Severe hyperhomocysteinemia (HHcy) due to genetic alterations in cystathione-β synthase (CBS), methylenetetrahydrofolate reductase (MTHFR), or cobalamin metabolism (CblC) results in neurological abnormalities and premature death from vascular complications. In the general population, HHcy is associated with increased risk of cardiovascular disease and stroke. However, mechanisms by which HHcy causes heart and brain pathologies remain obscure. Due to the fact, that homocysteine is a redox active compound, induction of oxidative stress is one of the most favored postulated mechanisms of homocysteine toxicity. Despite numerous studies, the mechanism of oxidative stress and its role in hyperhomocysteinemia are not fully understood.

The aim of the project is to elucidate the mechanism of oxidative stress response and its role in toxicity of hyperhomocysteinemia. We will study the mechanism of oxidative stress and its role in the long-term survival of hyperhomocysteinamic knock-out mice (*in vivo*) and also in mouse cells *in vitro*. Our methodology includes basic science approaches such as moues models, cell culture models, protein science, biochemistry, enzymological and immunological assays developed or adapted in our laboratory and described in detail in numerous publications. A novel concept that oxidative stress has an adverse effect on long-term survival in mice with hyperhomocysteinemia will be examined.

The main hypothesis of this proposal is that oxidative stress is the cause of shorter life span in humans and mice in hyperhomocysteinemia. This hypothesis will be examined through the following specific aims:

1) Long term survival of mice exposed to dietary hyperhomocysteinemia
2) Does Paraoxonase 1 (Pon1) affect long term survival of mice?
3) Oxidative stress biomarkers in mouse tissues
4) Mechanism of oxidative stress in hyperhomocysteinemia in mouse liver and kidney cells in vitro

In addition to eluciadting fundamental aspects of oxidative stress induced by hyperhomocysteinemia in mice (*in vivo*) and in mouse liver and kidney cell lines *(in vitro)*, findings of this project will also provide insights into possible mechanisms underlying shorter life span in humans and mice with hyperhomocysteinemia.