Small non-coding RNAs as early indicators of carcinogenesis in inherited DNA repair disorders

Cancer diseases in Poland and worldwide usually affect adults. Despite this, 900 new cases of childhood cancer were diagnosed in Poland in 2022 and, unfortunately, an increase in morbidity is observed in this group. The most common cancers among children include leukemia (28%) and lymphomas (15%), and as many as 10% of all childhood diseases are hereditary cancers associated with, among others, DNA repair disorders characteristic of Ataxia-Telangiectasia syndrome (AT) and Nijmegen syndrome (NBS).

AT and NBS are rare genetic diseases associated with mutations in the *ATM* and *NBN* genes, respectively. The proteins encoded by these genes play important roles in DNA repair mechanisms associated with double-strand DNA breaks that arise as a result of exposure to factors such as ionizing radiation. In people with AT or NBS, a loss of the ability to repair DNA damage is observed, which results in immune disorders, problems with the nervous system and a high risk of cancer, especially lymphomas and leukemias, which are the main cause of death in these syndromes. Additionally, due to the high radiosensitivity associated with DNA repair damage, it is necessary to reduce exposure to ionizing radiation by, among other things, limiting the use of computed tomography, which makes it difficult to conduct screening tests for the development of cancer. Finding effective biomarkers in the high-risk group of patients with AT and NBS will enable the creation of a non-invasive test in the future that would be able to control the course of the disease, and in the event of cancer, also to assess the course of treatment, which in patients with AT and NBS is often highly toxic and may contribute to recurrence of the disease.

Studies on cancers in adults, such as breast and ovarian cancer, also associated with DNA break repair damage (*BRCA1/2* mutations), have indicated the great potential of diagnostic tests based on short non-coding RNA (sncRNA) circulating in the blood. Additional studies on miRNA molecules in AT, belonging to the scnRNA group, indicate the possible use of sncRNA in the diagnosis and prediction of cancer in AT and NBS. However, there is currently a lack of studies confirming the accuracy of the test based on free sncRNAs associated with DNA repair defects, as well as studies predicting hematological malignancies based on these disorders.

To fill these knowledge gaps, a two-stage study was designed, in which the analysis of specific sncRNA molecules in patients with AT and NBS is planned. In the first stage, it is planned to recruit patients with AT and NBS in whom cancer has not yet been detected and to assess the amount of individual sncRNAs in serum associated with impaired DNA damage repair. In the second step, it is planned to follow up AT and NBS patients until cancer is diagnosed and collect samples at 3 time points in order to recognize a specific signature of tumorigenesis and the course of treatment. The resulting signature will be compared with the identified DNA deficiencies signature as well as sncRNA characterization obtained from tumor cells to test the ability of the assay to predict treatment response.