(State the objective of the project, describe the research to be carried out, and present reasons for choosing the research topic - max. 1 standard type-written page)

Homocysteine (Hcy) is a sulphur amino acid, which is formed from methionine received from food. The state of elevated 'total' Hcy (tHcy) level in the blood, called hyperhomocysteinemia (HHcy) leads to cardiovascular disease (CVD) in the general population and is a strong predictor of mortality in CVD patients. However, large randomized controlled trials (RCTs) show that tHcy-lowering by folic acid and B-vitamin supplementation does not improve vascular outcomes. A possible reason for these dissonant results is that tHcy is a composite marker that does not encompass Hcy-thiolactone (HTL), a toxic metabolite which has been independently implicated in CVD. Recent studies from the PI's group using samples from a large-scale RCT show that HTL is a predictor of acute myocardial infarction in CVD patients, independent of established risk factors and plasma tHcy. Plausible mechanisms by which HTL can promote atherothrombosis and CVD have been demonstrated. We therefore hypothesize that HTL causes CVD by promoting thrombosis and an auto-immune response. To test this hypothesis we will built on our prior studies of the Western Norway B Vitamin Intervention Trial (WENBIT) cohort and a comprehensive dataset based on more than 3,000 CVD patients.

Proposed study will be performed using plasma samples collected at baseline (n=2,364) and 38-months follow-up (n=2,131). We will analyze how fibrin clot lysis time and anti-*N*-Hcy-protein antibody titers are affected by B-vitamin supplementation in CVD patients from a large-scale, prospective, randomized, placebo-controlled WENBIT trial. We will analyze associations of fibrin clot lysis time and anti-*N*-Hcy-protein antibody titers with subsequent myocardial infarction (cardiovascular death, non-fatal myocardial infarction) and mortality. The usefulness of fibrin clot lysis time and anti-*N*-Hcy-protein antibody titers as predictors of these outcomes will be determined. Associations of fibrin clot lysis time and anti-*N*-Hcy-protein antibody titers with PON1 activity, HTL, CVD history, gender, smoking, hypertension, diabetes, microalbuminuria, MTHFR 677C->T polymorphism, plasma B-vitamins, betaine, tHcy, glomerular filtration rate (GFR), and circulating inflammation markers (CRP, neopterin, and KTR - kynurenine/tryptophan ratio) will also be investigated.

We believe that this study will generate new fundamental information regarding mechanistic link between HTL, fibrin clot lysis and anti-*N*-Hcy-protein antibodies and will lead to new insights into the causes, prevention, and treatment of cardiovascular pathologies associated with HHcy. This project is innovative at the conceptual level by proposing several previously unexplored ideas that might lead to identification of new risk factors for CVD and explain lack of efficacy of tHcy-lowering by folic acid and B-vitamin treatment in RTCs.