Junior Research Group **Andreev**

Title:

Exploring the Metabolic and Epigenetic Rewiring of Eosinophils Governed by the Tissue Environment

Keywords:

Eosinophils, Type-2 Immunity, Metabolism, Tissue-specific microenvironment

Detailed description:

Eosinophils have usually been linked to immune defense against parasites and immunopathologies including asthma and inflammatory bowel disease (IBD) (1, 2). However, recent findings from our group and other leading labs have redefined this perspective, revealing that eosinophils also play pivotal roles in tissue development, homeostasis, and regeneration (3-5). Despite this, the molecular mechanisms underlying these pleiotropic functions remain entirely unknown, particularly how eosinophils lose their homeostatic potential and become cytotoxic during inflammation.

Our omics data offer novel insights into eosinophil polyfunctionality, revealing that their phenotypes are shaped by the tissue environment they inhabit. We propose that these spatial adaptations are driven by metabolic and epigenetic rewiring, supported by my discovery of unique metabolic profiles in different eosinophil subtypes (4).

This project aims to leverage recent technical breakthroughs to establish a comprehensive metabolic, transcriptomic, and anatomical atlas of eosinophil populations at mucosal sites compared to their bone marrow origins during health and disease. By using cutting-edge methodology such as isotope tracing, SCENITH, scRNA-seq, scATAC-seq, Epi-CyTOF, 3D light sheet- and confocal microscopy, the project will explore how metabolic and epigenetic rewiring underpins eosinophil plasticity. We seek to identify characteristics that distinguish harmful, inflammatory eosinophils from their beneficial, tissue-regulating counterparts.

Subsequently, We will validate the relevance of newly identified molecular pathways in priming inflammatory eosinophils, and their contribution to asthma and IBD in both mouse and human. The overarching goal is to develop therapies that selectively target pro-inflammatory eosinophils while preserving the homeostatic eosinophil population. This approach aims to pave the way for more precise treatments of eosinophil-driven diseases, promoting remission without compromising tissue integrity.

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2 Chen, Z. *et al.* Th2 and eosinophil responses suppress inflammatory arthritis. *Nat Commun* **7**, 11596 (2016). https://doi.org/10.1038/ncomms11596

3 Weller, P. F. & Spencer, L. A. Functions of tissue-resident eosinophils. *Nat Rev Immunol* **17**, 746-760 (2017). https://doi.org/10.1038/nri.2017.95

4 Andreev, D. *et al.* Regulatory eosinophils induce the resolution of experimental arthritis and appear in remission state of human rheumatoid arthritis. *Ann Rheum Dis* **80**, 451-468 (2021). https://doi.org/10.1136/annrheumdis-2020-218902

5 Andreev, D. *et al.* Eosinophils preserve bone homeostasis by inhibiting excessive osteoclast formation and activity via eosinophil peroxidase. *Nat Commun* **15**, 1067 (2024). https://doi.org/10.1038/s41467-024-45261-8