

## **Duck Hepatitis B Model and Assessment of Antiviral Therapy**

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The Pekin duck model of hepadnavirus infection has provided many valuable insights into hepadnavirus replication, antiviral therapy, and antiviral resistance. It has also proven very useful in the understanding of other clinically relevant observations seen in patients on antiviral therapy.

The duck hepatitis B virus (DHBV) was first described in 1980 by Mason et al.<sup>1</sup> Using this model, the unique replication of hepadnaviruses was described.<sup>2</sup> We adapted the primary hepatocytes system to screen compounds for antiviral activity in 1987 when there were no primary hepatocyte cultures to support HBV. Using this system, we described the potent antiviral effect of prodrugs of ddG.<sup>3</sup> Subsequently, the mechanism of action of purine dideoxynucleosides was due to blocking the protein priming of hepadnavirus DNA synthesis.<sup>4,5</sup> The duck model of HBV was used to screen many nucleoside analogues as inhibitors of hepadnaviruses, including lamivudine, which was shown to be a chain terminator for the viral DNA synthesis.<sup>6</sup> Resistance to lamivudine was produced in DHBV by mutating the YMDD motif of the viral polymerase to YVDD; this finding predicted the major problem of lamivudine resistance during treatment of human HBV infection.<sup>7</sup> The DHBV polymerase can incorporate lamivudine into DHBV DNA, and the L-isomer is resistant to “proofreading” by the polymerase in the presence of pyrophosphate.<sup>8</sup> Recently we have utilized the DHBV model to demonstrate “superinfection exclusion” and the importance of establishing “replicating space” in an infected liver before the lamivudine-resistant virus can establish an infection in the host.<sup>9</sup>

### **References**

1. Mason W.S., Seal, G. and Summers, J. (1980). *J. of Virol.* 36:829-836.
2. Summers, J. & Mason, W.S. (1982). *Cell* 29:403-415.
3. Lee et al. (1989). *Antimicrob. Agents Chemother.* 33:336-339.
4. Wang, G.H. & Seeger, C. (1992). *Cell* 71:663-670.
5. Howe, A.Y.M. et al. (1996). *Hepatology* 23:87-96.
6. Severini et al. (1995). *Antimicrob. Agents Chemother.* 39:1430-1435.
7. Fischer, K.P. & Tyrrell, D.L.J. (1996). *Antimicrob. Agents Chemother* 40:1957-1960.
8. Urban, S. et al. (2001) *Proc. Natl. Acad. Sci. U.S.A.* 98:4984-4989.
9. Walters, K-A. et al. (2004) *J. of Virol.* 78:7925-7937.