Cancer and cardiovascular diseases pose a serious threat to public health and are the leading causes of death worldwide. Although the number of cancer-related deaths has decreased significantly due to continuous advances in anticancer therapy, majority of the drugs used in oncology have adverse effect. Anti-cancer drugs often cause cardiovascular complications leading to an increase in patient mortality. This is partly because in most cases the mechanisms leading to these serious side effects remain poorly understood, significantly limiting cancer treatment effectiveness.

The aim of the current project is to understand the mechanisms of cardiovascular side effects caused by anticancer therapy using tyrosine kinase inhibitors (TKIs). These drugs, although they revolutionised the approach to the treatment of many cancers and initiated the so-called targeted therapy in oncology also lead to serious side effects, mainly associated with the heart. The cause of these effects remains unclear, although it is assumed that TKIs affect the vascular endothelium leading to its dysfunction. Recent research indicates that many cardiovascular diseases, e.g. atherosclerosis, are based on inflammatory processes and excessive activity of the immune system. We assume that the TKIs, we would like to test, may also directly or indirectly influence the function of the immune system, leading to exacerbation of cardiovascular symptoms.

The research will be conducted primarily on zebrafish larvae (*Danio rerio*), a small tropical fish, often used as a model organism in biomedical research. Thanks to the transparency of zebrafish larval stages, it will be possible to study the interactions of the tested TKIs with the vascular endothelium lining blood vessels. The vascular endothelium also creates a hematopoietic niche that produces immune cells in a process called hematopoiesis. Therefore, we will examine the effect of TKI, not only on peripheral blood vessels, but also on the process of hematopoiesis, which, when excessively stimulated, leads to increased production of leukocytes, including pro-inflammatory ones. These leukocytes, causing inflammation in the circulatory system, may also contribute to progression of cardiovascular diseases. In the project, we will particularly focus on analysing the TKI-induced changes in the number and activity of specific types of immune cells, as well as the pro-inflammatory reactions they trigger, especially changes in the function of the endothelium. Subsequently, some of the results obtained from studies on zebrafish will be confirmed in a mouse model that even more closely resembles humans. The obtained data will allow a better understanding of the impact of leukocytes and inflammatory processes on cardiovascular changes resulting from the use of TKIs and to propose effective solutions to alleviate their side effects.

This project will be performed as part of cooperation between two research units of the Jagiellonian University with the necessary experience and infrastructure for its implementation: the Department of Evolutionary Immunology, specialising in research on the immune system using the zebrafish model, and the Jagiellonian Centre of Experimental Therapeutics, which is a centre of excellence in studying endothelial pharmacology. We believe that this cooperation will ensure efficient implementation of the project's research tasks and will lead to improved therapies used in oncology in the future.