HEPATITIS B FOUNDATION
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Hepatitis B Foundation
6th Annual Princeton Workshop

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Doylestown, PA

Submitted by
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President and Chief Scientific Advisor

The *6th annual Princeton HBV Workshop* was unique, even by the workshop's standard because this year the workshop departed from its usual venue to respond to a specific mandate. This year the Workshop was held at the Foundation in Doylestown, PA, to showcase its facilities and research labs.

In a joint effort, the Hepatitis B Foundation and the American Liver Foundation (ALF) called upon the group of 22 world-renowned scientists to generate a list of the most important research objectives that if pursued, would have the greatest likelihood of advancing hepatitis B "cure research". **Janine Witte**, HBF Co-Founder, and **Alan Brownstein**, ALF President, spoke eloquently about the need for a national hepatitis B research agenda. The agenda would help guide the two nonprofit foundations, and others, in their advocacy and fundraising efforts.

Timothy M. Block, **Ph.D.,** HBF President and Chief Scientific Advisor, prepared the following summary of the six research priorities that were identified during the Workshop and the proposed tactical plan to address the priorities.

National Hepatitis B Research Agenda 2000 – *6 Research Priorities*

*Please note that the order of these priorities does not indicate their rank of importance.

1) Early Detection of Disease

- Promote research to evaluate and make further use of current clinical information to better predict outcomes of chronic HBV carriers who have been treated or remain untreated.

- Research to discover additional early detection markers for liver disease and hepatocellular carcinoma is also urgently needed.

- Research to determine how liver biopsies can best be used/implemented is needed. Should the clinical community more actively encourage liver biopsies? What are the risk-benefits of liver biopsies?

2) Therapeutics

- Support the development of new antivirals that either target virus functions or modulate host functions.

- Alternatives and complements to lamivudine and α-interferon therapy are needed.

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3) Evaluation of the Efficacy of a Therapeutic

- Research into the development of predictive, surrogate intermediate markers of clinical disease endpoints should be pursued. Some compounds may be effective in preventing disease by mechanisms that might be overlooked or underestimated by conventional endpoints (such as viral load) evaluated over a short time period (e.g. 6 months).

4) Virology

- The role of viral mutants in causing resistance to therapies in promoting new or recurrent disease should be explored.

5) Standardization of HBV DNA Determinations is Needed

- This is not so much a research question as an implementation issue. There are several excellent existing methodologies to quantify HBV DNA levels.

6) Theoretical Studies

- Fundamental research plays a broader role than as a tool for troubleshooting practical problems. Its role is to provide a framework for understanding what is possible or not possible in developing new therapies.

TACTICAL PLAN TO ACHIEVE THE SIX RESEARCH PRIORITIES

1) Early Detection Of Disease

- There is a growing body of data regarding the range of clinical courses and outcomes in individuals chronically infected with HBV (carriers). This includes individuals who have been treated with HBV therapeutics as well as a large volume of historical data and archived material from the natural unchecked progression of HBV infection and disease in chronic carriers. Special focus should be placed upon the asymptomatic carrier as an early stage prior to the development of severe liver disease sequelae. More work is needed to exploit this information and these resources. For example, conventional correlation studies to determine relationships between existing markers (serologies, liver function tests, physical assessments, age of milestone events such as infection, sero-conversions) and disease outcomes should be performed.

- The possibility of exploiting "new technologies" for the detection of liver disease should be pursued. Proteomics, SELDI, post genomic and genomic technologies may be useful in helping identify markers that can predict disease progression/outcome in HBV carriers. These technologies may also be helpful in predicting who will or is benefiting from therapeutic intervention.

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2) Therapeutics

- New antivirals that either target virus functions or modulate functions should be explored. Alternatives and complements to lamivudine are needed.

- How do we make best use of current antivirals now in clinical trials? There is a need to organize combination therapy trials long before licensing of monotherapies. How can this be accomplished while still maintaining an equitable share among potentially competing pharmaceutical companies? How do we get these new therapies to physicians as soon as possible? What incentives are needed to develop cooperative initiatives among competing companies and their candidate compounds?

- How can patients be recruited for trials? Is there a need for a national reference site/organization to help identify or inform potential patients? Can existing organizations be used for this purpose? Is a web-based recruitment appropriate?

- New therapy research. It is important to determine whether there are previously unappreciated steps in the virus life cycle that can be exploited for antiviral drug intervention.

- Models to evaluate the efficacy and toxicity of combination therapies should be pursued. Consideration should be given to those methods most likely to be of benefit using existing clinical technologies. Other therapeutic methods or ideas of equal or greater potential benefit, but which require extensive long-term development of new implementation technologies, should also be strongly encouraged.

- Immuno-intervention strategies should be explored. Continued advances in understanding of the basic immunobiology of chronic HBV infection and methods of manipulating the host immunological responses to the virus offer promise that new information can be harnessed for the benefit of HBV infected individuals. Combinations of antivirals and immuno-intervention are a specific area of research identified as important. The possibility of exploiting advances in the understanding of stem cell biology for the benefit of patients with HBV associated chronic liver disease should be explored.

- The problems associated with persistence of HBV cccDNA in the liver as the main endogenous reservoir, continued infection, and the need to reduce and eventually eradicate the level of this molecular form should be studied. Fresh new approaches here are needed. Methods to accurately quantify cccDNA from small sample sizes (e.g. small portions of live biopsies) also need to be emphasized and pursued vigorously. Newly developed methods are already being commercialized and need to be put into practice.

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3) Evaluation Of The Efficacy Of A Therapeutic

- Research into the identification and use of predictive, surrogate disease markers as clinical should be pursued. Some compounds may be effective in preventing disease by mechanisms that would be overlooked or underestimated by conventional endpoints (such as viral load) evaluated over a short period of time (e.g. 6 months).

- If and when discontinuation of therapy can be attempted safely must be determined.

- The possibility of a recommended "Standard of Care" for HBV chronic carriers should be pursued.

- New endpoints of therapeutic efficacy should be studied. Disease associated with HBV often takes decades to unfold. Clearly, surrogate endpoints for actual disease progression could be better applied in evaluating the efficacy of a therapy. Viral loads, histology and serology have been used in the past. It is likely that as new therapies are introduced in the future (such as immuno-interventions), existing methods for predicting the success of the approach will need to be expanded. This area of study is likely to benefit from new technology and information generated in the Early Detection of Disease programs.

4) Virology

- The role of viral mutants in causing resistance to therapies and in [promoting new or recurrent] disease and should be explored.

- The virology of HBV needs more attention. The pathobiology of lamivudine-resistant viruses should be explored. The role of viral diversity in HBV pathogenesis, resistance to interferons and other host defenses, should be studied further.

5) Standardization Of HBV DNA Determinations Is Needed

- This is not so much a question of research as it is]an implementation issue. There are several excellent existing methodologies to quantify HBV DNA levels. Leaders in the field should develop a consensus on universal methods of determination and/or normalization of values from lab to lab. This is particularly important in patient profiling before, during and after therapies are implemented. Who/what organization(s) are to administer such a standard and determine the methods for its development?

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6) Theoretical Studies

- There is a need to develop more complete theories that explain viral replication, immunopathogenesis, and the biology of liver cancer. Further understanding in these areas will have a positive impact on the development of new therapeutics. The mechanisms by which HBV is cleared during natural self-limited infections have not been completely elucidated. Nor have all the mechanisms associated with the initiation and maintenance of chronic infection and eventual disease progression. More fundamental research is needed in the early stages of such infections using model systems because the spontaneous clearance of HBV infections, especially in self-limited infections, can serve as a useful paradigm for effecting the most beneficial therapeutic and clinical outcome(s). The mechanism for progression to liver cancer in humans remains unknown. It is important to study this for several reasons. First, it is possible that immune selection against infected cells results in re-population of the liver with cells in which HBV expression is turned off secondary to mutations in cellular genes. If so, the identity of these genes and the mechanism whereby they regulate HBV replication should be determined. Are such cellular genes perhaps valid targets for antivirals? The answers to these questions might also help in the patient evaluation of the extent of progression to liver cancer, or even suggest ways in which such progression could be prevented.

Princeton Workshop Participants 2000

The Hepatitis B Foundation extends a sincere thank you to the 6th Annual Princeton Workshop attendees for their important contributions: **Drs. Charles Arntzen, Harvey Alter, Tim Block, Nat Brown, Lynn Condreay, Paul Cote, John Gerin, Jenny Heathcote, Jay Hoofnagle, Leslye Johnson, Brent Korba, Johnson Lau, Steve Locarnini, Tom London, Bill Mason, Chuck Rogler, Ray Schinazi, Chiaho Shih, Jean-Pierre Sommadossi, David Standring, Lorne Tyrrell, and Jack Wands.**

Thank you to the following scientists who reviewed the final draft of the research priorities, but were unable to attend: **Frank Chisari, Adrian DiBisceglie, Jules Dienstag, and Jesse Summers**

Finally, thank you very much to the steering committee:
Timothy Block, Brent Korba, Tom London and Bill Mason

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