Elevated oxidative stress lies at the heart of many manifestations of cardiovascular disease, including atherosclerosis. In atherogenesis, uncontrolled uptake of oxidized low density lipoprotein (oxLDL) via scavenger receptors on macrophages in the artery wall leads to foam cell formation, pro-inflamatory signaling and plaque accumulation. Oxidized sterols (oxysterols), which are prominent components of oxLDL, are abundant and readily detected in atherosclerotic plaques. Most recent studies have focused on redox-inert cholesterol oxides such as 7-hydroxide (7-OH), 7-ketone (7=O), and 27-hydroxide (27-OH). The novelty and unique strength of this proposal is that it focuses on a special type of oxysterol, namely 7-OOH, which is a cholesterol hydroperoxide (ChOOH) species. 7-OOH is redox-active and cytotoxic, and gives rise to the 7-OH and 7=O observed in high quantities in atherosclerotic plaques. We have recently shown that 7-OOH, when transported to/into macrophage mitochondria via a StAR protein network can induce damaging lipid peroxidation. This alters mitochondrial function and inactivates the inner membrane enzyme, 27-hydroxylase (Cyp27A1), which regulates the expression of transporters involved in export of excess cholesterol via the reverse cholesterol transport (RCT) pathway. This proposed project will characterize this oxidative process more extensively, explore its role in atherogenesis, and develop preventative antioxidant approaches.