Hyaluronic acid receptor stabilin-2: determination of the crystal structure and biochemical characterization of its binding to hyaluronic acid.

The aim of this project is to determine the three-dimensional structure of stabilin-2 by means of methods of X-ray crystallography, as well as to biochemically characterize its binding to hyaluronic acid.
This project constitutes basic research in life sciences; in particular, in the field of biochemistry, molecular biology and structural biology.
The main reason for conducting the research on stabilin-2 is the potential involvement of stabilin-2 in cancer progression.

Stabilin-2 belongs to the group of the scavenger receptors and plays a crucial role in clearance of more than 10 ligands from bloodstream, including products of degradation of the extracellular matrix and metabolic products. One of these ligands is hyaluronic acid that binds to the Link domain of stabilin-2. Present knowledge of ligands' recognition and binding, as well as mechanisms of signal transduction by stabilin-2, is limited.
It has recently been demonstrated that the stabilin-2 knock-out or blocking of the receptor by an antibody effectively opposes cancer metastasis by elevating the level of the circulating hyaluronic acid.
According to the World Health Organization, cancers figure among the leading causes of morbidity and mortality worldwide. In 2012, approximately 14 million new cases of this disease and 8.2 million deaths related to it were identified. It is expected that annual cancer cases will rise to 22 millions within the next 2 decades. One defining feature of cancer, a generic term for a large group of diseases that can affect any tissue in any part of the body, is the rapid creation of abnormal cells that grow beyond their usual boundaries. These cells can then invade adjoining parts of the body and spread to other organs in the process referred to as metastasizing. Metastases are the major cause of death from cancer.
Recent research has shown that a dramatic increase of the circulating hyaluronic acid level (in contrast to hyaluronic acid that builds the extracellular matrix) was observed in the stabilin-2 knock-out mice without any overt phenotype. The Stab2 knock-out mice showed the decreased level of metastases in melanoma cancer cells. Moreover, administration of the monoclonal antibodies specific towards stabilin-2 to mice with the normal stabilin-2 expression caused the increase of circulating hyaluronic acid and prevented metastasis of melanoma and human breast cancer cells to the lungs. Results of this research showed that blocking the stabilin-2 function, either by the gene knock-out or monoclonal antibodies towards the receptor, effectively opposes cancer metastasis by increasing the level of the circulating hyaluronic acid.
Experimental structures of any of the stabilin-2 domains are not known until today. Determination of the three-dimensional structure of the Link domain of stabilin-2 responsible for the hyaluronic acid binding, possibly with the domains surrounding it, would provide valuable information for understanding the mechanism of the hyaluronic acid ligand binding and clearance. Determination of the crystal structure of stabilin-2 would also allow for the rational design of the tightly binding small-molecule antagonists of this protein and, consequently, open up a prospect for new chemical probes for studying the signaling in the stabilin-2 pathway. Another reason for the proposed research is that the structural information can enhance structural studies on proteins with a similar domain organization and function. Moreover, the detailed biochemical characteristics of the hyaluronic acid binding would bring more insights into the involvement of stabilin-2 in cancer progression and metastasis.