B-cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) are the most commonly diagnosed hematologic malignancies in the Western world. Despite considerable progress in their management, they are still incurable diseases. They affect mostly elderly and frail individuals that suffer from other comorbidities. One of the most successful advances in the treatment of these malignancies are monoclonal antibodies (mAbs) targeting CD20 molecule, such as rituximab. Nevertheless, numerous reports on the resistance to anti-CD20 mAbs and other targeted therapies stimulate research aiming at identifying novel therapeutic schemes. Given the advanced age of the patients, a considerable number of already administered therapeutics and the problem of tumor-derived immunosuppression, it is of utmost importance to design chemotherapy-free therapeutic schemes with minimal adverse effects and maximal efficacy. Moreover, accessible and cheap markers to predict the progression and response to the treatment are highly needed.

One of the mechanisms of resistance to anti-CD20 therapeutics depends on the downregulation of CD20 molecule in the cell membrane. Since years our team has concentrated on increasing the efficacy of the currently used immunotherapies proposing novel combination schemes that aim at improving the efficacy and safety of monoclonal antibodies. We have published several papers demonstrating possible molecular pathways that regulate the expression of CD20 protein and influence the efficacy of anti-CD20 immunotherapy. Our studies have led to the identification of drugs that both positively as well as negatively influence the efficacy of anti-CD20 mAbs and may be used in the clinics. In this project, we will concentrate on characterizing the direct impact of decreased expression of CD20 protein on the biology of malignant B-cells. We believe that a thorough characterization of such alterations will help us to propose novel therapeutic schemes that in the future may provide a good alternative for the patients refractory to rituximab. Since the preliminary data of our work strongly suggest that loss of CD20 decreases the expression of another B-cell specific protein - CD37, we would like to focus on deciphering the impact of this finding on possible novel therapeutic options. Importantly, these two molecules belong to the same family of tetraspanins, proteins that cross the cell membrane four times and form large complexes in the cell membrane. CD37 is also a therapeutic target for the emerging immunotherapies that are being tested in the therapy of B-cell leukemia and lymphoma. CD37 has been demonstrated to control the proliferation and survival of B cells. Importantly, there is a strong body of evidence showing that it may also control the process of tumorigenesis. Recent publications indicate that CD37 loss promotes the progression of lymphoma.

In the project we intend to decipher the mechanisms of the reciprocal regulation of CD20 and CD37 using the advances of modern molecular biology. To this end, we have created biological tools – cell lines resistant to rituximab as well as CD20 knockout cell lines. Moreover, we plan to perform a thorough screening of the molecular pathways that are modulated following CD20 and CD37 loss. Such characterization will allow us to identify novel antigens that in the future could become therapeutic targets forthe patients resistant to the currently used immunotherapies. Furthermore, thanks to our longstanding collaboration with the clinicians from the Institute of Hematology and Transfusion Medicine in Warsaw, we will perform an analysis of the levels of CD20 and CD37 in primary material isolated from B-cell lymphoma and CLL patients at diagnosis and at early relapse. We will perform both prospective and retrospective analysis investigating the correlation between the levels of CD20 and CD37 together with clinical parameters such as survival and response to treatment. We will try to answer the question if a simple, cheap and accessible analysis of the expression of CD20 and CD37 may become a novel predictive or prognostic biomarker in the therapy of B-cell malignancies. Finally, we believe that the results of this project will not only help to identify novel therapeutic options, but also will provide us with novel information on the biology of CD20 protein. Although this molecule has been used as a therapeutic target since years, its role in shaping the biology of the B cell has not still been sufficiently described. We believe that our studies will shed new light on the role of tetraspanins in the biology of B cells and their potential as therapeutic targets.