4.1. Final publishable summary report

4.1.1. Executive summary

In ‚inflammatory arthritis', only a subgroup of patients has clear features of autoimmunity with classical autoantibodies (exemplified by rheumatoid factor-positive rheumatoid arthritis, RF+ RA), while the other variants are 'seronegative' arthritis syndromes (i.e. spondylarthritis, SpA; psoriatic arthritis, PsA; juvenile idiopathic arthritis, JIA) with a predominance of innate immune disturbances. These seronegative forms of joint diseases frequently show extra-articular manifestations of epithelial tissues like skin and gut. **MIAMI's main goal was to consolidate existing and develop novel biomarkers for individual adaptation of therapies (personalized medicine) for seronegative arthritis.**

1) Mechanisms of initiation and progression of the disease. MIAMI researchers investigated the role of proinflammatory innate immune mechanisms in early inflammatory arthritis and bowel disease, aiming for translation into improved/novel diagnostics (short-term) and therapeutics (long-term). From the results we concluded that S100-DAMPs are important in the development of disease in different animal models of seronegative arthritis and in the acute state of bowel inflammation in human SpA patients. Overall, our results pave the way for further investigations that will be key to understand the biology of these S100-DAMPs in different disease settings.

2) Biomarkers for patient identification and stratification. MIAMI partners deliver improved/novel methodologies to enable early diagnosis of chronic joint and gut inflammation. In particular, the early identification of the disease in at-risk populations as well as disease extension (e.g. from the joint to the gut or skin) has been addressed in WP3 and WP6. In different clinically relevant diseases presenting with seronegative arthritis like JIA, SpA and PsA we have defined novel cut-offs for S100-proteins defining stages of active and inactive disease which are innovative and useful parameters for prediction of relapses in clinical settings. We provide evidence that phagocyte specific S100-proteins can be used for prediction of systemic dissemination of primarily local inflammatory processes, e.g. intestinal inflammation in SpA or systemic flares in SJIA in remission on medication.

3) Identification of novel disease markers for monitoring activity. To develop improved methodologies to support early diagnosis of chronic joint and gut inflammation, we aimed for the discovery of novel markers and innovative means of monitoring inflammation. In vivo optical imaging of S100A8 was found suitable for monitoring inflammation in IL-1Ra-/- mice, but not in SCW induced arthritis. We defined the innate inflammatory response patterns in joint and gut by cytokinomic, transcriptomic and proteomic analysis. Statistical analysis has been undertaken on the discovery data obtained independently from all three omics approaches. This will be used to generate a 'megaplex' assay for each of the clinical question raised in all MIAMI patient sample cohorts. We focused on monitoring of disease activity by

biomarkers to support individualised medicine. We demonstrated the performance of biomarkers when used in therapeutic decisions concerning medication use in JIA.

4) Monitoring local disease activity and extension. For the diagnosis and therapy follow-up we have technically and clinically validated the S100A8/A9 ELISA as well as the lateral flow test, which are now ready to come as CE marked *IVDs* on the market. The MIAMI SME partner Bühlmann has developed and validated the lateral flow test system for S100A8/9 in stool extract samples and in serum. As there is a need for an easy detection system of lateral flow tests the project included the development of an App to be run on a series of different smartphones.

The MIAMI project has lead to significantly improved understanding of seronegative arthritis and also an excellent transfer of knowledge for innovative solutions that will be available for clinical applications in the monitoring of disease activity and prediction of complications. The results lead to numerous scientific publications in peer-reviewed high-impact journals as well as data presentations at major congresses. In light of the proceedings we are confident that MIAMI will continue to have significant impact and use when the final results become available after publishing further manuscripts that are already in preparation. MIAMI will facilitate the quick translation of significant innovations into clinical practice, with the aim to directly improve patient care.

In conclusion, the MIAMI project has delivered improved and/or novel methodology for early diagnosis of disease in people at risk, who don't exhibit clinically relevant conventional indicators (yet). We could establish a list of biomarkers indicating onset and course of inflammation. With the help of SMEs that have a strong R&D commitment to biomarkers and personalized medicine solutions, assays have been developed that go beyond academic research formats. This lead to the development of proprietary point-of-care tests for easy and unrestricted use in the clinic or at the bedside. These tests will now be available for further validation. Lateral-flow immunoassays have been developed for simultaneous detection of a variety of proteins and evaluated in a prospective setting. Novel targets such as microRNA have been addressed. Finally, pilot data on the applicability of novel identified biomarker targets to be used in cutting-edge molecular imaging approaches have been provided, which will foster future validation studies. The latter holds great potential of further innovations going beyond the scope of in vitro biomarker determination.