Granulomatosis with polyangiitis (GPA) is an infrequant, autoimmune disease with still unknown etiology. One of the characteristic outcomes is serum presence of cANCA (anti-neutrophil cytoplasmatic antibodies – ANCA, IgG anti-PR3). IgG anti-PR3 antibodies are detectable in about 80% of patients with Granulomatosis with polyangiitis which may suggest that they play an important role in the physiology of GPA. The main target for c-ANCA is proteinase-3 (PR3), a serine proteinase found in azurophili granules and secretory vesicles of the neutrophil. In patients with GPA, PR3 expression on the neutrophil surface is high and correlates with disease severity. Polymorphonuclear leukocytes (neutrophils) are known as an important component of innate immune system and are described as one of the most important players in pathophysiology of GPA. The current paradigm of ANCA-associated vasculitis assumes neutrophil activation by ANCA. This causes neutrophil activation, degranulation, generation of reactive oxygen species and eventually trans-migration through the endothelial cell layer. It is still very little known about molecular aspects of those processes, but one of the factors probably involved are extracellular vesicles (EV). EV are heterogeneous group of small round-shape structures (30-1000 nm) which can be released by substantially all cells types – including immune cells. Presence of EV was confirmed in mainly all body fluids – blood, urine, semen or amniotic fluid. As EV can carry protein and nucleic acids they can participate in cell-to-cell communication. However their function in GPA is still unknown. In our project we would like to focus on miRNA/mRNA profile of EV and analysis how they can modify endothelial cells function and neutrophils-endothelial cells interaction. Project will be divided in 3 parts: I – miRNA/mRNA profiling of EV isolated from patients with GPA; II – miRNA/mRNA profiling of EV released by neutrophils stimulated with IgG anti-PR3; III – activation of endothelial cells by neutrophils-derived EV.

Despite significant improvement in understanding pathophysiology of GPA which has been recently made, treatment and treatment results assessment are still being challenges and cause many difficulties. Beside treatment related adverse effects, currently used protocols are still insufficient as far as sustained remission induction is concerned. Long-term clinical assessment and management of GPA patients remain complex. One of the major problems is discrimination between GPA-related disease activity and treatment related symptoms. ANCA, which are highly specific for diagnosis of the disease and can be found in serum of more than 80% patients with GPA, according to current knowledge are not very useful as a biomarker of disease activity, flare risk and remission status. As a result, the current gold-standard methods for defining these parameters in GPA require estimation of some consensus-derived clinical indices, which may lead to under or overestimate disease activity in some patients. That is why searching more discriminant biomarkers of disease activity in GPA remains a challenge. Moreover, better understanding of mechanisms involved in inflammatory process present in patients with GPA, especially understanding the role of neutrophils and their interactions with other cells, may lead to new therapeutic targets development and may improve therapeutic decision and overall outcome of individual patients.