White blood cells or leukocytes belong to the immune system that is responsible for defense mechanisms in the body i.e. the cells are able to recognize and kill invading pathogens (e.g. bacteria), and they achieve so by releasing various mediators such as cytokines or chemokines, direct phagocytosis of the pathogens and their intra- and extracellular killing. During immune responses, different types of leukocytes (neutrophils, monocytes/macrophages and lymphocytes) interact with each other e.g. they exchange information, activating or suppressing each other. Depending on the pathological conditions, such as those accompanying various diseases or syndromes, the cells might leave the blood and migrate to inflamed tissues but they might also fight infection in the blood if this is the site of infection. The latter situation occurs during sepsis which is a systemic inflammation of the body and is a major cause of death for patients in the intensive care units and the third common cause of death in western countries. In fact, sepsis kills 11 million people each year out of 49 million annual cases (app. 30% mortality), many of them are children (up to 50%). Many of survivors will be disabled for life. Moreover, patients who are critically ill e.g. those with severe COVID-19 are at higher risk of developing and dying from sepsis. The unfavorable statistics result mainly from the fact that no specific therapies exist to treat septic patients (also diagnosis is difficult as no unique symptoms are displayed), and the treatment relays mainly on fluid resuscitation, delivery of antibiotics, lung protective ventilation, or blood transfusions. To propose a therapy, mechanisms of a given conditions have to be known and furthermore, specific targets have to be recognized (e.g. cells, receptors, transduction signals). Scrutinizing for the mechanisms of sepsis, we hypothesized that thus far not all cellular players of hematopoietic origin (hence the same as leukocytes) were studied in detail in sepsis, and in particular, red blood cells (erythrocytes) and platelets were hardly studied in the context of the immunological response. These two cells/cellular components (platelets are fragments of megakaryocytes that break up, thus biologically platelets are not cells) are highly specialized. Whereas red blood cells are responsible for oxygen distribution in the body, platelets are critical for coagulation when bleeding occurs. However, we recently learnt that similarly to leukocytes, also RBCs and platelets can bind pathogens, store cytokines/chemokines, and collaborate with each other and/or leukocytes to cause thrombosis. This strongly implies that the two carry immunological functions but their impact on the course of sepsis was not studied in detail and especially not *in vivo* i.e. in the living organism. We hypothesized, based on the above facts and our preliminary data, that all cellular components of blood are critical for the course of sepsis and that overall erythrocytes and platelets might be as important as leukocytes during systemic inflammation (their functioning or fate might impact sepsis outcome). We will test the hypothesis on a mouse model and on 3 types of sepsis ($Gram^+$, $Gram^-$ and polymicrobial) and we shell use advanced microscopic technique called intravital microscopy (*in vivo* microscopy) that allows for visualization of processes occurring in blood vessels of live mice in real time. With this technique we can observe and record any cell interactions, their consequences and overall study the inflammatory process characteristic to sepsis.

In the studies we will further evaluate significance of these interactions by selectively (pharmacologically) removing from the body one blood cell population at the time to verify if their lack will change the course of sepsis. We will study neutrophils, monocytes, Kupffer cells (macrophages residing in blood vessels of the liver) and lymphocytes interacting with erythrocytes and platelets. As RBCs cannot be completely removed due to their function in gas transport/exchange, we will employ 3 models of their partial depletion (pharmacological, diet-induced or genetic models of anemia). Among the parameters that we will measure, the following functions of leukocytes will be monitored: bacteria phagocytosis, release of stored cytokines (cytokine storm), secretion of microvesicles, as well as formation of extracellular traps (ETs). The latter structures are composed of externalized DNA decorated with proteins (e.g. originating from granules) of the cells casting ETs. Whereas neutrophil extracellular traps (NETs) were proven to be ejected *in vivo*, their monocyte/macrophage counterparts (METs) were not. We will undertake a task of verifying if also METs are casted in blood vessels in sepsis and what impact platelets and RBCs have on this process. Whereas at first ETs function to trap and immobilize bacteria, as they persist in vasculature, they damage our own tissues, thus it is important to learn about mechanisms of their removal from blood vessels. For this we will also investigate engagement of erythrocytes and platelets in removal of any ETs based on recent findings on their unique expression of relevant receptors.

Once we learn how and to what degree, erythrocytes and platelets are engaged in the course of sepsis, we will propose strategies to modulate the identified processes. We already propose some strategies, e.g. in relation to cellular metabolism. Overall we aim at explaining significance of erythrocytes and platelets for functioning of the immune response in the course of sepsis, and we believe they might be of importance also in other pathological conditions, especially those blood-related.