Macrophages are innate immune system cells that have many biological functions and their major role is protecting organisms from infections and regulating tissue homeostasis. They are capable of engulfing pathogens and cellular debris but also secrete a large variety of factors that help to kill invaders and modulate activity of other immune cells. Macrophages reside in every tissue of the body, which guarantees very rapid response to a potential threat. Macrophages may, however, also contribute to pathological states such as autoimmune disease, fibrosis, obesity and diabetes. Furthermore, growing evidence indicates that macrophages present in tumours instead of being effective in host-defence, actually contribute to cancer progression.

Macrophages are phenotypically highly plastic cells and can change their physiology depending on the environmental cues they receive. This ensures that macrophage response is adjusted properly to the specific insult. The high phenotypic plasticity, however, requires extremely precise mechanisms that orchestrate gene transcription. This is achieved by the involvement and cooperation of several signalling pathways and transcription factors. For example, bacterial infection triggers so called classical activation of macrophages. These macrophages are characterised by the secretion of large amounts of different factors that help to kill invading bacteria. This requires an increase in protein synthesis which depends on several elements such as ribosomes and transfer RNAs (tRNA).

tRNAs are synthesized by RNA polymerase III (Pol III), a highly evolutionarily conserved enzyme. Apart from tRNAs, Pol III is also responsible for synthesis of other small RNAs that are crucial for cell growth and proliferation. Deregulation of Pol III transcription has been implicated in a variety of human diseases, including cardiovascular disorders and cancer. Our own results and those of others also show that Pol III may be implicated in immune responses. Specifically, our previous work shows that under conditions mimicking bacterial infection (and also classical activation), macrophages induce Pol III activity and produce more tRNAs. We also showed that tRNA upregulation is required for proper macrophage function. The mechanism, however, that underlies the induction of tRNA synthesis is not fully understood. Therefore, the aim of this project is to elucidate the mechanisms that activate Pol III in macrophages during classical activation. The proposed research will provide new insights into molecular mechanisms of Pol III regulation in macrophages and expand our knowledge about the biology of these fascinating and important immune cells. Connecting Pol III transcription to macrophage function may help to find new targets for therapeutic intervention in autoimmune diseases or in life-threatening macrophage activation syndrome or septic shock.