

# HEPATITIS 2006

*Hôtel de l'Indépendance, Dakar, Senegal*

*Saturday, February 25<sup>th</sup> to Monday, February 27<sup>th</sup>, 2006*

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## **Running Order of Oral Presentations**

1st – Dennis Revie (1)	6th – Olusegun Ojo	11th – Farid Badria
2nd – Otedo Amos	7th – Maurizio Bonacini (1)	12th – Tomas Hanke
3rd – Brian Carr	8th – Gerlinde Teuber	13th – Flavio Lirussi
4th – Maimuna Mendy	9th – Dennis Ndububa	14th – Dennis Revie (2)
5th – Olumuyiwa Odusanya	10th – Maurizio Bonacini (2)	15th – Roland Strand

## **Titles/Abstracts of Presentations / Summaries of Participants**

Listed Alphabetically by Family Name [ Number and/or Type of Presentation(s) in Parentheses ]

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### **Otedo Amos [ Oral 2 ]**

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**Title: Hepatocellular Carcinoma in Patients with HIV**

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### **Farid Badria [ Oral 11 ]**

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**Experimental and Clinical trial to develop a new natural Endogenous Interferon Inducer for treatment of Hepatitis**

**Farid A. Badria, Ph. D.  
Faculty of Pharmacy, Mansoura University, Mansoura 35516 Egypt**

The immunomodulatory and antiviral bioassay-guided fractionation of the oleogum resin of frankincense (*Boswellia carterii* Birdwood) resulted in the isolation and identification of 9 compounds; palmitic acid and eight triterpenoids belonging to lupane, ursane, oleanane, and tirucallane skeleta were isolated from the resin. These triterpenoids are lupeol,  $\beta$ -boswellic acid, 11-keto- $\beta$ -boswellic acid, acetyl  $\beta$ -boswellic acid, acetyl 11-keto- $\beta$ -boswellic acid, acetyl- $\alpha$ -boswellic acid, 3-oxo-tirucallic acid, and 3-hydroxy-tirucallic acid. The structures of the isolated compounds were deduced based on spectroscopic evidences. The lymphocyte transformation assay of the isolated compounds proved that the total extract retained more activity than that of any of the purified compounds. Biologically, the oil exhibited a strong immunostimulant activity (90% lymphocyte transformation). The Antiviral assay of *Boswellia*, *curcumin*, and *glycyrrhizin formula* (OMNI) proved that the total boswellic acid mixture showed the highest activity against *Herpes simplex* type I virus by reducing the number of the plaques by 100 % with a minimum antiviral at 20  $\mu$ g/ml and followed by glycyrrhizin (75% inhibition at 20  $\mu$ g/ml), curcumin (50% inhibition at 40  $\mu$ g/ml), and Omni (75% inhibition at 30  $\mu$ g/ml).

Moreover the combination of , *glycyrrhizin*, *curcumin* and *Boswellia carterii* proved to exhibit a *hepatoprotective effect* and used as endogenous inteferon inducer, demonstrating that two phases of the induction of IFN in serum takes place; the induced IFN was regarded as IFN- $\gamma$ . This induction may be followed by activation of macrophages and augmentation of natural killer (NK) activity through the action of the induced IFN. This combination was successfully tried in a clinical study as endogenous interferon inducer for treatment of hepatitis C.

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### **Maurizio Bonacini [ Oral 7 & 10 ]**

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#### **Oral 7**

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**Histological and clinical cirrhosis associated with hepatitis C varies according to race-ethnicity**

Race-ethnicity appears to be an important variable in the progression of liver fibrosis in hepatitis C (Am J Gastroenterol 2001;96:2438-41). Little is known of the frequency of cirrhosis and its complications in Asians patients in the U.S. AIM: To compare clinical and histological features of hepatitis C in Asian patients in San Francisco METHODS: Retrospective query of an electronic medical record for non-Caucasian HCV-positive patients evaluated between

1999-2004. We excluded patients who had died or received a liver transplant. Clinical cirrhosis was defined as the presence of any of the following: varices by endoscopy, ascites or splenomegaly (clinically or imaging). Histologic cirrhosis was defined as either advanced stage 3 or 4 fibrosis (Metavir) at biopsy. Chi-square and t-tests were performed where appropriate (Statview) Multivariable (MV) analysis was conducted (SPSS). RESULTS: 439 patients were categorized into 4 racial-ethnic groups: 23 American-Indian (AmInd), 147 Hispanic (H), 123 African-American (AA), 146 Asian (As) patients. Median age of AA (54 years) and As (53) was higher than either H (50) or AmInd (49) ( $p < 0.01$ ). Percentage of males varied from 45% to 54% (NS). BMI was significantly lower in Asians. AmInd and H had the highest percentage of alcohol abuse (61 and 40%) higher than AA (32%) and As (9%) ( $p < 0.0001$ ). Favorable genotypes (non1) were more frequent in AmInd, H and As vs. AA ( $p = 0.003$  table). AST, Albumin, Platelet counts, and INR were not statistically different across groups. A liver biopsy was performed in 52% AmInd, 56% As, 59% H and AA. Twenty percent were found to have cirrhosis (LC): 10% had clinical cirrhosis, 6% had histologic cirrhosis and 4% had both. H and AmInd patients were more likely to have LC compared to AA or As (table). Histologically, H had significantly higher hepatic fibrosis score vs. As. MV analysis showed that female sex had lower OR (OR=0.34, 95% CI 0.2-0.7,  $p < 0.001$ ) and non-Hispanic race had lower risk for LC (OR 0.44, CI 0.3-0.6,  $p < 0.001$ ). Alcohol abuse, genotype were not independently associated with LC.

N=	23 Am Ind	147 H	123 AA	146 As
Median BMI	33	30	28	24 ♠
Genotype non 1	39%	26%	8%	34%
Fibrosis Median (range)	3 (0-4)	2.5 (0-4) ♦	2.25 (0-4)	2 (0-4)
Histologic cirrhosis	13%	20%	4%	5%
Clinical or histological cirrhosis (LC)	26% ♣	35% ♥	10%	13%

♠ $p < 0.0001$  vs. all other groups  
♥ $p < 0.001$  vs. AA and As

♣ $p < 0.05$  vs. AA and As  
♦ $p = 0.01$  vs. As

CONCLUSION: In our cohort, hepatitis C presentation including genotypes and severity of disease varied by race and gender. Using expanded criteria for the definition of cirrhosis (histological and/or clinical) AmInd and H patients were significantly more likely to have cirrhosis than AA and As. Studies assessing racial differences and restricting the definition of cirrhosis to histologic criteria may significantly underestimate the prevalence of cirrhosis.

## Oral 10

Title: HBV Vaccination and Treatment

Brian Carr [ Oral 3 ]

Title: Use of 90-Yttrium Intra-Hepatic Arterial Microspheres for Treatment of Unresectable HCC

Tomas Hanke [ Oral 12 ]

Development of T cell vaccines for HIV-1

Tomas Hanke, Andrew McMichael and Lucy Dorrell

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The main hypothesis we aim to test is that high frequency and/or quality of vaccine-induced HIV-1-specific T cells, in the absence of viral envelope-specific antibody, can substantially improve resistance to HIV-1 infection.

Induction of cell-mediated immunity is the goal of many current vaccine strategies. This is particularly true for pathogens such as HIV-1, against which induction of broadly neutralizing antibodies has proven extremely difficult. Key to determining the character and magnitude of induced T cell responses and their memory are the circumstances of T cell priming. At least in some models, the initial burst size of the primary response determines to a great extent the size of T cell memory, however, the correlation of the magnitude of acute responses and their antiviral efficacy is more complex. This is because the qualities of T cells required to control a particular virus vary depending on the biology of the virus and its interaction with the host immune system. By analogy, the choice of vaccine vectors, route of delivery and vaccine dose determines the characteristics of evoked T cells and may be critical for development of effective anti-viral immunity.

We found initially in mice and confirmed in non-human primates (NHP) that a successive immunization with DNA- and modified virus Ankara (MVA; an attenuated poxvirus)-vectored vaccines expressing a common immunogen is a potent way of inducing immunogen-specific CD8<sup>+</sup> T cell responses. For clinical trials, we constructed immunogen called HIVA, which was derived from consensus sequence of HIV-1 gag clade A and a string of immunodominant CD8<sup>+</sup> T cell epitopes. The DNA.HIVA and MVA.HIVA vaccines have now been tested in several hundreds of healthy and HIV-1-infected subjects in Europe and Africa. These trials showed that the vaccines were safe and while DNA.HIVA alone primed consistently weak and mainly CD4<sup>+</sup>, but also CD8<sup>+</sup> T cell responses, MVA.HIVA delivered a consistent boost to both CD4<sup>+</sup> and CD8<sup>+</sup> T cells, which was particularly strong if the HIV-1-specific T cells were efficiently primed e.g. by HIV-1 infection. Thus, we are currently searching for a means of more efficient T cell priming.

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**Spiridon Kintzios & Antonis Perdikaris [ Poster ]**

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Poster Presentation In Absentia

**Title: EMBIO Sensors Based on Bioelectric Recognition Assay (BERA) for Ultra Rapid and Cheap Detection of Hepatitis: New Wave Diagnostics in the Developing World**

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**Flavio Lirussi [ Oral 13 ]**

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**Hepatitis C virus infection in a resident elderly population: a ten-year follow-up study**

**F. Lirussi**<sup>1</sup>, F. Monica<sup>2</sup>, I. Pregun<sup>2,3</sup>, F. Vasile<sup>2</sup>, L. Okolicsanyi<sup>2,3</sup>

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**Background.** The natural history of hepatitis C virus (HCV) infection in the elderly is poorly known. **Objectives.** To assess the mortality rate, the progression of liver disease, the HCV carrier state and the co-morbidity in a cohort of 35 out of 1063 anti-HCV positive elderly people followed-up prospectively from 1992 to 2002. **Methods.** Liver function tests (LFTs), HCV-RNA analysis, HCV genotyping and abdominal ultrasonography (US) were carried out annually during the first five years of follow-up. At the end of the ten-year period, causes of death were recorded, while surviving patients underwent again a medical examination, routine laboratory tests and abdominal US. **Results.** Twenty-three patients were alive, two (5.7%) died for liver related disease (1 hepatocellular carcinoma, 1 liver failure), and ten (28.5%) passed away for extra hepatic causes. Thirteen patients were HCV-RNA positive, the majority of whom being infected with genotype 2 (69%). Eleven patients had persistently normal ALT levels; five of them died for extra-hepatic causes, the remaining six had asymptomatic HCV infection. In addition, more than half of the surviving patients were suffering from concomitant severe diseases, frequently more than one. Despite the presumably long duration of infection, liver-related mortality was relatively low (5.7%), while extra hepatic mortality was five-folds higher. The slow progression of liver disease in our cohort could be related to the low prevalence of genotype 1b and, possibly, to the low rate of alcohol abuse in this population. **In conclusion,** elderly patients with HCV chronic infection exhibited a rather benign course of their disease, and a strict follow-up does not seem necessary in these patients. It remains to be seen whether these results apply to the cohort studied or can be extended to the elderly with HCV-related liver disease.

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**Maimuna Mendy [ Oral 4 ]**

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**Title: Longitudinal Studies of HBV Infection in The Gambia**

**Maimuna Mendy**

Hepatocellular carcinoma (HCC) is a major cause of death in sub-Saharan Africa and Asia (Kew, 2002). The primary etiologic factors associated with the development of HCC are chronic infection with HBV or hepatitis C virus (HCV), exposure to aflatoxin in the diet [Groopman and Kensler, 2005] or alcohol abuse (reviewed in (Morgan, Mandayam, and Jamal, 2004). Epidemiological studies have shown that whilst aflatoxin exposure and HBV infection are both independently linked to the development of HCC, when both factors are present the risk rises in a geometric fashion (Qian et al., 1994).

HBV infection is endemic in The Gambia, affecting over 90% of Gambians, with 15% of Gambians chronically infected with HBV (Whittle et al., 1990). Due to consumption of aflatoxin contaminated food, greater than 90% of the population have detectable level of aflatoxin-albumin adduct in their serum and the interactions between this dietary aflatoxin

exposure, HBV infection and HCC has been examined (Turner et al., 2000). The combination of aflatoxin exposure plus HBV infection is thought to account for HCC being the most frequent form of cancer in this country (Bah et al., 2001). A Cancer Registry is maintained to document all new cases of HCC and hepatic cirrhosis occurring in the Gambia.

The MRC Laboratories in the Gambia has a long history of aflatoxin, HBV and HCC research. In collaboration with The International Agency for Research on Cancer (IARC) and the Government of the Republic of the Gambia, The Gambian Hepatitis Intervention Study (GHIS) was established here in 1986 and has provided a detailed and valuable assessment of the longterm efficacy of HBV vaccination on HCC (Montesano, 2002). This study has facilitated related efforts examining other HCC risk factors including hepatitis C virus infection, aflatoxin exposure and p53 mutation, and HBV variants. The Unit has examined the epidemiology and genetic factors linked to HCC (Kirk et al., 2004; Kirk et al., 2005b; Whittle et al., 2002; Wild et al., 2000; Wojnowski et al., 2004) as well as the distribution and detection of the aflatoxin-induced S249p53 mutation (Kirk et al., 2000a; Kirk et al., 2005a). The Unit has experience in serum detection of p53 mutations, in viral load measurement, and in HCC diagnosis and biopsy and in diagnostic marker studies (Mendy et al., 2005). An important recent case-control study documented the role of the S249p53 mutation in the progression to HCC, finding the S249p53 mutation in about 40% of tumors from HCC patients, 15% of chronic HBV carriers with cirrhosis and 3.5% of controls (Kirk et al., 2005a)

The natural history of HBV infection within the infected host, particularly the changes in viral load and the host's immune responses are poorly understood. This is in contrast to the long-term pathogenic consequences of chronic HBV, which are liver failure, cirrhosis and HCC. From repeated cross-sectional studies we know that the majority of those who are chronically infected with HBV, who initially had detectable 'e' antigen, appear to lose this during adolescence and young adulthood [Mendy et al., 1999].

To gain more information on the natural history of chronic hepatitis B infection in The Gambia, we recently conducted a longitudinal study in chronic carriers from two villages of Keneba and Manduar. One hundred and sixty chronic carriers, aged between 1-15 years were identified in 1984 and followed at 4 time points (1989, 1993 and 2003) for a period of 20 years [Whittle et al., 2002; Whittle et al., 1991; Whittle et al., 1995]. Blood samples were tested for various HBV markers. Thus the long term changes in serological status, and HBV viral load was charted over a period of between 2.5 to 20 years in individual participants.

An overview of our efforts to understand hepatitis will be provided, with particular attention on the natural course of chronic HBV infection and the changes in viral load and the effect of aflatoxin exposure.

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**Dennis Ndububa [ Oral 9 ]**

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**Title: Prevalence of Liver Disease in Nigerian Asymptomatic HBsAg Carriers – A Preliminary Report**

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**Olumuyiwa Odusanya [ Oral 5 ]**

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**HEPATITIS B MARKERS AMONGST STUDENTS OF THE LAGOS STATE UNIVERSITY COLLEGE OF MEDICINE, IKEJA**

AUTHORS: O.O. ODUSANYA<sup>1</sup>, F.P. MEURICE<sup>2</sup>, B. HOET<sup>2</sup>

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- Objective:** To estimate the prevalence of hepatitis B (HBV) infection amongst medical students of the Lagos State University College of Medicine, Ikeja, Nigeria.
- Methods:** Data was collected through a self-administered questionnaire and blood analysis for the surface antigen, (HBsAg), the “e” antigen (HBeAg), antibodies to the core (antiHBe), surface (HBsAb) and the “e” (HBeAg) antigens.
- Results:** Three hundred and thirteen out of 325 students (96% response rate) participated. The mean age was 24.3 ±3.98 years; 231 (74%) were preclinical students. Only 8 (2.6%) had received three doses of vaccination against HBV. Eighty-one (26%) tested positive for antiHBe; 12 (3.8%) were positive for HBsAg and 57 (18.2%) had protective antibodies to the surface antigen. A significant relationship was

found between those who had a positive family history of hepatitis B in the nuclear family and antiHBc (p=0.03) and increasing age was also significantly associated with HBsAg (P=0.0002). Two hundred and forty-one (77%) were susceptible to the infection and require vaccination.

**Conclusion:** Most of the medical students are susceptible to hepatitis B virus and should be vaccinated on entry to the medical school.

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**Olusegun Ojo [ Oral 6 ]**

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Title TBA, Subject: ASLIN and the Hepatitis Scene in Nigeria

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**Dennis Revie [ Oral 1 & 14 ]**

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**Oral 1**  
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**Transmission of human hepatitis C virus from patients in secondary cells for long term culture and analysis**

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Infection by human hepatitis C virus (HCV) is the principal cause of post-transfusion hepatitis and chronic liver diseases worldwide. A reliable *in vitro* culture system for the isolation and analysis of this virus is not currently available, and, as a consequence, HCV pathogenesis is poorly understood. We report here the first robust *in vitro* system for the isolation and propagation of HCV from infected donor blood. This system involves infecting freshly prepared macrophages with HCV and then transmission of macrophage-adapted virus into freshly immortalized B-cells from human fetal cord blood. Using this system, newly isolated HCV have been replicated *in vitro* in continuous cultures for over 130 weeks. These isolates were also transmitted by cell-free methods into different cell types, including B-cells, T-cells and neuronal precursor cells. These secondarily infected cells also produced *in vitro* transmissible infectious virus. Replication of HCV-RNA was validated by RT-PCR analysis and by *in situ* hybridization. Western blot analysis shows the synthesis of major HCV structural proteins. In order to assess the nature of the *in vitro* replicated HCV, we sequenced the 5'UTR. Comparisons of a 269 bp segment of the 5'UTR from patients and *in vitro* isolates were performed. Extensive analysis of these sequence comparisons will be discussed. We present here, for the first time, a method for productively growing HCV *in vitro* for prolonged periods of time. This method allows studies related to understanding the replication process, viral pathogenesis, and the development of anti-HCV drugs and vaccines.

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**Oral 14**  
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**Title: Comparative Analysis of the 5'UTR of *In Vitro* Replicated HCV and Primary Isolates**

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**Roland Strand [ Oral 15 ]**

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**Title: Jaundice in Pregnancy**

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**Gerlinde Teuber [ Oral 8 ]**

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**Title: Treatment strategies for chronic HBV in Germany**