

Karlstrom, A. R. and R. L. Levine. 1991. Copper inhibits the protease from human immunodeficiency virus 1 by both cysteine-dependent and cysteine-independent mechanisms. *Proc.Natl.Acad.Sci.U.S.A* 88:5552-5556.

**Abstract:** The protease of the human immunodeficiency virus is essential for replication of the virus, and the enzyme is therefore an attractive target for antiviral action. We have found that the viral protease is inhibited by approximately stoichiometric concentrations of copper or mercury ions. Inactivation by  $\text{Cu}^{2+}$  was rapid and not reversed by subsequent exposure to EDTA or dithiothreitol. Direct inhibition by  $\text{Cu}^{2+}$  required the presence of cysteine residue(s) in the protease. Thus, a synthetic protease lacking cysteine residues was not inhibited by exposure to copper. However, addition of dithiothreitol as an exogenous thiol rendered even the synthetic protease susceptible to inactivation by copper. Oxygen was not required for inactivation of either the wild-type or the synthetic protease. These results provide the basis for the design of novel types of protease inhibitors.