

Rheumatoid arthritis (RA) is a severe autoimmune disease that affects up to 1.8% of adult population. Strikingly, highly elevated levels of several **chemokines** (small cytokines that regulate migration of proinflammatory cells into the inflamed joint) were detected in joints of RA patients. On the other hand, citrullination (protein modification) of some specific proteins was attributed to RA disease years before the onset of a disease. Currently available in literature data about the role of citrullination in rheumatoid arthritis (RA) are quite controversial. **Our main goal is to understand the actual functional importance of protein citrullination in the development and progression of RA.** *We hypothesize that the citrullination of small cytokines chemokines is a key event in RA pathogenesis and the presense of anti-citrullinated peptide antibodies (ACPA) directed against anti-citrullinated chemokines (expecially anti-citrENA-78 which we found to be most relevant to RA disease progression) could serve as a basis for poor disease prognosis.* Therefore we chose a system approach while focusing on the detection of **ACPA specific to citrullinated chemokines as the potential main prognostic factor for evaluation** of functional effects of protein citrullination in RA development and progression:

1. we will detect ACPA specific to citrullinated chemokines MCP-1/CCL2, MIP-1 $\alpha$ /CCL3, ENA-78/CXCL5 and IL-8/CXCL8 in synovial fluids and sera of a) at the time of diagnosis b) progressed disease and c) severity of the disease according to DAS28 versus d) healthy individuals and/or patients suffering from non-autoimmune joints' diseases;
2. we will validate *in vitro* and *in vivo* the functional impact of chemokine citrullination into RA disease development using monocyte and neutrophil chemotaxis and adenoviral ectopic expression of PAD enzymes in the knees of experimental animals;
3. we will *investigate* a molecular mechanism of protein targets citrullination into inflamed joints using *PADI4* promoter analysis *in vitro* performed with primary human synovial fibroblasts

Our work aims to shed light on the molecular mechanisms and functional impact of chemokine citrullination in RA development and progression and will evaluate the usefulness of detection of ACPA specific to citrullinated chemokines in RA disease diagnostics and prognosis. Due to the fact that the rheumatoid arthritis is a chronic and often leads to severe motoric disability, studies leading to a better understanding of the pathogenesis of this disease are of major socio-economic importance. It is also supported by the fact that the RA is the most common autoimmune disease of adults.