As our population is aging and efficacious treatments for the disease are not available, identification of risk factors for neurodegenerative diseases including Alzheimer's disease (AD) and elucidation of mechanisms of their action has important public health implications.

Elevated plasma homocysteine (Hcy), *i.e.* hyperhomocysteinemia (HHcy), and low activity of paraoxonase 1 (PON1), an enzyme carried in the blood on high-density lipoprotein (HDL – 'good cholesterol'), which deactivates toxic metabolite Hcy-thiolactone (HTL), are emerging risk factors for AD. HTL forms amide bonds with protein lysine residues, causing protein damage in a process called *N*-homocysteinylation. *N*-Hcy-proteins have altered function and tend to form cytotoxic aggregates. HHcy is characterized by elevated level of HTL and attenuated autophagy, a process responsible for removal of damaged cell components, which promotes the accumulation of toxic protein aggregates and would lead to the development of AD. This project focuses on the pathophysiological consequences of impaired HTL detoxication in mouse models of AD and HHcy.

The central hypothesis of the present project is that Pon1 protects against the development of AD by facilitating hydrolytic deactivation HTL, thereby attenuating the accumulation of toxic protein aggregates in the brain.

To test this hypothesis we propose the following specific aims:

1. Explore role of Pon1 in the development of AD (by following the accumulation of amyloid aggregates in the brain) and in cognitive function (by behavioral tests) using an AD mouse model (5xFAD) combined with *Pon1* gene knockout under dietary HHcy and control conditions.
2. Elucidate mechanisms by which Pon1 and HHcy mediate cognitive decline and AD in these mice by studying biological processes such as: endoplasmic reticulum stress, unfolded protein response, and apoptosis; inflammation and immune activation; epigenetic regulation of mTOR signaling and autophagy.

This project will explain mechanistic links between HHcy, Pon1 and AD pathophysiology and provide new insights into the causes, prevention, and treatment of neurodegenerative diseases. Understanding of how HHcy and impaired Pon1 activity promote the development of cognitive decline and AD is essential for public health.