Alzheimer's disease, the most common multifactorial neurodegenerative disease associated with dementia in the elderly, is one of the major public health problems in industrialized societies. The disease affects tens of millions of people worldwide and is characterized by the deposition of toxic proteins known as β-amyloid (Aβ) and phospho (p) Tau in the brain parenchyma and blood vessels in the brain, resulting in neuronal loss and cognitive impairment. Identifying risk factors for Alzheimer's disease, and understanding how it develops, is of particular importance for public health policy in our society.

Previous research has shown that elevated levels of homocysteine (Hcy) as well as decreased activity of a protein called bleomycin hydrolase (BLMH), which removes a toxic substance called homocysteine thiolactone (HTL) from the body's tissues, triggers neuropathic changes in the brain proteome, and is risk factors for Alzheimer's disease. HTL is also an independent risk factor for cardiovascular disease that contributes significantly to Alzheimer's disease. HTL is toxic because it chemically reacts with proteins and damages their structure. The proteins damaged by HTL form deposits that cause cell death and thus may contribute to the development of Alzheimer's disease. Our preliminary studies have shown that Blmh deficiency and elevated HTL levels activate mTOR signaling, inhibit the removal of damaged proteins (autophagy), and lead to the accumulation of amyloid Aβ deposits in neurons. The present project builds on these findings to investigate in murine models of Alzheimer's disease the mechanisms by which BLMH deficiency may influence the development of the disease.

The overall goal of the current project is to test the hypothesis that BLMH has a neuroprotective function in the brain due to its ability to detoxify HTL and prevent the accumulation of toxic protein aggregates. In order to verify this hypothesis, we will implement the following specific goals:

(1) To investigate effects of Blmh deficiency on cognitive function and development of Alzheimer's disease features, using a mouse model (*3xTg-AD*) with Blmh gene turned off under dietary elevated Hcy and control conditions by measuring (1a) cognitive performance and (1b) accumulation of Aβ deposits and pTau in the brain;
(2) To elucidate the mechanisms by which Blmh deficiency can accelerate the development of Alzheimer's disease using the Blmh knockout mouse model (*3xTg-AD*) under dietary elevated Hcy and control levels, as well as altering Hcy and HTL levels in mouse neuroblastoma cells (N2A-APPSwe) to test: (2a) endoplasmic reticulum stress, response to unfolded proteins and apoptosis; (2b) inflammation and activation of the immune response; (2c) epigenetic regulation of mTOR signaling and autophagy.

This project will explain the mechanistic links between Blmh, Hcy, mTOR signaling, autophagy, inflammation, and structural (Aβ and pTau accumulation) / functional (cognitive deficit) aspects of the pathophysiology of Alzheimer's disease, thus providing new insight into the causes, prevention and treatment of this disease.