Status of CIPKeBiP: Partner
Title of the project: **Role of cysteine cathepsins in inflammation-associated diseases**
Coordinator: **Prof.Dr. Boris Turk**
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CIPKeBiP Membership

Name	ARRS code	Research area	Position
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Abstract
Inflammation is a complex biological response of the host organism to invading pathogens, neoplasm, or physical tissue injury that involves various cells of the immune system as well as other local cells and components of extracellular milieu. While the onset of inflammation is normally beneficial because it represents an alarm signal to injury or disease emergence, the lack of resolution of inflammation can lead to several diseases, such as cancer and atherosclerosis. In addition, the inflammatory response can be induced because of degenerated crosstalk of the host's immune cells and surrounding tissue, which can lead to autoimmune conditions, such as in rheumatoid arthritis, psoriasis and type 1 diabetes. Monitoring onset of inflammation, its response to therapy and relapse in these diseases, collectively known as inflammation-associated diseases, is therefore crucial for successful treatment and efficient selection of therapeutics. Among the factors that are usually highly overexpressed in these diseases and therefore offer a major potential as both diagnostic and/or therapeutic targets are proteases. However, understanding the precise role of an individual protease in a disease remains a major challenge for successful therapeutic applications. Cysteine cathepsins, in particular cathepsins B and S, have often been linked with such inflammation-associated diseases, especially cancer, rheumatoid arthritis and atherosclerosis. Their genetic ablation and in some instances chemical inhibition were found to significantly delay or even prevent disease progression. However, it remains to be established whether this is a consequence of reduced inflammation or due to their broader role in disease onset and progression.

In order to address these issues, we propose to develop selective macromoleular imaging tools for cathepsins B and S, based on the designed ankyrin repeat protein technology, which is well-established for non-protease targets, and on the scaffold of stefin A, an endogenous thight-binding cathepsin inhibitor that has never been evaluated as such a tool, and characterize them. We will use in vivo imaging to evaluate these novel macromolecular imaging probes as tools for monitoring disease progression and drug efficacy, including that of novel antiinflammatory drugs, as well as to evaluate the causal role of the two cathepsins in animal disease models associated with inflammation, which have been established in our laboratory. This will enhance our understanding of disease progression at the molecular level and our ability to rapidly evaluate novel therapies, which would take Personalized Medicine to the next level. Selected macromolecular probes will be optimized to assess their potential as clinical diagnostics, whereas the inhibitory probes will be also evaluated for their theranostic potential.