CHAPTER 11

# *Optimization of Cyclophilin Inhibitors for Use in Antiviral Therapy*

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The discovery that cyclophilin A (CypA) is a requisite binding protein for the immunosuppressive activity of cyclosporine A (CsA) served to place CypA firmly in the sphere of immunology research. The demonstration that the CsA–CypA binary complex inhibits the calcium-dependent phosphatase activity of calcineurin (CaN), leading to inhibition of key activators of T-cells, provides a compelling explanation of the immunosuppressive activity of CsA.[1] However, an expanding range of activity demonstrated by CsA, including mitochondrial function, cell death, chemotaxis and motility, suggested mechanisms that were not easily ascribed to CaN inhibition.[2] The discovery of new CsA analogs that retained potent binding to CypA but prevented ternary complex formation with CaN allowed the biology of cyclophilins (Cyps) to be probed independent of immunosuppressive activities.[3] Finally, the use of knockdown and gene-silencing techniques has revealed a rich, and expanding, biology associated with Cyps. This chapter describes the application of Cyp inhibitors as novel antiviral agents and the factors to be considered when optimization strategies are designed.

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