Since several years, our scientific interests have been focused on urinary bladder cancer (UBC), a disease whose etiology still requires a better understanding. UBC is the most common cancer of the urinary tract and affects four times more men than women and mostly elderly patients. Among UBC patients, non-muscle invasive UBC (NMIBC) patients (70%) with a low degree of invasiveness are frequently observed compared to muscle invasive (MIBC) patients. MIBC patients are often diagnosed with metastasis and they require radical surgery, supported by neoadjuvant or adjuvant cisplatin-based combination chemotherapy. NMIBC patients do require surveillance and long-time monitoring for recurrences and progression by regular cystoscopies. To add, therapeutic efficacy of chemotherapy for advanced UBC is also limited by observed drug resistance during treatment. Thus, UBC treatment seems to be a significant economic burden for public health.

Circadian rhythm is a fundamental process that organizes the functioning of the organism in response to external stimuli. This adaptation process is observed in whole organism at physiological level, as well as peripherally - at the level of tissues and cells by influencing various molecular pathways regulated by circadian genes transcriptional-translational feedback loops, such as metabolism, cell proliferation, inflammation and DNA damage repair. Perturbations of these processes are hallmarks of cancer and chronic circadian rhythm disruption can lead to tumor development. Results of the sparse number of studies, mainly clinical investigation and analysis of The Cancer Genome Atlas project indicate alteration of circadian genes expression in advanced urinary bladder tumors. Although chronotherapy concept in cancer has rapidly evolved, investigations towards pharmacological modulation of circadian components may offer novel and promising anticancer strategy. Recently, a few reports on glioblastoma indicated antitumor effects of the REV-ERBs agonist SR9009. Regardless, the potential efficacy and antitumor mechanism of this synthetic REV-ERBs ligand in UBC remains poorly understood. Therefore, because UBC ethiology and effective therapy still require a deeper understanding, in the project proposal we will assess: 1) whether circadian rhythm is involved in noninvasive UBC - NMIBC and advanced UBC – MIBC; and 2) whether pharmacological activation of REV-ERα and REV-ERBβ (NR1D1 and NR1D2) might be a therapeutic approach in advanced UBC treatment.

Presented research hypothesis will be solved in two nodes of the project: 1) clinical study on specimens of tumor tissue and tissue surrounding the tumor from the patients with NMIBC and MIBC, together with normal bladder tissue from unrelated urological patients to reveal circadian genes alterations in relation to disease and its stage, grade, recurrence and the redox dysregulation-related aberrant DNA changes: telomere length and mitochondrial DNA copy number; 2) in vitro study on urothelial bladder cancer cell lines presenting various resistance to cisplatin to reveal a putative antiproliferative effect of pharmacological induction of REV-ERBs with SR9009 agonist, and to investigate a putative involvement of circadian rhythm and linked molecular mechanisms, including among others redox balance dysregulation: reactive oxygen species, reduced glutathione; mitochondrial potential; cell cycle changes; cell migration and invasion, cell proliferative potential.

Research hypothesis regarding a putative role of circadian genes in UBC stage, grade, recurrence and point out the specific circadian molecular target (REV-ERBs) may provide important knowledge towards UBC treatment. A comprehensive research 1) on the expression profile of genes together with aberrant DNA changes and 2) use of REV-ERBs agonist in UBC was not carried out as far. Presented pioneering research model will point to the circadian clock-associated adaptive mechanisms and it may provide a scientific background for UBC treatment. Thus, presented project hypothesis implies a relevant contribution to the development of innovative medicine in the implementation of new cancer treatment strategies.