MODULATION OF APOPTOSIS AS A THERAPEUTIC STRATEGY

Kevin J. Tomaselli, Ph.D.

Idun Pharmaceuticals, Inc., 11085 North Torrey Pines Rd., Suite 300, La Jolla, CA 92037;
(858) 623-1330; Fax (858) 625-2677
ktomaselli@idun.com

Cell death is a contributing factor in many human diseases. A significant proportion of the cell loss that occurs in tissue or organ injury and disease is by programmed cell death, or apoptosis. Apoptosis is a genetically controlled form of cell suicide effected by specific gene products acting within dying cells. A family of cysteine proteases, caspases, comprise the key effectors of the apoptotic pathway. Caspases are constitutively expressed in essentially all living cells as inactive zymogens. Following their interaction with caspase activator proteins (e.g. Apaf-1), caspases are converted to a catalytically active form, and cell death quickly ensues. Small molecule inhibitors of caspase proteases or caspase activator proteins represent a new approach to inhibiting cell death in the context of acute tissue and organ damage. The potential applications of apoptosis inhibitors for treating stroke, myocardial infarction and acute hepatic failure will be discussed.

REFERENCES.

1. Mittl, P.R.E., Marco, S., Krebs, J., Bai, X., Karanewsky, D., Priestle, J., Tomaselli, K., and Grutter, M. (1997) *J. Biol. Chem.* 272, 6539-6547
2. Blanchard, H., Kodandapani, L., Mittl, P.R.E., Di Marco, S., Krebs, J.F., Wu, J.C., Tomaselli, K.J., and Grutter, M.G. (1999) *Struct. Fold. Des.* 7(9), 1125-1133
3. Hengartner, M.O. (2000) *Nature* 407, 770-776