The liver, as the largest internal organ, plays a crucial role in maintaining metabolic functions and immune defense in the body, with over 500 recognized functions. When systemic inflammation (sepsis) occurs, it is in the liver where pathogens (e.g., bacteria) are captured by liver macrophages. Hence, liver failure can result in death due to infection or loss of metabolic support. Inflammation can be dual in nature: it can be initiated by infection (e.g. bacteria entering the body) or in response to injury. The latter can be caused by mechanical trauma, deposition of certain molecules, or overuse of drugs or alcohol. It is especially dangerous if it lasts for a long time and becomes chronic. Infectious inflammation is particularly dangerous when pathogens enter the bloodstream, as many organs can malfunction simultaneously. Such systemic inflammation (sepsis) is very dangerous and results in high mortality. Additionally, when a person with a malfunctioning liver develops sepsis, the chances of survival are very low. For this reason, it is important to study the course of inflammation in either case, i.e., chronic liver injury and sepsis, while scrutinizing for new therapeutic targets.

One particular type of white blood cell (leukocyte), called neutrophils, plays a significant role in both types of inflammation. While they have the capacity to eliminate pathogens and aid in healing, they also contribute to tissue damage and organ failure if overactivated and/or chronically present. Neutrophils release structures called neutrophil extracellular traps (NETs), which entrap and help eliminate pathogens. NETs are formed during both types of inflammation. However, they are not removed in a timely manner during sepsis, and their formation during sterile injury is not fully understood. The side effect of NET formation is tissue damage, fibrosis, and exacerbation of chronic injuries. Moreover, we now recognize that neutrophils are a heterogeneous (diverse) group of cells that express unique molecules during their lifespan. One such type of molecule is Siglec (Siglec-E and Siglec-F). Our preliminary data suggest that neutrophils with different patterns of Siglec receptors participate in various neutrophil activities, including the formation of NETs.

The aim of the project is to investigate and characterize different populations (groups) of neutrophils in connection with Siglec molecules and their capacity to form and remove NETs. The studies will require mouse models of diseases (chronic liver injury and sepsis), and neutrophils, NETs, and other cells will be studied using state-of-the-art techniques such as intravital microscopy, proteomics, and metabolomics. Major findings will then be verified in human blood samples. The project also aims to identify targets for developing targeted therapeutic strategies that could help treat chronic liver injury, fibrosis, and sepsis in the future.