Status of CIPKeBiP: Participating organisation
Title of the project: **Role of cysteine proteases in the process of cancerogenesis**
Coordinator: **Dr. Marko Fonović**
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CIPKeBiP Membership

Name	ARRS code	Research area	Position
Dr. Boris Turk	07561	Biochemistry and molecular biology	Researcher 2013-2016
Dr. Eva Žerovnik	03368	Biochemistry and molecular biology	Researcher 2014-2016
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Abstract
Proteases play a crucial role in cell surface signaling pathways and extracellular matrix remodeling. Cell surface proteins can be activated, inactivated or can undergo other changes in their function upon proteolysis. Cysteine cathepsins are a group of papain-like cysteine proteases, which are mainly located within the endosomes/lysosomes. They execute non-specific bulk proteolysis and participate in numerous specific physiological processes such as protein processing, antigen presentation and processing, bone remodeling and apoptosis. In certain pathological states such as cancer, cathepsins can be translocated to the cellular membrane or secreted in the extracellular space, where they are known to promote angiogenesis, proliferation and tumor invasion. Only a few extracellular cathepsin substrates have been identified to date and their exact role in cancerogenesis still remains largely unknown. In the course of our previous work (project J1-0185), we have used proteomic approach for identification of cell surface cathepsin substrates, that led to the identification of a novel group of membrane protein substrates for cathepsins L, S and B (manuscript in preparation). We were the first who have shown that cathepsins can act like sheddases and cleave specific protein domains from the cell surface. We have also shown that cathepsin extracellular activity directly promotes cancer invasion. Among identified cathepsin substrates are receptors (CD71, CD109, plexins, ephrin receptors, neuropilins), adhesion proteins (CD44, CAM proteins) and desmosome/hemidesmosome components (plectin, plakins, cytokeratins). The majority of identified susbstrates is known to be involved in cancer progression.

The main goal of the proposed research is the identification and validation of signaling pathways involving the identified substrates and expansion our substrate search to other interesting cysteine proteases (cathepsins K, V and legumain).

Since it is well documented that cysteine proteases play an important role in the process of cancerogenesis, we believe that a deeper physiological characterization of those proteolytic events will provide a completely novel insight into the regulation of cancer development at the molecular level. Results of the proposed project would likely reveal novel cancer biomarkers and open the way towards new therapeutical approaches for cancer treatment. We are convinced that our findings will achieve high international impact. Novel scientific approaches applied in this project will benefit not only our field of research but also the entire Slovenian scientific community.