Systemic lupus erythematosus (SLE) is an autoimmune disease with a variety of clinical manifestations. The pathological process leading to the autoreactive immune response is caused by erroneous recognition of self-antigens, dysregulation of immune components activity and chronic inflammation. Different tissue and organ involvement is associated with the formation and accumulation of immune complexes and the hyperactivation of immune cells. These immune cells and an altered expression and reactivity of the immune checkpoints are thought to be critical for the disease pathogenesis of SLE. Recent findings concerning targeting inhibitory co-molecules in cancer showed that blocking the inhibitory immune checkpoint receptors was also associated with further immune-related adverse events (irAEs) resembling autoimmune rheumatic diseases, including SLE [1]. With the increasing knowledge about the biology of immune checkpoints in autoimmunity, the interest in modulating immune cells over-activation via co-stimulatory and co-inhibitory pathways is incessantly growing.

The major goal of this project is to design and synthesise new peptides/peptidomimetics interacting with the BTLA-HVEM with the following in vitro evaluation of the immunomodulatory properties of these compounds in healthy and SLE-affected immune cells.

The work plan involves two basic parts: chemical and biological. The chemical part of the project encompasses the design and synthesis of immunomodulators of the BTLA-HVEM interactions. Moreover, the binding potential of new compounds to matching receptors will be evaluated. The enzymatic stability of peptides/peptidomimetics in plasma will also be measured. The second, biological task will include the comprehensive immunomodulatory evaluation of the synthesised compounds on biological material collected from healthy volunteers and SLE-affected individuals. We plan to perform flow cytometry analyses of activation, proliferation and apoptosis, gene expression and secretory profile of the immune cells (both healthy and SLE) exposed to the examined immunomodulators. The final evaluation of immunomodulatory properties of new compounds targeting the BTLA-HVEM complex and their plausible usefulness in SLE therapy will be based on the interactions between stimulated SLE-affected immune cells.

The evaluation of the immunomodulatory properties of synthetic peptides targeted at the immune checkpoints in SLE-affected individuals may result in better understating of SLE pathogenesis and lead to new therapeutic options.