The primary aim of this project is to investigate the short- and long-term effects of the adipose-derived mesenchymal stromal cells treatment of sepsis in clinically-relevant murine models. Sepsis has been recognized by the World Health Organization as the global health priority and it has been estimated that as much as 11 million people die of sepsis annually. Mortality rates in septic shock reach 50% but as many as 60% of survivors do not fully recover. Especially the older population is at risk of the long-term consequences of sepsis which include muscle weakness, cognitive dysfunctions and emotional and anxiety disorders. Altogether, it often leads to the deterioration of the quality-of-life and even the necessity to live in the nursing facilities. Moreover, immune disturbances appear which increase risks of re-infections and death due to them. So far, no specific sepsis treatment exists apart from antimicrobials, fluids and supportive therapies. Studies investigating the influence of administered treatment on the long-term health effects of the sepsis survivors are missing. One of the promising therapeutic option for sepsis is the use of mesenchymal stromal cells (MSCs). MSCs are present in virtually all tissues and can easily be isolated and cultured. Of interest, these cells exert multiple immunomodulatory effects, they act anti-inflammatory but at the same time they boost bacteria clearance. Early studies in animal models of sepsis showed protective effects of MSCs application. On this base pahse I clinical trials have been performed which confirmed safety of MSCs but little biological effects have been observed. In order to facilitate the successful clinical use of MSCs we developed this study which aims to investigate whether MSCs therapy can improve the clinical course and long-term survival in peritonitis sepsis in old mice and humanized mice (with transplanted human immune cells). We also plan to evaluate the effects of MSCs treatment on the quality-of-life of surviving animals (muscle strength, physical activity, cognitive functions, anxiety disorders). To accomplish these goals, we will use advanced biotelemetry monitoring systems, clinical assessment scales and physiological and behavioral tests. In the second part of the study we plan to investigate the changes induced by the MSCs treatment at the molecular level (transcriptomic, protein and metabolomic). Also, a retrospective correlation analysis of these changes with the clinical effects will be performed. By the retrospective analysis we will also try to identify factors that may indicate treatment-responder's subgroup.

This project includes numerous clinically-relevant translational aspects. The experiments will be performed with the use of two complimentary animal models. Old mice respond to sepsis with higher severity and their regenerative capacities are limited which models the clinical situation (most septic patients are >65y.o.). Humanized mice are unique model enabling studies of the human cells in their tissue niches in controlled manner. Therefore, species-specific effects can be studied. The study protocol will include important aspects such as randomization, delyed treatment, supportive therapies, monitoring. While designing this study we aimed to accomplish the 3Rs rule which include reduction number of animals, refinement of their treatment and replacement by in vitro experiments where possible.

We expect that the proposed study will be helpful in designing clinical therapy reducing the mortality and improving the quality-of-life of sepsis survivors. Obtained results will provide new knowledge on the pathophysiology of the long-term consequences of sepsis and will help to improve the design of clinical trials with cellular therapeutics.