For many years homocysteine (Hcy) is an object of intense research in the context of human pathophysiology. Elevated levels of Hcy referred to as hyperhomocysteinemia (HHcy) is a result of genetic defects in the Hcy metabolism and environmental factors such as: a high protein diet, lack of exercise, smoking or vitamin deficiencies. HHcy leads to pathological changes in many organs and premature death due to complications in the cardiovascular system.

Clinical studies have shown that elevated Hcy is a risk factor for Alzheimer's disease (AD). Elevated Hcy has also been associated with cognitive impairment and amyloidosis in mouse models. B-vitamin treatment that lowers Hcy levels, significantly improves cognitive function in humans, slows the rate of human brain atrophy in subjects with mild cognitive impairment and improves brain function in AD mouse models. Proteins modified by an toxic Hcy metabolite has autoimmunogenic and amyloidogenic properties and autoantibodies anti those proteins are associated with stroke. Our studies showed that Hcy-thiolactonase activity is reduced in the brains of AD patients. We also found that HHcy changes expression of mice brain proteins (brain-specific protein, oxidative stress response proteins and proteins responsible for the brain plasticity).

The main hypothesis of this project is that HHcy in the brain promotes inflammation which is a marker of aging and deregulates autophagy (cellular regulation of disassembles unnecessary or dysfunctional cellular components such as proteins), thereby causing neurodegeneration and impairment of cognitive function.
Our hypothesis will be tested using mouse models of HHcy by utilizing the following specific aims:

Aim 1: Identify changes in the mouse brain (hippocampus, cortex, cerebellum) proteome induced by dietary HHcy (high-Met and Hcy diet).
Aim 2: Investigate effects of HHcy on aging in mice.
Aim 3: Elucidate mechanisms by which brain autophagy is affected in HHcy.
Aim 4: Determine how HHcy affects cognitive function in aging mice.

Implementation of the project will enable a complete study of the proteome changes in the mouse brain, as well as analysis of selected processes such as induction of inflammation, immune response, and autophagy in aging and HHcy. At the same time behavioral studies will link specific alteration caused by HHcy in proteomes of brain regions with memory and cognitive functions in mice.

We believe that the completion of this proposal will provide new insights and fundamental information regarding the role of Hcy and its metabolites in the development of neurodegenerative diseases and explain the underlying molecular mechanism(s).