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CAUSE FOR A CURE
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10th Annual Princeton Workshop
Sponsored by the Hepatitis B Foundation
November 4 – 5, 2004

SUMMARY

Prepared by Dr. Timothy M. Block

The 10th Annual Princeton Workshop, sponsored by the Hepatitis B Foundation (HBF) and held Nov. 4-5, 2004, in Princeton, New Jersey, took a close look at a small, but troubling topic: hepatitis B viral DNA.

The hepatitis B virus (HBV) chromosome is made of DNA and can exist as a “covalently closed circle” form, abbreviated as “cccDNA.” This cccDNA is a different, sturdier form than what is found in the actual virus itself and persists inside liver cells during chronic infection. Even after long term antiviral therapy, cccDNA can be the source of resistance and can lead to "relapses" and "re-establishment" of infection, even after it is thought that antiviral drugs have worked.

This year’s Princeton Workshop was considered to be one of the most stimulating ever, and the international group of 25 leading hepatitis thought leaders and decision makers reached consensus on a key issue: cccDNA has got to go.

How to get rid of cccDNA, does interferon reduce cccDNA and how does interferon work, and can drugs be developed that eliminate cccDNA were four of the lead questions the group asked itself this year.

How does a patient’s cccDNA level contribute to their responsiveness to therapy? One observation is that regardless of which of the current antiviral therapies are used, there always seems to be only a minority of the treated population that has a sustained response.

In making this point, one must bear in mind that the definition of "responders" varies (such as, Ag conversions, DNA negativity, ALT normalizations, and improvement in histology). However, even allowing for some differences in definition, there seems to be a constant minority of individuals who are predisposed to responding to the various antiviral or immune-mediated

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therapies currently available. The question then becomes: are these responders the same individuals or are they overlapping groups?

There is also a growing consensus that reliance upon eAg status (or conversion) as a milestone of therapy may be too limited. HBV DNA levels (or, perhaps, reduction during therapy) may be a better marker. Ultimately, it will probably be a combination of markers that serves the purpose of prognosis best. Reduction in cccDNA levels, if they could be determined, might lead to an excellent indicator of favorable outcome. However, detection of cccDNA is very difficult for technical reasons. Perhaps sAg, which is made from the cccDNA template and easily detected in the blood, could be a good surrogate for cccDNA.

In many individuals, reductions in HBV DNA levels can be achieved with antiviral therapy, and the DNA levels will remain low indefinitely - even in the absence of presumably useful immunological activations. What holds the DNA level down? Are there innate cell defenses, some type of cell sensor that does this? The group heard evidence that liver cells harboring HBV are "resistant" (refractory) to re-infection, and that this may be related to the viral envelope proteins.

It is unclear if cccDNA in liver cells can be reduced without harming the cell in which it is housed. cccDNA is difficult to study since it exists, usually, in very low amounts (except in the case of the duck system). There is conflicting evidence about control of cccDNA. Some think its fate is integrally linked to that of the cell in which it is housed (you have to burn the house down to destroy the cccDNA) and others believe there is good data suggesting cytokines or other immune modifiers, factors that influence cell cycle state, can significantly reduce its abundance without harming the cell.

Clearly, this is one of the most important frontiers in HBV research, with tremendous implications for therapy as well as for basic science – since how cells manage small "foreign" DNA (a family to which cccDNA belongs) is a key question in what is now fashionably called "innate host defense from infection."

Can the interferons affect cccDNA stability? When effective, interferons can certainly serve to "turbo charge" the infected individual's immune system, forcing immune cells to take a look at HBV and see it as "foreign." In addition, interferons can apparently work directly on the infected cell, perhaps by influencing HBV capsid stability. Can they take a direct whack at cccDNA? This is controversial.

The new wave of HBV antivirals coming up for testing is generating a great deal of excitement. Although several have a mechanism similar to the currently approved oral HBV drugs, some of the new drugs - entecavir, telbivudine, or perhaps clevudine - are extremely potent, generate little resistance, and may be so potent that they might result in therapeutic reductions in cccDNA. That is, if they can be taken for long enough without generating resistance.

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If the approved drugs and the new antivirals coming up can't do the job alone, perhaps combination with another therapeutic that complements their mechanism of action will do the trick. It will hopefully become realistic to use cytokine or even therapeutic vaccine type approaches that may correct HBV antigen levels, while the antiviral drugs reduce DNA levels.

Finally, perhaps gene silencing holds the most exciting, if uncertain, promise, since it can selectively reduce the level of almost any viral gene product, by simply altering the design of the gene silencer (see page 7). In combination with a drug that controls viral reproduction and another that activates the immune system, a powerful cocktail might be created. Now that is something we could all drink to (non-alcoholic, of course!).

The bottom line for the hepatitis B community is to not give up. We must not become complacent or satisfied with therapeutics that only reach a limited population and may leave the rest as if nothing has ever been done.

Photo Caption: 10th Annual Princeton Workshop Attendees
(Front L to R): T. London, P. Cote, T. Block, L. Seef, L. Tyrrell, B. Korba; (Middle L to R): D. Standring, S. Xiong, C. Brosgart, S. Wieland, H. Alter, N. Brown, M. Feitelson, K. Laessig, E. Doo, R. Colonno, C. Rogler, C. Pachuk; (Back L to R): W. Mason, S. Locarini, R. Schinazi, A. Mehta, D. Berard, B. Tennant, R. Gish, J. Hoofnagle, M. Bouchard, S. Chandran; (Missing): C. Seeger (Nov. 2004).