

Sepsis—a life-threatening multiorgan dysfunction caused by a dysregulated host response to infection—is a major global health issue, contributing to high mortality (20% of global deaths in 2017), healthcare expenditures (~\$28,000/ per patient), and leading to long-term complications, particularly in patients over 65 years of age. Among these complications, persistent skeletal muscle weakness is especially burdensome, significantly reducing patients' quality of life, for example, by hindering their return to professional activity.

To date, the underlying mechanisms of organ dysfunction in sepsis have been only vaguely described, primarily in young male mice and mainly during the acute phase of the disease, while the immunological context, which is particularly important in sepsis, has often been overlooked. Only a few available studies provide evidence on the causes of long-term muscle impairment after sepsis. Therefore, our current knowledge remains insufficient and requires urgent expansion, particularly concerning studies involving female mice, skeletal muscle, chronic dysfunction, and immune context. Our study combines these elements in an attempt to fill these critical knowledge gaps.

With the support of this funding, we will comprehensively characterize the immune state of skeletal muscle, referred to as the immune profile, during both the acute and chronic phases of sepsis. For this purpose, we will induce sepsis in a group of 18-month-old C57BL/6 mice. We will evaluate their physical performance and other clinically relevant parameters such as body temperature and weight, followed by tissue collection for cellular and molecular analyses. A comprehensive approach will be ensured by integrating results from widely used immunological techniques, including flow cytometry, cytokine level quantification, and proteomic analysis. The result of this integration will be the development of a numerical scoring index for assessing the immune profile of skeletal muscle in prolonged sepsis (SMIPS). In the final phase, we will examine whether the SMIPS score correlates with functional test performance. A similarly innovative approach, with this level of complexity, has not yet been applied in studies of skeletal muscle after sepsis.

We believe that our research will demonstrate significant differences in the immune profile of skeletal muscle between the acute and chronic phases of sepsis. Furthermore, it will identify key immune cell populations, cytokines, and signaling pathways involved in the development of long-term muscle weakness following sepsis. The SMIPS index may in the future serve as a comparative tool in translational studies, bridging laboratory findings with clinical knowledge and facilitating further research into diagnostics and treatment of patients affected by sepsis-related complications. The importance of such studies is underscored by recent analyses pointing to a growing number of patients with long-term sequelae of sepsis.