Bladder cancer (BC) and nephrolithiasis (urolithiasis) are among the most common diseases of the urogenital system. Urolithiasis, a lifestyle disease, is characterized by the presence of insoluble deposits in the urinary tract, which impede the proper flow of urine. These deposits are a consequence of the precipitation of insoluble urine components, including oxalic acid, phosphates, urates, and cystine. The incidence of urinary tract stones in the general population reaches approximately 15% and continues to increase, and in addition, over 50% of patients with the first episode of renal colic experience a recurrence of the disease. On the other hand, BC includes a heterogeneous group of tumours with varying malignant potential, but 90% of tumours are cancers of the transitional epithelium lining the urinary tract (so-called urothelial carcinoma). BC is the second most common cancer of the urogenital system. Over the last 10 years, an increase in the incidence of BC in Poland has been observed by approximately 50%. According to the National Cancer Registry, the number of new cases of BC is over 8,000 per year. BC is particularly dangerous because, in the early stages of development, it remains asymptomatic and is characterized by a high risk (70%) of relapse after treatment.

Until recently, the pathogenesis of both diseases was associated mainly with exposure to environmental factors, such as smoking, obesity or occupational exposure. It is currently accepted that both BC and urolithiasis may have genetic causes. A family history of BC or urolithiasis increases the risk of developing these diseases. Recent studies have shown that patients with urinary tract stones, especially those with stones located in the urinary bladder, were almost twice as likely to develop BC compared to people who have not previously been diagnosed with urolithiasis. Therefore, more and more reports point to the role of interconnected biochemical pathways in the development of bladder cancer and kidney stones, which may suggest their interdependence at the molecular level. Previous studies have shown that high levels of reactive oxygen species (ROS) can induce pro-inflammatory cytokines and factors that stimulate angiogenesis, e.g. interleukin 6 (IL-6), tumour necrosis factor α (TNF-α), vascular endothelial growth factor (VEGF) and metalloproteinase matrix 9 (MMP-9). In turn, the inflammatory environment may further stimulate ROS generation. In the case of kidney stones, increased levels of lipid oxidation products and pro-inflammatory cytokines, e.g. IL-8, are observed, and the polymorphism located in the *MMP-9* gene modulates the risk of developing kidney stones. Previous research also indicates that nephrolithiasis and BC may be a consequence of disorders in purine metabolism and the urea cycle. Some studies suggest that a deficiency of the enzyme involved in adenine metabolism, adenine phosphoribulose transferase (APRT), may contribute to the formation of deposits in the urinary system. L-ornithine deficiency, a key amino acid in the urea cycle, is also indicated as a potential cause of the formation of kidney stones. In turn, BC showed overexpression of phosphoribosylaminoimidazole succinate carboxamide synthetase (*PAICS*), the enzyme responsible for *de novo* purine synthesis, while minimal expression of argininosuccinate synthetase 1 (*ASS1*), the rate-limiting enzyme of arginine synthesis, was associated with BC resistance to cisplatin treatment. However, despite the constantly increasing number of new cases of BC and nephrolithiasis and evidence confirming their genetic determinants and mutual dependence, the molecular characterisation of biochemical pathways important in the pathogenesis of both diseases remains undefined.

Therefore, the project's main goal is to determine the role of interrelated biochemical pathways, such as oxidative stress, inflammation, angiogenesis, purine metabolism, and urea cycle in the development of nephrolithiasis and BC. The project aims to determine the relationship between the frequency of polymorphic variants of selected genes of the studied biochemical pathways and the development of BC and/or nephrolithiasis. Expression at the mRNA level, as well as the degree of methylation of the promoter regions of the tested genes, will also be determined both in the bladder tissue (BC tissue *vs*. the RNA pattern of normal bladder tissue) and blood (patients with these studied diseases *vs.* healthy volunteers). The phenotypic variability in the activity of antioxidant enzymes, the concentration of small molecular antioxidants and pro- and anti-inflammatory factors in the serum and urine of all study participants will also be comparatively analysed. A complementary test will be an analysis of the chemical composition of urinary stones.

Elucidating the molecular mechanisms of the development of BC and urolithiasis (including demonstrating the connections between the studied biochemical pathways) may significantly contribute to the development of markers enabling the identification of people at risk of developing these diseases of the genitourinary system, and in the future may be important for the definition of new targets