„Rozwój metod badawczych opartych o białka rekombinowane do charakterystyki potencjalnych leków w immunoterapii nowotworów”

„Development of recombinant protein-based methods for characterization of potential drugs in cancer immunotherapy”

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Streszczenie w języku angielskim

Abstract

Immuno-oncology brought the third wave of revolution in cancer treatment. After an early first generation of nonspecific and toxic chemotherapy, through the breakthrough of personalized targeted therapy with the kinase inhibitor Imatinib as the first blockbuster, immunotherapy is a unique solution. It targets cells of the immune system instead of cancer cells, by training them to recognize and fight cancer.

The following dissertation was realized within the scope of Implementation Ph.D. Programme (Doktorat wdrożeniowy) in cooperation between Jagiellonian University and Ryvu Therapeutics S.A. and aimed at optimization of biochemical and biophysical methods to allow identification and characterization of low-molecular-weight compounds that are modulators of selected proteins engaged in immunological processes, in order to activate the immune system for battling cancer. The research was focused on three protein targets: STING, HPK1 and RIG-I.

The mechanism of action for modulators of selected targets in immuno-oncology is different from standard anti-cancer treatment based on chemo- and radiotherapy. It allows solving imperfections in current therapeutic strategies by stimulation of the patient’s own immune system and reinforcement of existing natural defence mechanisms. Research work conducted as a part of this dissertation is an attempt to response to the unmet medical needs, presenting both strong implementation potential and business value, as the obtained results contributed to the development of potential new drugs in the field of immunotherapy. Workplan assumed the optimization of methods and investigation of the modulation mechanism of selected proteins by small molecule compounds. The aforementioned methods were then used for both high throughput screening to identify new chemical matter, as well as

supporting the process of rational drug design in selection and characterization of the best Ryvu's compounds, in parallel to testing competitor compounds.

Experimental work was divided into three projects corresponding to the three target proteins:

- Research activities focusing on STING protein covered the adaptation of existing methods and introduction of new biophysical tests for identification of new compounds that stabilize wild-type protein as well as proteins that carry polymorphic mutations occurring naturally in the human population, and the proteins of selected preclinical species. This study contributed to the discovery of lead compounds and further efforts aiming at the selection of preclinical candidate.
- The study on HPK1 kinase included optimisation of biochemical assays and conducting a high-throughput screening cascade, as well as the characterization of compounds in terms of inhibition of the enzymatic activity of this protein.
- In the studies focused on RIG-I protein, novel research methods were used to test the hypothesis concerning the mechanism of action of compounds causing functional activity of this protein.

Conducted research and obtained results constituted a significant scientific value to the projects carried out at Ryvu Therapeutics and thus contributed to the development of potential future drugs that may become either first in class (with respect to HPK1) or best in class (with respect to STING).