Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease of the joints and surrounding tissues. RA is a serious medical problem, diagnosed annually in 41 people per 100,000 (affects 1% of the human population) and is the most common autoimmune disease of the joints. The disease is twice as likely to occur among women than men. Typically, the disease manifests itself in the age of 30-60 years. RA manifests itself disability. The pathogenesis of RA is not still fully elucidated and the risk is mainly attributed to genetic, environmental, lifestyle and hormonal factors. The incidence of RA in identical twins suggests that epigenetic factors may be another risk factor for onset or progression of this disease. Lack of basic knowledge of RA the pathogenesis and the delay in diagnosis have hampered its effective management and impose the treatment regimen. The main goals of treatment are to reduce inflammation and pain, prevent joint damage and slow the progression of the disease. The poor prognosis of the RA has led to emphasis on early diagnosis. In 60-90% of patients, there is a persistent active inflammatory process that leads to permanent damage to joints and disability within a few years. Early diagnosis of RA results in a better control of the inflammatory process, lower morbidity and even higher probability of disease remission. Thus, there is an important challenge in understanding the molecular background of RA pathogenesis, and also in identification of novel biomarkers useful for its early RA diagnosis and monitoring.

RA may have wide heterogeneous manifestations, especially regarding progression rates. The substantial heterogeneity of RA is also present at the molecular level, which are likely to be the cause for the presence of a plethora pathogenic phenotypes. RA is consider as an autoimmune disease marked by autoantibodies production against a wide spectrum of proteins (the formation of autoantibodies to the citrullinated peptides may precede clinical diagnosis over several years). Another characteristic marker of RA is an inflammation involving initially the synovial membrane in the joints, tendon sheaths, and then for the propagation of inflammation. The local inflammation process results in systemic elevations of cytokines and proinflammatory proteins such as CRP, atherosclerosis, osteoporosis due to systemic inflammation or increased risk of developing malignant neoplasms. The synovial membrane is overgrown and infiltrated by cells of the immune system (mostly T and B cells). RA patients lymphocytes are characterized by incomplete activation and lack of response to mitogens. Some of these observations are a consequence of metabolic alternations of lymphocytes. Recent rare evidence (including report from the authors of this proposal) suggest that these metabolic alternations include, but are not limited to, the DNA damage response (DDR).

The aim of the project are:

1. To establish a correlation between the DNA damage response and rheumatoid arthritis on functional, epigenetic and genetic levels.
2. To identify novel biomarkers of rheumatoid arthritis

These objectives will be realized through:

- the analysis of endogenous DNA lesions level including oxidative ones in T and B cells isolated from RA patients,
- the determinations of the sensitivity of T and B cells isolated from RA patients to DNA damaging agents,
- the analysis of DNA repair pathways in T and B cells isolated from RA patients,
- the analysis of the expression of key genes in DNA repair pathways including their promoters methylation status,
- the genotyping of the functional single-nucleic polymorphisms (SNPs) in key genes in DNA repair pathways,
- the correlation between functional, epigenetic and genetic levels,
- the determinations of the DDR role in RA treatment.

Obtained in this project result would allow to: propose novel biomarkers potentially useful for RA diagnosis, stratification of patients, and monitoring of therapy as well as to identify new treatment targets. Moreover, obtained data will contribute to better understanding of molecular mechanism underlying the RA, as it would help to elucidate the heterogeneity of the disease.