Medical University of Graz

Pathobiology-Driven Disease Classifications in Autoimmunity

Summary

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Supervisor:	Prof. Dr. Martin Stradner
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 10, 2020 00:00 and March 30, 2020 23:59 (Europe/Zurich)

Description

Background: Autoimmune diseases such as Systemic Lupus Erythematosus (SLE) or Rheumatoid Arthritis (RA) cause considerable morbidity and mortality. Most of these entities were defined more than seven decades ago when knowledge about (auto-) immunity was scarce. Therefore, diseases were classified based on symptoms and the occurrence of typical autoantibodies. As the knowledge on mechanisms underlying autoimmunity advanced, it became obvious that the pathophysiology observed within the traditional disease classifications was highly heterogeneous. (Figgett et al. 2019) This notion of heterogeneity is also supported by the fact that a given therapy may allow symptom free remission for a subset of patients, while others suffering from the same disease do not benefit.(Smolen and Aletaha 2015) Biologic disease-modifying anti-rheumatic drugs (bDMARDs) are such therapies allowing to target defined aspects of the immune system. Therefore, achievement of remission by a bDMARD implicates the immunological aspect targeted by the bDMARD was crucial to the development or persistence of the symptoms. Interestingly, a bDMARD targeting a specific aspect of the immune system can be effective in multiple autoimmune diseases.

Hypothesis and Objectives: We propose that response to a specific bDMARD treatment defines a common immunological basis of various autoimmune symptoms in patients across traditional systemic autoimmune diseases. We aim to identify patients highly responsive to a given bDMARD independent of the traditional autoimmune disease definition. We will identify common clinical, immunological and metabolic features of these patients not shared by responders to other bDMARDs or non-responders. Thereby, we will establish biomarkers allowing to diagnose patients according to the immunological mechanism underlying their symptoms.

Methodology: We will characterize response of patients suffering from systemic rheumatic autoimmunity to treatment with bDMARDs. Leucocytes will be analyzed by flow cytometry and single-cell RNA sequencing. We will evaluate the serum metabolome by nuclear magnetic resonance spectroscopy and quantify soluble serum components by digital ELISA. Appropriate statistical analysis will identify the parameters for diagnosing bDMARD-defined immunological classifications.

References: Figgett, William A, Katherine Monaghan, Milica Ng, et al. 2019. “Machine Learning Applied to Whole-Blood RNA-Sequencing Data Uncovers Distinct Subsets of Patients with Systemic Lupus Erythematosus.” Clinical & Translational Immunology 8 (12): e01093. https://doi.org/10.1002/cti2.1093.