Scavenger receptors (SRs) represent a heterogeneous group of receptors, expressed mainly in macrophages and dendritic cells, the defining feature of which is the ability to bind oxidized low density lipoproteins (oxLDL). SRs are characterized by very wide ligand binding repertoires, which, in addition to oxLDL, include numerous other, negatively charged compounds, and enable SRs to participate in several functions of macrophages, such as different forms of endocytosis, adhesion to extracellular matrix and to other cells. In addition to their role in physiological functions of macrophages, SRs have been implicated in the pathogenesis of atherosclerosis, Alzheimer's disease and diabetes associated pathologies, due to their role as receptors for oxLDL, β-amyloid fibrils and proteins modified with advanced glycation end products.

SRs have been also identified as major receptors mediating phagocytosis of unopsonized bacteria by macrophages. As concomitantly, SR-deficient mice exhibited impaired bacteria clearance and increased mortality during bacterial infections, these observations led to the view that SR-mediated phagocytosis of unopsonized bacteria constitutes an important, early mechanism of antibacterial host defense. However, results of our recent study undermine this view. We have observed that, in comparison to phagocytosis of killed and fluorescently labeled bacteria, which were used in previous studies, phagocytosis of live bacteria is very inefficient or unimpaired in macrophages deficient in predominant SRs: SR-A/CD204 and CD36. Increased mortality of SR-deficient mice during bacterial infections is directly caused by excessive production of pro-inflammatory cytokines. A similar, exaggerated reactivity of SR-deficient cells to bacterial products is also observed in experiments in vitro. We therefore put forward a hypothesis, which we are going to test in planned studies, that the impairment of antibacterial resistance in SR-deficient mice is caused to a larger extent by inhibition of intracellular killing of bacteria in phagocytes, produced by an excessive stimulation with pro-inflammatory cytokines, than by defect in phagocytosis of unopsonized bacteria by macrophages.

Adaptive immune responses (engaging lymphocytes) are mainly directed against non-self proteins. However, T helper (Th) lymphocytes, which initiate and coordinate the course of immune responses, are not able to directly recognized native proteins, but require them being presented as complexes of oligopeptides dissected from proteins (epitopes) with class II major histocompatibility complex (MHC-II) molecules on the surface of antigen presenting cells (APCs). Consequently, in order to be able to induce immune response, protein antigens have to be first taken up by APCs and subjected to intracellular proteolytic processing. Together with C-type lectins, SRs are major receptors mediating uptake of antigens by APCs. Paradoxically, the majority of purified proteins stimulate at most weak immune responses, which seem to be caused the fact that they do not belong to ligands of endocytic receptors. In our previous study, we have described a mechanism that improves uptake of proteins in inflammatory foci and, consequently, significantly enhances their immunogenicity. It turned out that oxidation by hypochlorous acid (HOCl), which is produced by neutrophils infiltrating sites of inflammation, confers on proteins the ability to bind with high affinities to endocytic receptors, including several SRs. In practice, the so-called adjuvants are added to protein vaccines to improve their immunogenicity. As a shared feature of chemically and structurally different adjuvants is their ability to induce acute inflammation, we are going to test the hypothesis that stimulation of HOCl-mediated oxidation of proteins represents the shared mechanism of their immunoenhancing effects. It is likely that increased immunogenicity of chlorinated proteins might be exploited in the development of safer and more effective vaccines, which, possibly, would not require co-administration of adjuvants and therefore would be devoid of all caused by adjuvants, harmful side effects.

Under the influence of stimuli provided by APCs during antigen presentation, chiefly cytokines (intreleukin (IL)-6, IL-12, IL-23), Th lymphocytes undergo differentiation into different types of effector cells (Th1/Th2/Th17/Treg), which are responsible for the induction of different types of adaptive responses. Differentiation of Th1 and Th17 lymphocytes is promoted by cytokines which are produced by APCs upon detection of specific bacterial or fungal products, but it remains unclear what governs differentiation of Th2 lymphocytes, which occurs in allergies, during infection with parasitic worms, and under the influence of one out of only two adjuvants being in the clinical use - alum. As endocytic receptors are capable of regulating production of cytokines, which drive differentiation of lymphocytes, we are going to verify the possibility that activation of these receptors during antigen uptake promotes differentiation of Th2 cells.

In conclusion, in the planned study we will tackle the most basic, still not fully elucidated questions in immunology: mechanisms of antigen presentation, polarization of adaptive immunity, and immunoenhancing effects of adjuvants, so their results are very likely to significantly contribute to the development of this scientific discipline.