Summary

Thesis Title: **The role of the complement system in cancer development and anticancer therapy**

The complement system acts in the framework of innate immunity, playing a key role in defense against pathogens but also in the maintenance of the body's homeostasis. Several activation pathways and various pattern-recognition molecules, as well as multiple effector mechanisms including opsonization, anaphylaxis, and direct cell lysis, ensure a wide spectrum of direct and indirect cytocidal activities. The complement system is initiated by conformational and/or proteolytic changes upon the recognition of invaders. The subsequent cascade of enzymatic reactions is tightly regulated to assure that complement is activated only at specific locations currently invaded by pathogens, thus avoiding a misguided attack on host cells and tissues. Noteworthy, complement can be also targeted onto tumor cells since the transformation from normal to malignant phenotype is reflected in cell membrane composition due to accompanying metabolic changes or appearance of mutated proteins. Exposure of such novel tumor epitopes distinguishes cancer cells from their normal counterparts and makes them visible to the immune system. There is an increasing number of scientific reports suggesting that disturbances in the functioning of the complement system lead to many pathologies, including the formation of tumors. However, is still not clear how exactly complement interferes with tumorigenesis and whether the complement is a friend or foe of tumor cells. On the one hand, therapeutic modulation of complement activity emerges as an attractive target in clinical approaches and there are several anti-cancer drugs approved, which utilize the complement system as their effector mechanism. On the other hand, research shows that cancer cells can also benefit from complement activation under certain conditions.

In my Ph.D. project I propose three objectives aimed at expanding knowledge of the role of the complement system in cancer development together with basic and practical issues regarding complement role in therapeutic approaches based on anti-cancer antibodies:

1. ***Analysis of the complement activation markers during treatment of B-cell leukemia patients with anti-CD20 antibodies. Correlation of the obtained results with clinical data.***

We have analyzed the cytotoxic activity of sera collected before subsequent infusions of therapeutic antibodies alemtuzumab and ofatumumab from twelve patients participating in the clinical trial. We used a new method, described by our team, to measure complement-dependent cytotoxicity (CDC). In the next study, we investigated the complement consumption and drug accumulation in patients during anti-CD20 antibody therapy with rituximab. Serum and plasma samples from patients with chronic lymphocytic leukemia and B-cell lymphomas were obtained thanks to the collaboration with the Department of Hematology and Transplantology, Medical University of Gdańsk and Department of Hematology, Karolinska University Hospital in Stockholm.

2. ***Exploring the applicability of pathogenic factors causing complement-dependent autoimmune diseases as universal supporters of anti-CD20 immunotherapeutics.***

In this part, I propose an innovative idea based on the use of the gain-of-function variants of human complement proteins to enhance the cytocidal effect of immunotherapeutics. Results were presented at the European Meetings on Complement in Human Diseases (EMCHD, Madrid 2019, where the presentation was awarded) and they are either protected by a patent in Poland or become the subject of analogous patent applications submitted in the EU and US.

3. ***Understanding the role of factor I (complement inhibitor) in the development of solid tumors using a model of human non-small cell lung cancer.***

Recent research shows that cancer cells can benefit from complement activation under certain conditions. We examined the link between the expression of FI in cancer cells of patients with non-small cell lung cancer (NSCLC) and clinical outcome. The clinical material with the available database was received from prof. Ruben Pio and prof. Luis Montuenga from the University of Navarre in Pamplona. During the EMBO Short-Term Fellowships at the Sanquin Institute in Amsterdam, I used the CRISPR / Cas9 method to permanently remove factor I from cells of cell lines in which this protein is naturally present. The obtained cell lines were used for further research including functional assays and transcriptome analyses aimed to elucidate the role of factor I (FI) in the development of lung cancer.