Serum PAD-activity: Risk Factor in Development and Novel Biomarker in Rheumatoid Arthritis

Rheumatoid arthritis (RA), a severe systemic autoimmune disease manifested by chronic joint inflammation causing pain, disability and increased mortality, affects 0.5-1.0% of human population worldwide. Previously, diagnosis of RA has relied on clinical criteria, laboratory (rheumatoid factor) and radiographic results. Discovery, development and clinical implementation of the RA specific anti-citrullinated proteins antibodies (ACPAs) assays in the last decade immensely improved proper diagnosis of early-undifferentiated arthritis.

Peptidylarginine deiminases (PADs) play a critical role in generation of citrullinated autoantigens in RA, but mechanisms underlying their up-regulation at this early stage of disease remain unknown. Recently they also have become prominent targets for drug development. Mounting evidence clearly shows that early diagnosis and timely and personalized treatment are key factors for preventing joint damage and subsequent disability. Currently a "trial-and-error" approach is used in prescribing biological treatment for RA. Obviously this practice carries significant disadvantages such as potentially exposing patients to drugs that they do not respond to, unnecessary side-effects, delaying administration of an effective treatment regimen and also causing a significant economic burden to society.

Therefore, our ambition with conducting this project is to improve early identification and treatment response-based stratification of RA patients. In our project we will investigate serum PAD-activity as a novel early biomarker for detection of sub-clinical states of RA. Reasoning when following the current state-of-the-art knowledge gives us reason to believe that PAD-activity may not only preceed ACPA-seropositivity, but also could allows for more specific patient stratification and aid monitoring and biological parameter-guided treatment.

We will also explore molecular mechanisms impacting PAD-activity and evaluate potential mechanistic link explaining the correlation between development of RA and statin based therapy. Intrinsic knowledge of factors regulating PAD-activity in the serum will also open new possibilities for drug development targeting enzyme activity. This, in turn, will allow not only for an earlier detection and effective modification of the current treatment approaches, but also may significantly decrease the disease progression improving patient quality of life and at the same time reducing the financial the burden of RA treatment imposed on the health system.

The specific objectives of this project are:

- Investigate the PAD-activity in the serum of arthralgic (pre-RA) and early RA patients and controls.
- Establish if increased serum PAD-activity can be used as a predictive factor for development of RA.
- Establish patients "target group" for the use of future PAD inhibitors.
- Investigate the use of the serum PAD-activity as a novel stratification tool for prediction of treatment outcome and parameter for monitoring and guiding therapy of RA.
- Investigate effects of serum from patients and controls on activity of externally added PAD.
- Investigate the effect of statins on activity of PAD.
- Investigate the effect of statins on expression of PAD enzymes *in vitro.*
- Establish a relationship between the use of statins and presence/levels of anti-citrullinated protein antibodies in RA patients
- Investigate association between PAD-activity and disease severity in various treatment schemes.