

Cardiovascular diseases and cancers are said to be the scourge of the twenty-first century. Furthermore, according to World Health Organization statistics, both of them are leading reasons of mortality worldwide, causing tens of millions deaths each year. Obesity, unbalanced diet, lack of physical activity, and genetic factors may predispose to the occurrence of the above diseases. The situation in Poland is equally dramatic and the importance of the problem was emphasized even more by recent COVID-19 pandemic. The occurrence of these diseases is a strong factor contributing to the severe progression of coronavirus infection. In case of both diseases, the anticoagulants are one of the most basic therapy components, although systematically improved, still cause a wide variety of side effects such as thrombocytopenia, bleeding, and dermal changes. Therefore, there is a constant need to develop new anticoagulants with improved profile of action.

One of the most extensively studied therapeutic target of many anticoagulant therapies is thrombin due to its numerous roles played in human organism. First of all, this protein is responsible for catalysis of the most crucial reaction in blood coagulation cascade – conversion of fibrinogen into fibrin. What is more, thrombin takes a part in angiogenesis and in stimulation of proliferation and migration of several different types of cells such as epithelial cells and fibroblasts. One of the representative of nucleic acids, able to effectively inhibit thrombin activity, is thrombin binding aptamer (TBA). TBA adopts the structure of an intramolecular G-quadruplex, whose anticoagulant properties are the results of binding to target protein with high affinity in its exosite I.

The main goal of this project is the in-depth exploration of the physicochemical and biological properties of novel TBA variants modified with completely new, flexible nucleotide residues possessing protein-like side groups. Importantly, a set of novel nucleotide residues (SUNAs) composed of acyclic sugar from unlocked nucleic acids (UNAs) and pyrimidine residues with additional amino acid-like side chains will be developed during realization of proposed research. The introduction of the above modifications into aptamer will allow to better mimic the antibodies chemical composition and the way of action, what will provide the improvement of interactions of these particles with target proteins while maintaining exceptional advantages of nucleic acids i.e. ease of synthesis and modification. We expect that proposed project will be a starting point not only for providing basic information about the influence of modifications on physicochemical and biological properties of nucleic acids but will also contribute to development of novel compounds characterized by exceptional anticoagulant and antiproliferative properties. The above research fit perfectly in the current trend of designing and synthesis of compounds for potential therapeutic application based on deep recognition of the processes and mechanisms at the molecular level.