Interleukin-6 receptor inhibition restores the kinase activity signature of $CD4^+$ T cells and promotes migration of regulatory T cells in rheumatoid arthritis

With a global annual incidence rate of around 1%, rheumatoid arthritis (RA) leads to severe disabilities and premature mortality. Animal studies have demonstrated the critical role of Th17 cells and the role of interleukin-6 (IL-6) in their development. Inhibition of the IL-6 receptor-signaling pathway improves autoimmune arthritis in animal models. Moreover, as IL-6 is a key player of immune activation and inflammation. Targeting the IL-6 signaling axis by inhibiting the IL-6 receptor has become a compelling strategy to treat RA. Treatment with the IL-6 receptor blocker tocilizumab normalizes inflammatory markers as well as increases IL-6 secretion while IL-6 mRNA expression is not affected. Albeit the broad knowledge of IL-6 and its role in inflammation is immense, only little is known about the influence of IL-6 and the blockade of the IL-6 receptor on kinase activity.

The aim of this study was to identify kinases and kinase networks that show altered activity in RA in order to identify potential new candidates for targeted therapy approaches. The results of the kinase activity assay show for the first time that treatment with tocilizumab not only restores regulatory T cell (T_{reg}) frequencies and diminishes Th17 cell numbers in the peripheral blood but also promotes migratory functions of $CD4^+$ T cells from RA patients by altering the kinase activity signature. Furthermore, we identified kinases (GPSM2, VTNC, and PTK6) with a significantly altered kinase activity in RA patients, when compared to healthy individuals. Those kinases might be promising new candidates for targeted therapy approaches.

In summary, this study provides further evidence, that treatment with tocilizumab not only improves the patient's outcome but also changes the kinase activity signature of $CD4^+$ T cells dramatically. Kinome analysis reveals a specific *ex vivo* kinase activity and IL-6R inhibition restores the specific kinase activity signature. These findings also give new insight into the migratory functions of $CD4^+$ T cells in RA. Additionally, IL-6R inhibition promotes T_{reg} cell migration towards specific chemokines in patients with RA. Finally, kinome profiling identifies new potential candidates for targeted and advanced therapy of RA.