Structural studies of signaling receptors HVEM/CD160 as potential targets for immunotherapy against melanoma

dr Marta Orlikowska
Faculty of Chemistry, University of Gdańsk

Melanoma is responsible for 90% of deaths caused by skin cancer and is considered one of the worst cancer. Globally, in 2012, it occurred in 232,000 people and resulted in 55,000 deaths. Recent discoveries in cell signaling have provided a greater understanding of the biology that underlies melanoma. These advances are being exploited to provide targeted drugs and develop new therapeutic approaches. Currently it is believed that immunotherapy may be the promising solution for effective treatment of melanoma. The newest drugs, scheduled to be registered by the US Food and Drug Administration (FDA), are immune system stimulating agents. Although targeted therapies are still not a standard of the treatment and their use is mainly limited to clinical trials, they appear to be the future of effective treatment of metastatic melanoma.

In the immune response against melanoma are involved BTLA (B- and T- lymphocyte attenuator) and CD160 receptors, which inhibit the activation of $CD4^+$ T cells, as a result of complex formation with HVEM protein (herpes virus entry mediator) present on the surface of melanoma cells. Blocking the interaction between BTLA/CD160 and HVEM proteins can be the way to stimulate immune response.

Blocking inhibitory receptors of the immune system for better therapies of cancer is now highly encouraged by many specialist in the field. That is why the main objective of this project is to recognize the interactions between cancer cell and immune cells in the context of anticancer drugs design. We are targeting inhibitor receptor CD160.

We plan to determine crystal structure of apo CD160 and HVEM-CD160 protein complex. The research will be conducted mainly by crystallographic methods, based on X-ray diffraction on protein monocrystals. Proteins used for crystallization will be expressed in bacterial system and purified using suitable chromatographic techniques. Crystals will be obtained using vapor diffusion hanging drop method. Diffraction data will be collected on European synchrotron beam lines. Received structural data will provide the structural basis for the rational design of small-molecules therapeutics that disrupt the HVEM-CD160 interaction. Designed peptides will be synthesized, purified and their affinity to the CD160 will be tested.