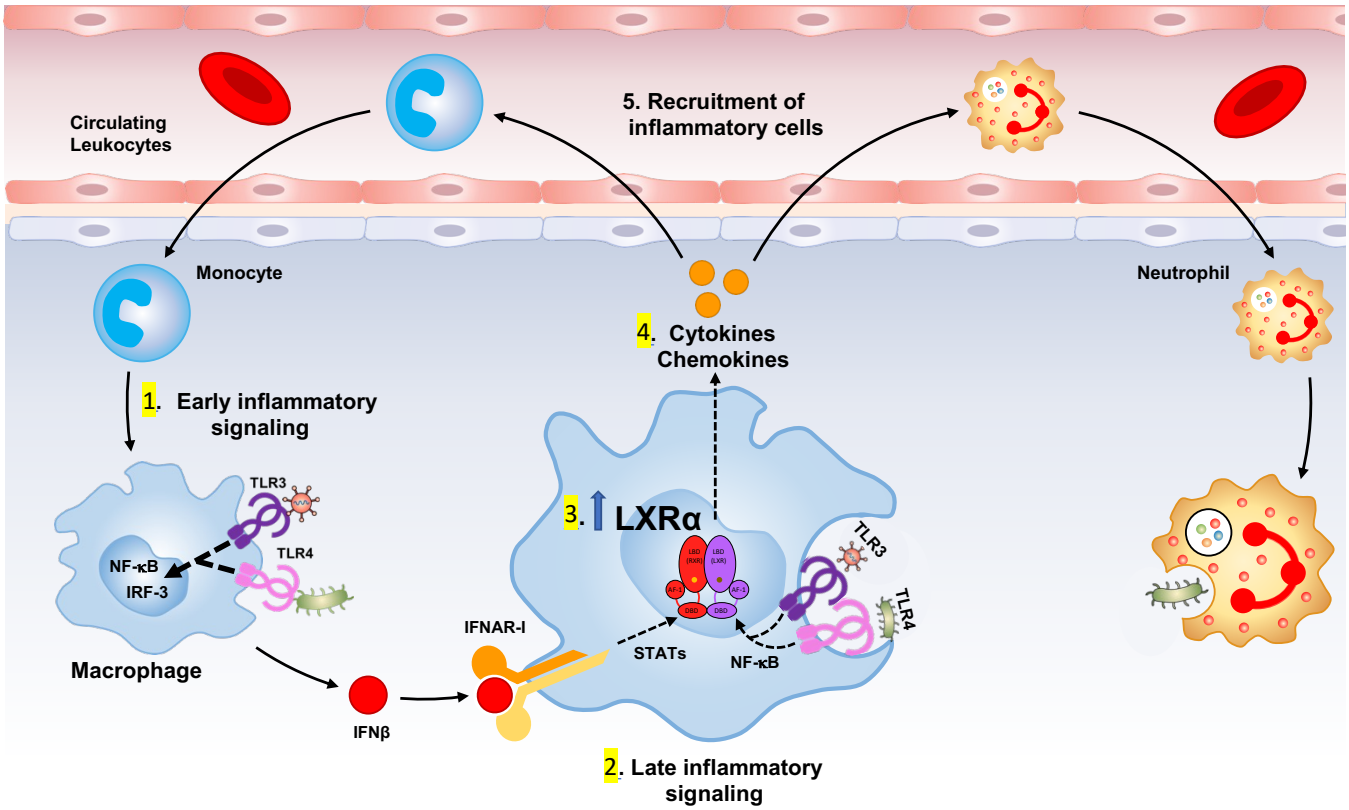
Significance and broad interest



Macrophages are phagocytic cells that regulate essential aspects of innate immunity against pathogens. In response to microbial components, macrophages induce sequential activation of primary and secondary inflammatory gene programs that are crucial for host defense.
(1.) First responses involve Toll-like receptor signaling and other sensors that lead to activation of inflammatory transcription factors, including NF-κB and IRFs, so-called ´Signal-Dependent Transcription Factors´, SDTFs, which rapidly promote the expression of cytokines, chemokines and interferons, such as IFNα,β.
(2.) Autocrine and paracrine action of IFNα,β activates STAT proteins which induce the expression of secondary-response genes. Although the role of pre-existing transcription factors such as NF-κB, AP-1 or IRF-3 has been extensively studied in macrophages, less is known about factors that are transcriptionally induced at later phases of inflammatory activation. **The objective of this study** will be to investigate the transcriptional regulation, differential DNA binding and *in vivo* activity of the nuclear receptor LXRα in response to a prototypical microbial component, the TLR4 agonist LPS.

(3.) Coordinate activation of inflammatory SDTFs facilitate the transcriptional induction of LXRα during late macrophage responses. (4.) Newly synthesized LXRα then facilitates cytokine and chemokine gene expression through its direct binding to DNA consensus sequences within target cis-regulatory regions of inflammatory genes.
Using primary macrophages with genetic inactivation of key inflammatory signaling components, transcriptional profiling and ChIP-seq studies, we will study how TLR4 signaling induces a secondary inflammatory response and the possible role of LXRα in the regulation of inflammatory gene expression.
In summary, our goal is to study the TLR-LXRα axis that controls macrophage inflammatory gene expression and *in vivo* immune-cell recruitment during inflammatory responses to microbial ligands and their role in the regulation of inflammation.