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Structure-Based Development of Variola H1 Phosphatase Inhibitors. D.S. Waugh, J. Phan, J.E. Tropea, Macromolecular Crystallography Laboratory, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, MD 21702 USA.

Smallpox was officially eradicated more than 20 years ago but there remains a serious concern that undeclared stocks of the variola major virus may still exist and could be used as a bioterrorist weapon. Although there is a vaccine, it is not without risks and serious side effects. Consequently, there is an urgent need for effective antiviral drugs. In addition to providing potential therapy for infected people, the availability of antiviral drugs could decrease the risks associated with the smallpox vaccine by providing a treatment for vaccine-associated complications. Essential viral enzymes have frequently proven to be good targets for antiviral drugs. The dual specificity protein phosphatase (H1) encoded by the smallpox virus is essential for viral replication. We have determined the crystal structure of this enzyme, the first of any protein encoded by the variola major virus, at a resolution of 1.8 Å, thereby creating an opportunity for structure-based development and optimization of inhibitors. *In silico* screening methods have led to the identification of several small molecules that inhibit variola H1 phosphatase with IC₅₀ values in the low micromolar range.