Dr. Stavroula Kousteni

An integral component of our research is the identification and mechanism of action of novel molecules that control bone mass in the adult and aging population. In this context we have elucidated common mechanisms that link the biology of aging with the pathogenesis of osteoporosis. One of the major links to this age-related process is the generation of reactive oxygen species (ROS). Aging as well as the pathogenesis of age-associated diseases, has been linked with a failure of the organism (or cells) to resist an accumulative increase in oxidative stress as mediated by ROS. In contrast, physiological levels of stress activate survival signaling mechanisms that maintain cellular and organismal functionality by preventing the accumulation of ROS. We have identified anti-stress response mechanisms in osteoblasts that are involved in maintaining bone homeostasis. These mechanisms involve the NAD-dependent deacetylase, Sirtuin1 and its gene target, the transcription factor FoxO1. Both Sirtuin1 and FoxO1 have been implicated in modulating ROS and, in turn, have been linked to lifespan extension The aim of this research proposal is three-fold: to generate genetic mouse models that will determine the role and site of action of SIRT1; elucidate the role of the SIRT1/FoxO1 interaction in the control of bone mass in vivo; and, identify FoxO1 transcriptional targets that mediate the actions of SIRT1 and FoxO1 in bone.