

Genetic modification of T lymphocytes, resulting in the expression of chimeric antigen receptor (CAR) has revolutionized treatment of hematological malignancies. Reprogrammed T lymphocytes recognize specific antigens on the surface of malignant cells, which triggers cytotoxic response, eventually killing of the target cells. CD19 protein is expressed almost continually during B-lymphocyte development, hence anti-CD19 CAR T-cell therapy was found to be highly effective in the treatment of malignancies characterized by excessive proliferation of B lymphocytes and/or their dysfunction, including aggressive lymphomas.

Non-Hodgkin lymphomas (NHL) are heterogeneous group of lymphoid malignancies that originates from the B-cell lymphocytes. Anti-CD19 CAR T-cell products are used for treatment of patients with relapse/recurrence NHL, including diffuse large B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) after two lines of therapy. Despite the unprecedented clinical success, there is a group of NHL patients that do not respond to CAR T-cell treatment. Furthermore, some patients might initially respond to CAR T-cell therapy but then experience relapse. Therefore, it seems crucial to develop a tool that enables early identification of non-responders to predict and prevent disease recurrence. In fact, liquid biopsy has emerged as a valuable tool for therapy response monitoring. This minimally invasive technique is based on the assessment of circulating tumor DNA (ctDNA), which is a fraction of circulating cell free DNA (ccfDNA), in peripheral blood.

In this project, we aim to use the next generation sequencing (NGS) technology to analyze ctDNA for treatment response monitoring and identification of genetic biomarkers of therapy efficacy in patients with r/r DLBCL and MCL, who were qualified to anti-CD19 CAR T-cell therapy.

We have planned three research tasks within this study. Firstly, we aim to evaluate the prognostic value of ctDNA monitoring by performing ctDNA measurement in the selected time points after CAR T-cell infusion with respect to distinct clinical features in NHL patients enrolled to the study. Secondly, we plan to characterize biomarkers of therapy resistance by analyzing molecular profiles of pre- and post-CAR T-cell treatment ctDNA and tumor biopsies collected at diagnosis. Serial ctDNA genotyping will allow to identify molecular alterations, which could serve as potential therapeutic targets in non-responders. Finally, we will use various bioinformatic tools to develop a machine learning classifier for predicting complete response or disease recurrence in patients treated with CAR T-cell products.

Results of our study will allow us to determine the association between the level and molecular profile of ctDNA and the risk of relapse in patients with aggressive NHL subjected to anti-CD19 CAR T-cell therapy. Moreover, analysis of genetic profiles of malignant cells after CAR T-cell infusion might unravel mechanisms of treatment resistance and potential molecular target for therapy in individual patient. In summary, clinical and molecular data integration will enable better patient stratification into risk groups and early detection of disease recurrence. The proposed non-invasive approach might significantly improve outcomes in patients with r/r NHL.