HEPATITIS B FOUNDATION
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Hepatitis B Foundation
7th Annual Princeton Workshop
December 20, 2001
Maui, Hawaii

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President and Chief Scientific Advisor

In December 2001, the Hepatitis B Foundation convened the *7th Annual Princeton Workshop* for influential scientific and clinical thought leaders from academia, industry and the government to discuss the issues they see as most critical in hepatitis B therapeutics. This meeting has always been held in Princeton, N.J., hence the name.

This year, the Princeton Workshop was moved to Hawaii because many of the participants planned to attend the HepDART 2001 meeting in Maui, Hawaii. A special session for the workshop was structured as a wrap-up session to review research highlights from HepDART, as it related to advances in HBV therapeutics.

There was the usual trademark lively discussion, however, several of the challenges that were identified reflect priorities from the HBF's national research agenda that was generated at the Princeton Workshop 2000.

Even though there are likely to be at least two new HBV therapeutics within the next few years, the greatest concern continues to be the retention of efficacy against drug resistance. The current availability of pegylated interferon (peg-IFN) should immediately open the door for revisiting the use of interferon in the treatment of chronic HBV. Peg IFN has been shown to be far better than non-peg IFN in chronic hepatitis C, and early results suggest that HBV patients may enjoy similar benefits. Another area of concern is also emerging - treatment of the eAg negative carrier.

The summary of the 7th annual Princeton Workshop clearly frames the state of the new wave of hepatitis B therapeutics as well as provides alerts regarding the most pressing research problems.

HBF Workshop Summary 2001

CLINICAL HIGHLIGHTS

- New Antivirals - New antivirals for the treatment of eAg positive HBV carriers are moving through development and perhaps two or more are likely to be available within the next five years. Significantly, antiviral suppression appears to be sufficient, in some cases, to result in at least a degree of reversal of fibrosis.

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- Resistance To Conventional Antivirals - Advances in chemotherapy will be undermined by the emergence of resistance, if appropriate new drugs are not developed. Except for the modified interferon alpha (pegylated), current antivirals are mechanistically similar. However, the different nucleoside inhibitors could still complement each other's action, despite all being polymerase inhibitors, since they may prevent different functions of the HBV pol. The pol has several discrete functions, such as priming and elongation, and a drug active against one step may complement the action of another. Resistance to any drug that targets a specific viral gene product remains a serious possibility.

- Adefovir Dipivoxil Most Likely To Be Approved - Adefovir is fortunately active against conventional lamivudine-resistant virus and is the next best HBV antiviral most likely to be approved by the U.S. Food and Drug Administration.

- Entecavir and Clevudine Move Into Phase 3 Trials - Entecavir and Clevudine are notable for their ability to have a sustained impact upon viremia for a period of time well after end of therapy. These results, which were observed in woodchucks, are now being seen in human trials. In woodchuck studies, cccDNA was reduced, probably to an even greater extent than could be explained by the reduction in viremia and re-infection. This suggests that other mechanisms of action, beyond inhibition of the viral polymerase, may be in play. The therapeutic and toxicological implications of these other mechanisms, should this theory be correct (which could involve a degree of cell destruction), are not clear.

- Combination Trials Should Become A Priority - In this regard, it is noted that some companies are themselves sponsoring combination studies. The need for combination studies cannot be overstated.

- Promising Ldt/Ldc Compounds Moving Forward – These are a pair of compounds that are highly and specifically active against the HBV polymerase and are now in human trials. Although other such stereoisomers have been developed, the "L-nucleosides" are so named because of their unnatural "L" isomeric properties. In woodchuck studies, they have been shown to be efficacious alone and in combination. Combination studies of the two L nucleosides are also being planned, presumably reasoning that they either complement each other by targeting different functions of the HBV pol or have complementary pharmacologic properties.

- Vaccine and Immuno-Modulation Therapies - Therapeutic vaccination for HBV as well as other non-interferon based immuno-modifying strategies remains an extremely important and underdeveloped area for HBV. Although there was only limited discussion about this, it is clear that chronic HBV infection remains one of the most compelling indications for immuno-modifying therapies to be attempted.

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- Overlooked eAg Negative HBV Carriers: What If Any Therapeutics Are Indicated For Them? - The standard endpoint for antivirals (interferon as well as nucleosides) is seroconversion from e-antigen (eAg) positive to e-antigen negative. Discontinuation of lamivudine therapy, for example, may be indicated after seroconversion occurs. The eAg negative population, however, is generally not included in treatment plans because there is no clear therapeutic endpoint for these individuals and they are perceived to be at lower risk for progressive liver disease than eAg positive carriers. Yet, there is a growing appreciation that almost half of all liver cancer that occurs does so in those who are eAg negative. Therefore, the need for treatment options for this population is clear (see President's Message, pg. 2).

Basic Science Highlights

- Non-Traditional Interferon Pathway May Mediate An Antiviral Activity

- Non-Cytopathic Lymphocyte Response May Be Insufficient To Account For Viral Clearance In The Natural History Of HBV

Conclusion

The summary for this year's workshop, which was reviewed by all participants, is divided into clinical and basic science highlights. These challenges, taken together with a lively discussion as to which drugs should be used for first line HBV treatment, underscore the remaining need to call for consensus from thought leaders to guide the hepatitis B community in *answering the critical questions as to who should be treated and when, and with what drug.*

2001 Princeton Workshop Participants

The Hepatitis B Foundation thanks the following scientists for attending: **Devron Averett, Timothy Block, Nat Brown, Richard Colonno, Adrian Di Bisceglie, Geoff Dusheiko, Leslye Johnson, W. Ray Kim, Brent Korba , George Lau , W. Thomas London, William Mason, Robert Perrillo, Raymond Schinazi, Kathleen Schwarz, David Standring, and Lorne Tyrrell**. We also appreciate the contributions of **Harvey Alter** and **Eugene Schiff** who were unable to attend the actual session.

The Hepatitis B Foundation also thanks the Workshop co-chairs for this year: **Timothy Block**, **Ph.D.**, Thomas Jefferson U., Phila., PA, and HBF president **; W. Thomas London**, **M.D.**, Fox Chase Cancer Center, Phila., PA, and HBF board member; and **Lorne Tyrrell**, **M.D.**, U. of Alberta, Edmonton, Canada.