Lipogranulomas were excluded
- 25 non caseating epithelioid granulomas in 14 patients
- None of these patients had a granuloma on a pre-treatment biopsy
- 9/14 had received PEG INF
- 6/9 had undetectable HCV RNA

# #633

- The presence of granulomas in recurrent HCV does not warrant an etiologic workup for granulomatous hepatitis unless clinically indicated”

# Carcinoma

# #858

- **SIGNIFICANCE OF HEPATOCYTE PARAFFIN-1 EXPRESSION IN HUMAN INTRAHEPATIC CHOLANGIOCARCINOMA**

# #858

- 48 patients with intrahepatic cholangiocarcinoma
- Double staining with Hep Par-1 and CK7 and CK 19 ( markers of biliary differentiation)
- Staining for other hepatocyte markers (e.g. alpha fetoprotein) and stem cell markers (CD45 and CD 117

# #858

- 8 cases positive for Hep Par-1
- All of these were double positive for CK7
- All of these were positive for other hepatocyte markers
- Some focally positive for CD117
- More commonly had underlying chronic liver disease

# #858

- **Conclusions:**

1. Some ICC have features of HCC
2. Supports the idea that some liver cell cancers arise from stem cells

# #840

- **DOES COFFEE DRINKING PROTECT CIRRHOTIC PATIENTS AGAINST HEPATOCELLULAR CARCINOMA?**

# #840

- Cirrhosis was less common in coffee drinkers (more than 2 cups per day)
- Coffee drinking does not protect patients with cirrhosis against developing hepatocellular carcinoma

# Miscellaneous

# # 506 and #507

**PROSPECTIVE AUDIT OF LIVER BIOPSY PRACTICE: IS BIGGER BETTER?**

**and**

**PATIENT EXPERIENCE OF DAY CASE LIVER BIOPSY: PROSPECTIVE AUDIT**

# Trucut 18G vs. Menghini 15G (0.85mm) (1.35mm)

- 128 cases (49 and 79 respectively)
- No clinical differences in the 1,6 and 12hr pain scores
- No episodes of shock
- Only 1 readmission

| | Trucut 18G (49) | Menghini 15G (79) | P value |
|---|---|---|---|
| **Single pass** | 63% | 83% | |
| **length (mm)** | 15.8 | 25.8 | <0.001 |
| **Number of portal tracts** | 6 (2-12) | 8 (2-30) | <0.001 |
| **% ≥6 portal tracts** | 51% | 73% | 0.11 |
| **% ≥10 portal tracts** | 6% | 39% | <0.001 |

# #464

# LIVER REGENERATION IN ACUTE SEVERE LIVER FAILURE:

# A CLINICOPATHOLOGICAL CORRELATION

# #464

- 74 patients  with severe acute liver failure
- Stained with H and E and Mib1

# #464

- Threshold of 50% hepatocyte loss *and* significantly decreased proliferative activity in those remaining was necessary for extensive hepatic progenitor cell activation
- Activation occurs within 1 week
- Intermediate hepatocytes were seen after 1 week
- Extensive activation of hepatic progenitor cells and extensive hepatocyte loss were independent predictors of  poor outcome

# Surrogate Measures of Fibrosis

- Serum markers (FibroTest, ELF etc.)
- Liver stiffness (Elastography)
- Breath tests (13c-methacetin)

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### Highlights

- **Endpoints Single Topic Conference**
  December 8-9, 2006
- **Hepatitis Single Topic Conference**
  March 1-3, 2007
- **Hepatology Training Programs**
  Compiled list of hepatology training programs in the US and Canada.

**Members and Visitors**

Log-In ›

### Patient Resources

Information relating to liver diseases and treatment.

Find a hepatologist in your area.

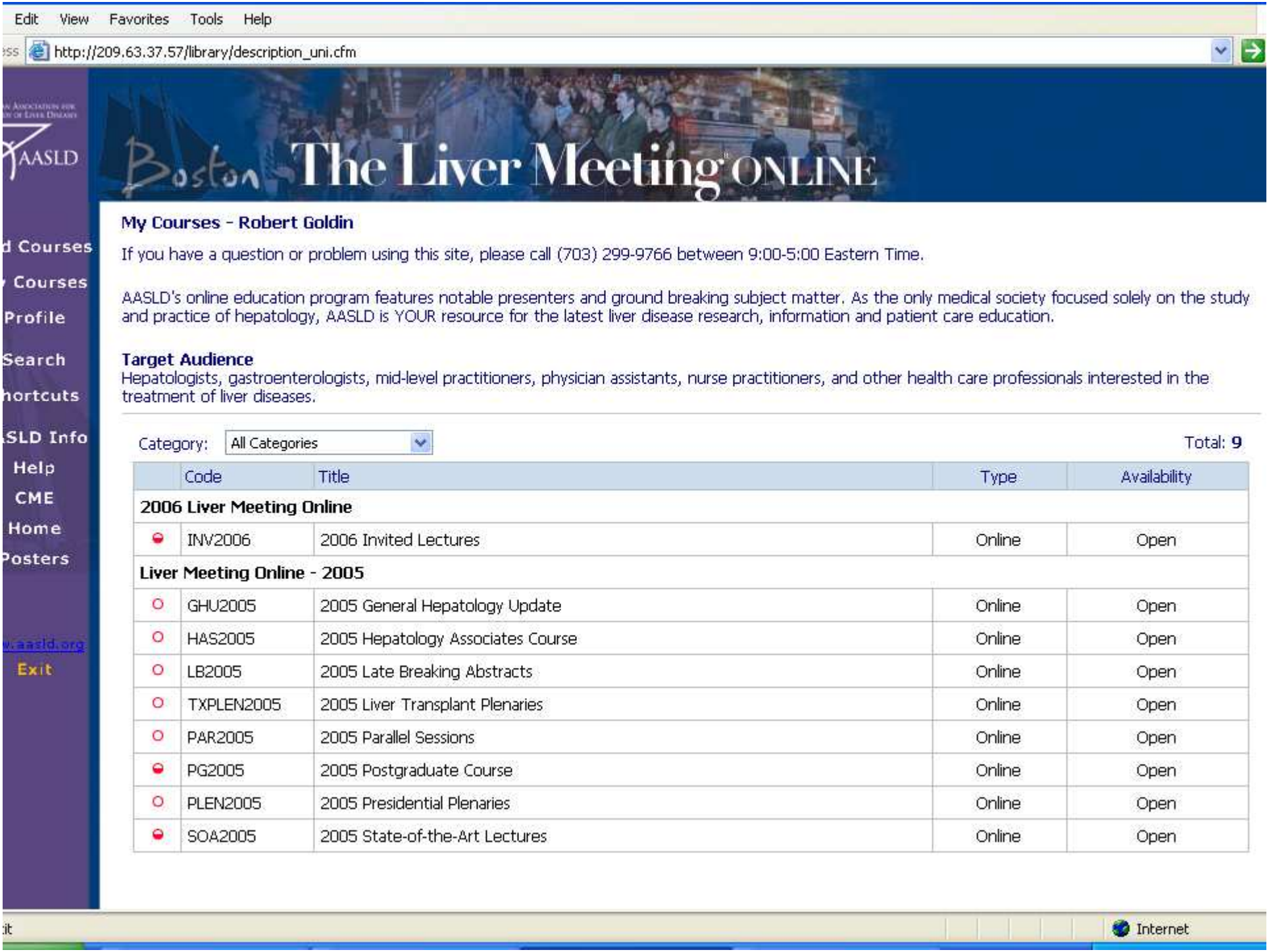
### Research Center

Information and events at NIH and AASLD supported research awards.

### Research/Career Dev. Awards

**2007 American Association for the Study of Liver Diseases (AASLD) NP/PA Clinical Hepatology Fellowship Program**- Application Deadline: February 15, 2007. More

Internet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Target Audience
Hepatologists, gastroenterologists, mid-level practitioners, physician assistants, nurse practitioners, and other health care professionals interested in the treatment of liver diseases.
Category: All Categories
Total: 9
Code
Title
Type
Availability
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# The *Next* Liver Meeting

Boston 2007

November 2nd -7th