Antiphospholipid syndrome (APS) is an autoimmune disease where circulating antiphospholipid antibodies lead to venous and arterial thrombosis and various pregnancy complications. The syndrome might appear as a primary phenomenon without symptoms of other autoimmune disease (primary APS – PAPS) or coexist with other autoimmune disease (secondary APS – SAPS), most frequently with systemic lupus erythematosus (SLE). Thrombotic complications are the leading symptoms of APS and so far the anticoagulant therapy is the only recommended treatment of this disease. There are, however reports of non-thrombotic manifestations of APS, being a result of underlying inflammatory processes. The pathogenesis of these manifestations is poorly understood. There have been reports of inflammatory infiltrates of the vascular intima and media, cell proliferation and ultimately fibrosis leading to APS-related nephropathy. Similar changes were found in coronary, carotid and mesenteric arteries of APS patients. It was recently suggested that an increased activation of the mammalian target of rapamycin complex (mTORC) might be responsible for this phenomenon. This kinase plays a pivotal role in the metabolism, growth, proliferation, differentiation and survival of the cells.

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis is a systemic necrotizing vasculitis affecting mainly respiratory tract and kidneys. The hallmark of this disease is the presence of anti-proteinase (PR)3 antineutrophil cytoplasmic antibodies (ANCA) leading to granulomatous inflammation of the respiratory tract, disseminated necrotizing vasculitis and gromeluronephritis. Epidemiological data suggest the both environmental and genetic factors might contribute to the disease development, however the exact pathogenesis remains unknown. The main pathogenic role is being attributed to ANCA, however there is growing evidence showing that T and B cells, neutrophils extracellular traps (NETs), fibroblasts, endothelial cells and inflammatory markers might also contribute to the complications of GPA. The thrombotic risk in the ANCA-associated vasculitides GPA and microscopic polyangiitis (MPA) is relatively high, about 7 per 100 person-years and remains increased even during remission of the disease.

The principal aims of the study would be:

1. To define possible pathological role of neutrophils extracellular traps (NETs) in the development of thrombotic and non-thrombotic complications of APS and GPA
2. To evaluate a potential role of mammalian target of rapamycin complex (mTORC) activation in the development of non-thrombotic symptoms of both diseases
3. To globally assess plasma thrombotic potential in association with the above by the in vitro measurement of thrombin generation and its potential and to calculate retrospectively association of thrombin generation measurements with the thrombotic risk in both diseases.

Secondary/future aims include:

1. Attempts to elucidate pathogenesis of thrombotic and non-thrombotic vascular complications of APS to find new targets for the future prevention of the syndrome
2. Improvement in thrombotic risk assessment of APS patients and creation of such risk assessment model in GPA
3. Elucidation of possible common pathogenic features and assessing their relative role in the pathogenesis of both autoimmune diseases.

During 3 years of the study we plan to enroll 270 patients: 60 patients with GPA and anti-PR3 antibodies, 60 patients with APS, 50 patients with APS and concomitant systemic lupus erythematosus (SLE), 50 patients with SLE without antiphospholipid antibodies, and 50 healthy control subjects, age and sex adjusted.

Neutrophils are considered as the mainstay of cellular innate immune responses. Neutrophils have adopted some efficient defense mechanisms. They can release their DNA in the presence of bacteria creating traps called NETs – a weave of DNA fibers consisting of histones and antimicrobial proteins [myeloperoxidase (MPO), elastase and PR3]. Little is known about the potential role of NETs in the pathogenesis of APS. However, their contribution to the manifestations of GPA and SLE has been quite well understood. In the present study we plan to assess NETs using 2 different methods: directly in the isolated and stimulated neutrophils and indirectly by measuring the circulating DNA-MPO complexes and free mitochondrial and genomic DNA.

In our previous studies we have investigated the role of inflammatory processes in the development of thrombotic and non-thrombotic complications of APS. As a continuation of this topic we plan to assess the potential role of mTORC activation in the development of non-thrombotic complications of APS. We also plan to investigate the role of mTORC activation in GPA, which, to the best of our knowledge, is going to be innovatory.

The symptoms of APS and GPA are mainly the result of vascular pathology, where thrombotic complications dominate in APS and vascular inflammation in GPA, however patients in GPA also have and increased risk of thrombosis. Patients with SLE without antiphospholipid antibodies also have and increased risk of thrombosis, mostly as a result of chronic inflammation and immunosuppressive therapy. To better assess this risk and hopefully in the future revise the recommendations of antithrombotic prophylaxis, we plan to measure thrombin generation in vitro. This is an useful, repeatable test that shows the kinetics of thrombin generation. In our previous work we have confirmed increased thrombin generation in APS, SLE and eosinophilic granulomatosis with polyangiitis (EGPA) [Mastalerz et al., unpublished data].

We do hope that the results of the present study will help to better understand the pathogenesis of APS and GPA and hopefully develop new treatment strategies of both diseases in the future.