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Supervisor's contact details

- Name: Arno HÄNNINEN
- E-mail: arno.hanninen@utu.fi
- Department: Institute of Biomedicine

Title of the project

Towards prediction of SLE and its individual course: from immune profiling to novel biomarkers

MSCA-PF Research Panel

☐ Chemistry (CHE)

☐ Social Sciences and Humanities (SOC)

☐ Economic Sciences (ECO)

☐ Information Science and Engineering (ENG)

☐ Environment and Geosciences (ENV)

☒ Life Sciences (LIF)

☐ Mathematics (MAT)

☐ Physics (PHY)

Description of the project

Systemic lupus erythematosus (SLE) is an autoimmune disease, which causes chronic inflammation in multiple organs. It usually presents with rash, fatique, arthralgia and changes is blood cell counts, and often leads to chronic kidney disease, heart and lung problems and even neuropsychiatric disorders. It is treated with immunosuppressive and immunomodulatory agents such as prednisolone, hydroxychloroquine and metothrexate, and nowadays also with Belimumab, a biological which blocks soluble BAFF. BAFF is a cytokine made by myeloid leukocytes in response to type 1 interferons produced by leukocytes activated by DNA, RNA or nucleoproteins, and able to drive B-lymphocyte activity and autoantibody production recognizing these autoantigens.

From the earliest clinical symptoms and signs suggesting possible SLE it usually takes even years for the clinicians to diagnose of SLE. Because it is a heterogeneous disease, its development varies from patient to patient, and autoantibodies, the only biomarkers in clinical use are mostly not specific to SLE. Thus, for better care and prevention of organ damage it would be mandatory to start the treatment of SLE earlier than currently possible and with a drug, which can be predicted to be the most effective drug to each and every particular patient.

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Therefore, this project aims at identification of novel biomarkers in blood leukocytes for earlier diagnosis of SLE and for better prediction of treatment response to immunomodulatory treatments.

The PI is an adjunct professor (M.D., Ph.D.) and a senior/chief physician with a track record in research and diagnostics of autoimmune diseases and immune deficiencies. In collaboration with rheumatologists, SLE patients have been enrolled for up to one year by now, and the recruitment and follow-up continue in the future. The applicant will become a member of the PI's research group and is supposed to collaborate with researchers of the InFlames consortium and Turku Biosciences. The work will focus on analyses of blood leukocytes sampled from patients. It may involve flow cytometry, in vitro stimulations and preparation of samples for mass cytometry and single cell transcriptomics. The applicant should be capable to work with multidisciplinary approaches and preprocessed omics data.

Research objectives or research questions of the project

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which often affects many organs simultaneously and causes irreversible organ damage. This is particularly evident in cases where renal insufficiency is the first clinical presentation. Although symptoms epitomizing SLE such as malar rash, arthraligias, fatique and cytopenias together with antinuclear autoantibody (ANA) –positivity allow SLE diagnosis, these usually develop in phases. This delays the initiation of proper treatment. To allow SLE diagnosis earlier than now, improved laboratory testing and novel biomarkers are needed.

Stratification of patients to subgroups according to different disease behaviors may pave way to personalized approaches to lupus treatment. This is facilitated by studying leukocyte transcriptomes and linking them to different clinical outcomes. Accordingly, individual patients can be categorized to distinct immunological groups. An alternative and more targeted approach to find signatures is to challenge leukocytes using receptor ligands mimicking viral or bacterial infections, and determine single-cell transcriptomes following challenge.

We run a prospective clinical study to recruit and follow patients with pending or recently diagnosed SLE. Because immune responses to microbes vary between individuals, and because infections may play a role in the pathogenesis of SLE, we challenge the patients' leukocytes in context of their transcriptomic profiling.

We address many specific research questions exemplified by the three research questions below:

1. By using single-cell transcriptome analyses of TLR-stimulated leukocytes, can we find in our SLE cohort individual variation in the tuning of immune responses in B-cells, monocytes, and dendritic cells, or in a network of cells associating to a clinical trait? For studying underlying cause(s) of dsDNA-antibody-associated disease flares in SLE, we ask if it is possible to identify an origin to autoreactive B-cells secreting dsDNA-antibodies?
2. By implementing recently reported cellular markers associating with SLE activity to current laboratory testing of the SLE patients, can we improve the prediction of disease flares and its reversal and/or the reversal of renal insufficiency in the patients? Is it possible to build multivariate analyses for this by including extended

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phenotyping of B-cell subsets, ex vivo and in vivo neutrophil activation and by profiling serum for the levels of proinflammatory and regulatory cytokines and growth factors?

3. Similarly to the fact that transglutaminase-autoantibody levels fluctuate in coeliac disease in relation to gluten exposure, can we demonstrate that dsDNA-autoantibody levels fluctuate in SLE in relation not only to SLE activity but also to bacterial exposure? Can we identify barrier breach in some of the study subjects by monitoring serum levels of LPS-binding protein (LBP) and haptoglobin (zonulin), and of calprotectin, which is a promising new marker of neutrophil activation and NETosis. Does the increase in dsDNA antibody levels during SLE flare associate to a preceding increase in markers of leaky gut? Does this associate with dysbiosis?