



Figure 11.5 Alisporivir and SCY-635 are currently under clinical investigation as non-immunosuppressive cyclophilin inhibitors for the treatment of hepatitis C virus infection.

(rs12979860) that has been shown to predict responsiveness to pegylated interferon-containing regimens suggests that the mechanism of action of this agent may be more closely aligned with an immunological response than with direct activity on the virus. The additional finding that dosing of HCV-infected patients with SCY-635 results in a transient increase in plasma cytokines (IFN α , IFN11, IFN13) points to a potential role for Cyp inhibition in the host innate immune response to HCV infection.⁸¹

11.2.3 Dengue, West Nile and Other Flaviviruses

Isoform-specific knockdown of CypA, CypB or CypC in Huh-7.5 cells was used by Tang and co-workers⁸² to demonstrate a role for Cyps in the replication of West Nile virus (WNV), dengue virus and yellow fever virus. The most significant inhibition of replication of the three flaviviruses was found for a double knockdown of CypA and CypB and the PPIase activity of CypA was shown to be essential for effective replication of dengue virus and WNV. They further showed that CypA directly interacts with the NS5 protein of WNV; however, this interaction did not affect the enzymatic activity of NS5 *in vitro*.⁸² Consistent with these findings, CsA was shown to block the interaction of CypA with NS5 of WNV, suppress viral RNA synthesis and inhibit a broad spectrum of RNA viruses at non-toxic concentrations.

CypB was demonstrated to be involved in the replication of Japanese encephalitis virus (JEV) by the rescue of JEV replication by expression of wild-type CypB, but not PPIase-deficient CypB, in various mammalian cells in which endogenous CypB was suppressed.⁸³ This finding was again supported by the finding that CsA potently inhibits the replication of JEV *in vitro*.⁸³

11.2.4 Non-flaviviruses

While a role for Cyp inhibition in restricting flavivirus replication has been demonstrated, the activity of Cyps in other viruses is less clear. A convincing