

## **PHARMACOLOGICAL MANIPULATION OF STRESS RESPONSE AND AGING**

Gordon J. Lithgow (P), Matthew S. Gill, Michael Benedetti, Amanda L. Foster, James N. Sampayo, Gawain McColl, Maithili C. Vantipalli, Anders Olsen and Mark P. White

The Buck Institute, 8001 Redwood Blvd., Novato, CA 94945

The causes of death during aging are not well understood. There is considerable evidence that acute stress and aging share characteristics and that different types of extrinsic stress, such as thermal and oxidative stress, have similar biochemical outcomes. Here we have tested if survival of the multicellular metazoan, *Caenorhabditis elegans* following acute heat shock is influenced by oxidative stress. We demonstrate that young adult nematodes subjected to heat shock produce reactive oxygen species (ROS) in a wide variety of tissues and accumulate oxidatively damaged protein. We then tested whether treatment with a range of antioxidant compounds would enhance survival. We show that propyl gallate and alpha-lipoic acid enhanced survival when administered at high doses but reduce survival when given at low doses. Other antioxidants have variable or no effects on survival. It appears that oxidative stress does influence survival during heat shock in multicellular animals but that pharmacological interventions can either enhance or compromise survival. We go on to show that a range of compounds increase both stress resistance and lifespan. We discuss the significance for interventions in oxidative stress-related disease and aging.