



## HEPATITIS B FOUNDATION

700 East Butler Avenue  
Doylestown, PA 18901-2697  
Phone: (215) 489-4900  
Email: info@hepb.org

CAUSE FOR A CURE

www.hepb.org

**Hepatitis B Foundation**  
**8<sup>th</sup> Annual Princeton Workshop**  
**November 7 – 8, 2002**  
Princeton, NJ

Submitted by  
Timothy M. Block, Ph.D.  
President and Chief Scientific Advisor

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For the past eight years, the Hepatitis B Foundation has invited a small group of the world's hepatitis thought leaders from academia, industry and government to gather in Princeton, NJ, for highly focused roundtable discussions of hepatitis B therapies. Despite the crowded scientific conference schedule, the workshop continues to draw leaders in the field because of its small size and unique format, as well as its important role in promoting scientific exchange and research collaborations.

This year's Princeton Workshop was an extremely significant meeting, characterized by lively discussion of some key issues. The matter of how to determine if a drug used in the treatment of chronic hepatitis B is actually having clinical benefit for the infected individual received, perhaps, the most attention. This question is not as simple as it would appear, and the discussion was energized and made all the more urgent by the presence of Dr. Debra Birnkrant (FDA, director of Antivirals), and the recent approval of Gilead's oral hepatitis B drug, adefovir dipivoxil (Hepsera). The ongoing clinical trials of telbivudine (LdT), entecavir, and clevudine (L-FMAU) also made the issue all the more timely.

### **Clinical Endpoints Need Definition**

The central question to hepatitis B drug development is: what should the primary endpoints be for determining an HBV drug's efficacy? In this discussion, "endpoints" refer to the physical and laboratory measurements taken as evidence of a drug's benefit.

Since symptoms of chronic hepatitis B usually take years, if not decades, to become apparent, it is not entirely straightforward to determine whether or not an anti-HBV drug is actually beneficial. The most unambiguous endpoint for an anti-HBV drug would be preventing the occurrence of life-ending or life-upsetting consequences of an infection. But most people with chronic hepatitis B will be infected for decades before serious problems develop. Thus, it is necessary to use "surrogate" markers or "surrogate endpoints" as substitutes for evaluating disease progression.

Agreeing upon "surrogate" markers that are truly predictive has not been easy, and there was a lively debate about this issue. Patients usually prefer blood tests (or serological markers) over more invasive procedures such as a liver biopsy, for obvious reasons.

Evidence that anti-HBV drugs, which target viral replication, are having the intended effect can most logically and easily be determined by measuring the amount of viremia (viral DNA) in the blood. However, it is not clear that reductions in viremia, alone, predict a beneficial outcome.



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### Hepatitis B Foundation Princeton Workshop Summary 2002

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#### **Role of the Liver Biopsy?**

There was general acceptance that histological information resulting from a liver biopsy, was the best measurement of “disease” and, thus, the best way to determine that meaningful benefit from a drug had occurred. Histology permits direct visualization of the amount of fibrosis and liver damage. Indeed, previous reports have suggested that fibrosis, a complication leading to cirrhosis, is most consistently predictive with regard to disease progression or reversal.

That being said, such studies have drawn their conclusions from population averages, and the value or accuracy of a biopsy for any given individual may vary. Add to this, the unpleasantness of a biopsy, it is easy to see why controversy remains and the desire for alternatives high.

Moreover, even if it is conceded that liver biopsy is the “gold standard”, on a population basis, should it be required for each individual when its value to the individual is unclear and there are other reasonable biomarkers of disease to choose from that are far less invasive?

*The overall sense of the meeting was that liver biopsy should not be required as a primary endpoint.* For most patient populations, the serological markers of viral load (viral DNA) and seroconversion from HBe-antigen positive to negative, with the appearance of HBe-antibody, and reduction of the ALT to normal levels, would seem to be the best, current substitute for liver biopsies.

For a drug to be approved with a specific use, the FDA must weigh in. They usually look to the professional community for guidance, and it is hoped they will consider the value of serological surrogate markers, rather than liver biopsy results. This will make it more pleasant for the patient and less expensive for the drug companies, enhancing the possibility that other drugs will be tested and approved for use in people.

#### **Drugs in the Pipeline**

Despite the excitement of the discussions of endpoints, the meeting moved on to many other topics. Of course, there was a great deal of interest in adefovir, and its ability to retain efficacy against lamivudine-resistant virus. This is certainly going to be a valuable contribution to the arsenal against hepatitis B. Some believe it should be a first-line drug. Others worry about long-term adversities (including spiking liver function tests, kidney toxicity, aberrant mutants) and suggest it be used only if lamivudine-resistance emerges.

Entecavir (BMS), Clevudine (Gilead/Triangle) and LdT/LdC (Idenix, formerly named Novirio) are predicted to be the next anti-HBV drugs that will come to market. Although these are in the same nucleoside analogue class as lamivudine and adefovir, they are being greeted with high hopes, since they may be more potent and in some cases also effective against lamivudine-resistant mutants.



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The fundamentals of HBV immunobiology, and how this knowledge can be exploited for therapeutics, new gene silencing approaches, DNA vaccines and unconventional small molecules were all discussed as well.

#### Princeton Workshop 2002 Participants

*The Hepatitis B Foundation gratefully acknowledges the support and participation of the following scientists: **Harvey Alter, Antonio Bertoletti, Debra Birnkrant, Timothy Block, Baruch Blumberg, Carol Brosgart, Nat Brown, Alessia Ciancio, Paul Cote, Mark Feitelson, Jay Hoofnagle, Leslye Johnson, Brent Korba, W. Thomas London, Anand Mehta, Brian McMahon, C. Satishchandran, Raymond Schinazi, Robert Schneider, Marvin Siegel, David Standring, Lorne Tyrrell, Robert Whalen, and Shelly Xiong.***

*The HBF also thanks the following scientists for serving on the Princeton Workshop 2002 Steering Committee: **Timothy Block** (The Jefferson Center and HBF), **William Mason** (Fox Chase Cancer Center), **Brent Korba** (Georgetown U. Medical Center), **W. Thomas London** (Fox Chase Cancer Center and HBF), and **Jesse Summers** (U. New Mexico) who was unfortunately unable to attend due to schedule conflict.*

\*\*View attached Program Schedule



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**PROGRAM SCHEDULE**

**THURSDAY, NOVEMBER 7, 2002**

**6:00-8:00PM Reception and Dinner in *The Ships Room***

*Updates on The Molecular Biology of HBV Meeting, and AASLD Meeting*

Speakers: Mark Feitelson and Chiaho Shih

**8:00-9:00PM Current methods for the treatment of HBV**

*What are the benefits and limits of the current approaches?*

Moderators: Jay Hoofnagle & Jenny Heathcote

Speakers: Lorne Tyrell  
Carol Brosgart

**9:15-10:15PM New Antiviral Therapies**

*How will the new antiviral therapies compliment existing approaches?*

Moderators: Leslye Johnson & Lynn Condreay

Speakers: Richard Colonno  
Nat Brown

**FRIDAY, NOVEMBER 8, 2002**

**7:00-8:00AM Breakfast and discussion in the meeting room**

*Thoughts regarding how the natural history of HBV influences therapeutic strategy, with special attention to the eAntigen negative carrier*

Moderators: W. Thomas London and Harvey Alter

Speaker: Brian McMahon

**8:00-9:15AM Immunotherapy for chronic HBV**

*What are the prospects for immunotherapy?*

Moderators: Harriet Isom & John Gerin

Speakers: Antonio Bertolotti  
Paul Cote

**9:30-11:30AM Non-traditional approaches to the treatment of HBV**

Moderators: Brent Korba & Howard Thomas

Speakers: Brent Korba  
Jesse Summers  
Bill Mason  
Anand Mehta



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**12:00-1:00PM Roll-in Lunch**

*“Regulatory Issues: How can the process of approval be expedited, and when are surrogate markers appropriate?”*

Moderators: Baruch Blumberg & Dave Standring

Speaker: Jeff Murray

**1:00-3:00PM Non-traditional approaches, continued**

Moderator: Timothy Block & Satish Chandran

Speakers: Raymond Schinazi

Robert Whalen

Marvin Siegel

**3:10-4:10PM New thoughts on HBV pathogenesis**

*How can knowledge of pathogenesis help innovations in therapy?*

Moderators: Mark Feitelson & Chiaho Shih

Speakers: Robert Schneider

Chuck Rogler

**4:10PM Closing remarks**

Timothy Block, HBF President

**4:30PM Meeting adjourns**