Hepatitis B Foundation
Princeton Workshop
Viral Triple Threat: HBV with HCV/HIV Co-Infections Liver Disease
November 12-13, 2008
Princeton, New Jersey

Viral co-infections are fast becoming a major public health concern as drug therapies have significantly improved the management and control of single infections. While a so-called "cure" isn't around the corner, the outlook for HBV, HIV and HCV infected individuals is better than it was 10 years ago. However, the situation is much more complicated for those co-infected with one, two or three viruses.

To address this potential viral triple threat, the Hepatitis B Foundation has made HBV co-infections one of its national priorities. The Foundation's bi-annual *Princeton Workshop*, held November 12-13, 2008 in Princeton, NJ, was dedicated to looking at the critical research needs for HBV co-infections with HCV and HIV.

A small group of the nation's thought leaders from academe, industry and government were invited to think about the most important unanswered questions in the area of HBV co-infections for two days of highly interactive roundtable discussions. Participants were invited to refer to their own work, to that in the literature, or to simply raise topics they wished the group to hear and discuss. In addition, a special presentation was given about the National Cancer Institute's Early Detection Research Network (EDRN) and related opportunities.

2008 Princeton Workshop Highlights

Overall Striking Features of Co-Infection
There is a central need to understand the nature of the accelerated liver disease, including a greater frequency of liver cancer (most documented and reported for HBV/HCV, but expected for HIV co-infection, too) and at an earlier age, as compared to mono-infected individuals.

Overarching Clinical Question
Who should be treated and when? For example, should young people be treated or is it best to wait until clinical liver disease has declared itself?

Overarching Clinical Research Need
There is a need for research access to relevant cohorts and specimens for further study.

Key Scientific Questions and Observations
1. How does the immune response vary over time, during co-infection?

2. Does the order in which someone is infected influence outcome? Some of the results from a study conducted in Thailand suggest it could.

3. Do HBV, HIV and HCV all infect common cell types, particularly in the liver? HIV would be expected to be present in the liver because of the arrival of infiltrating T cells, but does the HIV actually enter and have synthetic activity in the hepatocytes? If so, and if some of these hepatocytes

are co-infected, is the course of infection altered? Infection of hepatocytes in culture by HIV was shown and others have shown HBV and HCV can replicate in the same cell.

4. Is HBV largely restricted to HCV infected cells in the HBV/HCV co-infected person because they may be more conducive (i.e. innate host defense pathway opposed)? If so, does this influence outcome?

5. There is a continuing need to understand the nature and causes of fibrosis. What is the role of steatosis and fatty liver disease in fibrosis?

6. Can biomarkers of disease help in early detection and improve outcomes? Can they help in understanding etiology and pathogenesis, even lead to new interventions?

7. Do viruses "evolve", in-vivo, to escape the innate host defense system? Thus, mutant viruses should be apparent as a function of time of infection and immunopressure.

The Following Co-Factors of Co-Infection Disease Deserve Much More Attention in Study
A. Microbial translocation: There is a growing appreciation that either micro-organisms or the products of micro-organisms (i.e. lipopolysaccharides), present in the gut, translocate into the circulation and may initiate or aggravate liver disease. Given the fact that the gut is a site of HIV replication, the importance of these trans-organ and microbial product dislocations may be especially relevant.

B. Alcohol: A clear risk factor for liver disease and accelerator of disease that could have unexpected effects on the co-infected.

C. Other environmental issues: Includes exposure to occupational hazards, as well as dietary contributions other than alcohol.

PHOTO CAPTION

Attendees at the Hepatitis B Foundation's Princeton Workshop 2008: Prakash Bhuyan, Timothy Block, Helena Brett-Smith, Carol Brosgart, Frank Chisari, Jeffrey Glenn, Scott Holmberg, Ira Jacobson, Jeffrey Jacobson, Brent Korba, Rajen Koshy, Thomas London, William Mason, Brian McMahon, Anand Mehta, Rob Murphy, Marion Peters, JoAnnRinaudo, Kenneth Sherman, Mark Sulkowski, John Taylor, Bud Tennant, Chloe Thio, David Thomas, and Paul Wagner (Nov. 11, 2008).