Unexplored role of blood platelet-derived Dickkopf-related protein 1 (DKK1) in the pathomechanism of axial spondyloarthropathy (axSpA).

Spondyloarthropathies (SpA) are a family of rheumatologic disorders characterised by an ongoing, chronic inflammation within joints and resultant pathological rearrangement of the body skeletal structure. Especially in axial form of SpA (axSpA) – in which the spine is primarily affected – the excessive bone formation results in serious disability due to movement impairment. It is already well established that the unrestrained bone formation – osteogenesis – is triggered by the localised inflammation within joints. However, as the disease progresses, the process of excessive bone tissue build-up continues despite the inflammatory response have long been resolved. The mechanism of such decoupling of inflammatory and osteogenic processes in the course of SpA is not yet understood. Thus, in order to slow down (or ultimately completely stop) the disease progression combating the unrestrained osteogenesis seems equally important as suppressing the joint inflammation. Wnt signalling pathway is considered the key player orchestrating numerous developmental processes including osteogenesis and the disruptions in wnt signalling have been linked to the pathomechanism of SpA. Dickkopf-related protein 1 (DKK1) is a specific inhibitor of wnt signalling pathway and as such is capable of regulating wnt-driven processes. Numerous research indicate that in SpA patients DKK1 serum levels are significantly lower compared to healthy people. However, the influence of dysregulated DKK1 levels on the disease mechanism as well as the actual impact of lowered DKK1 expression on the course of the disease has not been fully explained. It is thus of considerable interest to definitely establish the role of DKK1 in SpA progression.

The major goal of the project is to elucidate to what extend the DKK1 originating from blood platelets – which are believed (apart of endothelial cells) to be the main source of DKK1 present in the bloodstream – is crucial in the process of excessive osteogenesis observed in axSpA. Additionally we plan to unravel whether the current axSpA therapies involving non-steroid anti-inflammatory drugs (NSAIDSs) and biologic drugs (consisting of antibodies aimed at neutralising disease-driving factors or their receptors) might modulate the DKK1 expression in blood platelets. The obtained knowledge could shed new light on the possible mechanisms of these treatment modalities, which are still poorly determined. Moreover, we plan to establish, if lowered DKK1 levels in serum of axSpA patients might originate from the inherent properties of their blood platelets (e.g. subtle changes in *DKK1* genetic sequence) that could represent the novel axSpA hallmark/predictive factor.

In order to scientifically verify above research problems we intend to engage the multi-angle strategy involving both in-vitro studies and in-vivo SpA animal experiments. We plan to decipher the cause of the decreased DKK1 levels in axSpA by studying patient-derived biologic material (blood platelets, serum). Furthermore, the impact of common SpA therapies on DKK1 production by megakaryocytes - the precursors of platelets - will be evaluated using human megakaryocytic cell lines. Finally, we will utilise the advanced SpA animal model, in which human-like SpA disease can be studied in the absence of platelet-derived DKK1 (alternatively: endothelial-derived DKK1), in order to ultimately define the role of platelet-origin DKK1 in SpA progression.

We hypothesise that platelet-derived DKK1 plays the pivotal role in axSpA pathomechanism and that lowered DKK1 levels contribute significantly to the accelerated disease progression.