Junior Research Group **Andreev**

Title:

Unraveling the mechanistic role of heme peroxidases in the polarization of pro-resolving macrophages during inflammatory arthritis

Keywords:

Rheumatoid arthritis, classical macrophages, alternatively activated macrophages, heme peroxidases, eosinophil peroxidase, myeloperoxidase, resolution of inflammation

Detailed description:

Monocyte-derived cells exhibit a dual role in the progression of rheumatoid arthritis (RA). While classical macrophages and bone-resorbing osteoclasts drive the inflammatory and destructive processes in arthritis, alternatively activated macrophages (AAMs) mitigate inflammation through the production of anti-inflammatory cytokines and efferocytosis of dying immune cells. Our previous research has demonstrated that type 2 immunity, triggered by helminth infection or allergic asthma, facilitates the resolution of arthritis. Eosinophils, predominantly located within the articular tissue, are key players in this pro-resolving action. We have observed that eosinophils indirectly restore tissue homeostasis by inducing AAMs. However, the molecular mechanism responsible for eosinophil-dependent polarization of AAMs remains elusive.

Through screening the secretome of eosinophils, we have identified high levels of heme peroxidases, particularly eosinophil peroxidase and myeloperoxidase, suggesting these enzymes as potential pro-resolving agents. Building upon these preliminary findings, we hypothesize that heme peroxidases drive macrophage reprogramming towards AAMs. This project aims to characterize macrophages from rodent and human sources stimulated with heme peroxidases, evaluating their gene expression profile, metabolic state, and immunological function. Furthermore, we aim to elucidate the cellular and molecular mechanisms underlying AAM polarization by heme peroxidases both in vitro and in vivo during arthritic inflammation.

Overall, this proposal seeks to deepen our understanding of the role of heme peroxidases in the chronicity versus resolution of inflammatory arthritis and to explore novel therapeutic avenues.