

Preface

Rare diseases represent an exceptional challenge to our healthcare system. By definition a single rare disease affects fewer than 1 in 2,000 people. However, as there are up to 8,000 different rare diseases, collectively up to 5% of the European population suffer from a rare disease, often with debilitating and life-threatening consequences. Together with neurologic and metabolic diseases, inborn errors of the immune system represent the majority of rare diseases in humans.

The immune system has to maintain a fine-tuned balance between pro- and anti-inflammatory responses. Apart from pathogen defense it influences a plethora of processes in the human body. Many clinically diverse diseases result from mal-functions of immune surveyor mechanisms. However, these diseases are thought to be of multifactorial origin with both inborn and environmental factors contributing to the pathophysiology. The possibility to define a precise pathomechanism is limited, hindering the discovery of potential novel therapeutic targets. To overcome this problem, model organisms are frequently used and often referred to as potential alternatives with strong caveats with regard to inter-species differences. Therefore, studying patients with rare monogenetic defects of the immune system represent the best possible way to identify critical components and the relevant pathophysiological consequences. Gene discovery in humans used to be tedious and time-consuming and was limited to very large pedigrees and very high disease penetrance. In recent years, high-throughput sequencing technologies have revolutionized biomedical research by allowing insight into the genetic basis of human disease at an unprecedented efficiency. My vision and the focus of my laboratory is that with the advent of state-of-the art genomic technologies, we will for the first time be able to assemble an unbiased and comprehensive view of this complex group of diseases. The recent award of the FWF START Prize and an ERC Starting Grant to myself is testimony to an increasing awareness that rare diseases research at this internationally competitive level can help us understand fundamental biological principles relevant to many human diseases.

The aim of this thesis was to identify critical components of the immune system driving autoimmunity and lymphoproliferation in patients with primary immunodeficiencies. We focused on a cohort of patients with putative autosomal recessive, monogenic diseases and were able to identify 3 novel primary immunodeficiency diseases caused by bi-allelic loss of function mutations in *CD27*, *PRKCD* and *IL21*, respectively.

For *CD27* deficiency we described a large cohort of patients with this disease. As all patients shared the same causative missense mutation affecting *CD27*, but displayed diverse clinical presentations, we were able to provide a clinical overview of the disease spectrum. Moreover, we could show that the amount of invariant natural killer cells inversely correlated with Epstein Barr driven lymphoproliferative disease in these patients.

In another patient with severe systemic autoimmunity, we were able to identify a splice site mutation in *PRKCD* encoding protein kinase C delta, which led to complete absence of the protein. The patient displayed glomerulonephritis, was positive for various autoantibodies and previously diagnosed with systemic lupus erythematosus. We could show that in accordance with the previously published role of *PRKCD* in the literature, this patient exhibited increased mRNA levels of *IL6* after stimulation with Phorbol myristate acetate and showed decreased phosphorylation of the PKC δ target myristoylated alanine-rich C-kinase substrate

(MARCKS). The findings from this study enabled to propose treatment with Tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody currently in use for the treatment of rheumatoid arthritis. PRKCD deficiency is one of the first known, monogenetic causes underlying SLE-like systemic autoimmunity, thus the results of this study are relevant far beyond this individual patient, as they illustrate fundamental mechanisms of disease pathology.

In recent years, we and others have been able to identify monogenetic disease etiologies underlying early-onset inflammatory bowel disease, thereby enlightening our understanding of disease mechanism. In the course of these efforts, we identified IL21 deficiency as a novel cause of early-onset inflammatory bowel disease and immunodeficiency. With the help of *in silico* simulations we demonstrated that the mutated residue is highly conserved and that any change at amino acid position Leu49 would reduce the stability of the native state of the protein. Building on this finding we utilized recombinant wild type and mutated IL-21 protein to demonstrate a loss of function phenotype of the mutant displaying strongly reduced STAT3 phosphorylation upon in vitro cell stimulation. Moreover, as recombinant IL-21 is in clinical trials, we were able to propose an alternative potential curative treatment option for this patient.

Elisabeth Salzer has complete her PhD with distinction in July 2015 and is now specializing in pediatrics and adolescent medicine. Elisabeth shows a strong dedication to the field of immunology and I am sure she will become an excellent physician scientist in the future. She belongs to the very few clinicians who are able to use her background in medicine and combine it with the highest level of molecular research. I congratulate the Springer Best Med Diss selection committee for having selected Elisabeth's thesis for this prize!

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and Autoimmunity

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