The **immune system** of every human is designed to recognize and remove pathogens and cancer cells. It can be compared to a security system that scans our body for "bad" cells. In such a way, the immune system protects our body against pathogens and cancer cells. An important elements of the immune system are **T cells**. These are specialized cells that act as guards keeping order in our body, and if bad cells are detected, they remove them. T cells are also able to recognize and destroy cancer cells. However, very often T cells recognize cancer cells but do not destroy them. This happens because cancer cells can effectively hide from T cells. They do this by covering their surface with a special protein - **PD-L1**. This protein is recognized by T cells with their protein - **PD-1**. The interaction between these proteins prevents cancer cells from being recognized by T cells as bad cells. The PD-L1 protein is, therefore, a kind of camouflage for cancer cells, by which they become "invisible" to the immune system. Inhibiting the interaction of both proteins by targeting PD-L1 is currently considered a modern therapy that allows **activating the immune system to fight cancer**. Scientists who worked on PD-L1 and PD-1 proteins and other so-called immune checkpoints - James P. Allison and Tasuku Honjo - were awarded the Nobel Prize in 2018 in the field of physiology or medicine.

Currently, methods that activate the immune system to fight cancer are called **cancer immunotherapy**. This form of therapy may soon become the main method of cancer treatment. Nowadays, cancer immunotherapy is based mainly on the use of **monoclonal antibodies (mAbs)**, i.e. specific Y-shaped biomolecules that detect antigens on the cell surface. These antibodies bind strongly and specifically to the PD-L1 or PD-1 protein. There are also molecules in clinical trials targeting other proteins, such as **TIGIT**, which helps cancer cells in hiding by additional inactivation of cells known as **natural killers** (**NK**). Unfortunately, mAbs-based therapies have many drawbacks. These include the need for intravenous administration, the high cost of therapy and the possibility of adverse reactions from the immune system.

An effective solution to these problems may be the use of **small-molecule chemical compounds** that bind specifically to the PD-L1 protein and do not allow it to bind to the PD-1 protein (**Figure 1**). Our team has recently discovered a new generation of such molecules. They are unique because they are the **first in the world** to bind to the PD-L1 protein irreversibly by application of reactive functional groups that utilize **SuFEx** chemistry. The uniqueness of compounds containing SuFEx groups results from the fact that they are activated to form a covalent bond with amino acid residues only after the inhibitor has been bound to the protein surface. Then the **S-F** bond present in the SuFEx group is broken and is accompanied by the formation of a new covalent bond with the amino acid side chain. A similar approach has been used in recent years to design inhibitors of many proteins, but in medicinal chemistry of PD-L1 agents has not been demonstrated so far. In our project, we plan extensive research on the use of the SuFEx chemistry in the design of PD-L1/PD-1 interaction inhibitors, aimed at optimizing the chemical structure and detailed examination of their activity. In the final stage of the project, our most active molecules will be tested in a mouse tumor model alone and in combination with **anti-TIGIT** antibodies.

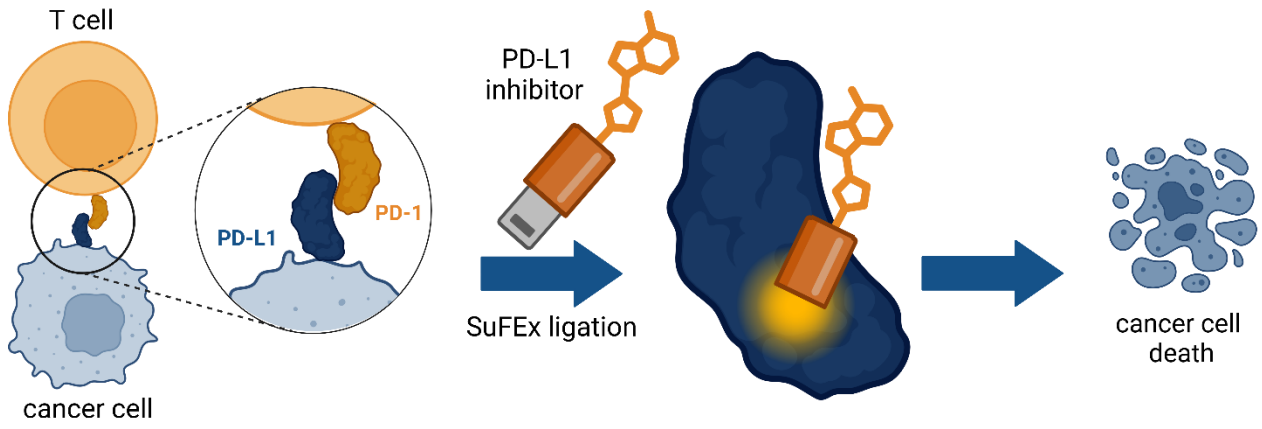

Figure 1 | Cancer immunotherapy with covalent PD-L1 inhibitors

The results of our project will greatly contribute to the development of cancer immunotherapy and will expand our knowledge about the possibility of activating the immune system to fight cancer cells. We cannot exclude that compounds developed by us may become drugs used in cancer immunotherapy in the future.