Project summary: Organ specific autoimmunity is initiated by autoreactive T helper (Th) 1 cells or Th17 cells. In contrast, regulatory T cells (Tregs) keep autoreactive T cells in check and prevent them from becoming effector T cells. The balance between inflammatory Th1/Th17 cells and Tregs was shown to play an important role in EAE as well as in MS patients. Therefore, clinical trials in MS patients aim to shift the balance of the T cell response towards regulatory cells, including experiments where the IL-23/IL-17 axis is manipulated. We have shown that pro-inflammatory Th17 cells and induced Tregs develop from a common progenitor cell in the peripheral immune compartment. We identified IL-6 as the most important “switch factor” that prevents a naive T cell from developing into a Treg cell while, in the presence of TGF-β, promoting the generation of Th17 cells. Thus, IL-6 is at a pivotal position in the shaping of immune responses. This is true not only in general immune responses, but also in EAE animals and MS patients, where high levels of IL-6 are associated with disease activity and gene deficiency in mice with disease resistance. Since IL-6 is produced upon various stimuli and by many cell types (including dendritic cells, B cells, and T cells themselves, but also by various parenchymal cells), we plan to address which cellular sources of IL-6 are relevant to direct an immune response towards the “Th17” phenotype in the peripheral immune compartment and in the target tissue of an immune reaction in vivo. Using selective depletion strategies of IL-6 producing subsets in reporter mouse strains, we intend to monitor the subsequent antigen specific CD4+ T cell responses and characterize their transcriptome and functional phenotype. Using this approach, we will define subsets of cell types which control nodal points of T cell fate decisions in the lymphoid compartment and the CNS, thus constituting promising targets for therapeutic interventions in MS patients.

Principal investigators:

Prof. Dr. Ari Waisman
Institute für Molekulare Medizin
Universitätsmedizin der Johannes Gutenberg-Universität Mainz
Obere Zahlbacher Str. 67
55131 Mainz
Tel.: + 49 6131 17-9129
Fax: + 49 6131 17-9039
Email: waisman@uni-mainz.de

Prof. Dr. Thomas Korn
Klinik und Poliklinik für Neurologie
Technische Universität, Klinikum Rechts der Isar
Ismaninger Str. 22
81675 München
Tel.: +49 89 4140-5617
Fax: +49 89 4140-4675
Email: korn@lrz.tum.de