Photoswitchable and chimeric molecules for spatially restricted and endoplasmic reticulum-specific blockade of PD-L1 protein

In recent years immunotherapy has become the fifth pillar of therapy of cancer, revolutionizing the treatment of several cancer types that were considered difficult to heal or even incurable. Immunotherapy focuses on the activation of the anti-cancer immune response, taking advantage of the natural protective functions of our immune system. Blockade of the PD-1/PD-L1 immune checkpoint is one of the most explored strategies of modern immunotherapy. Three therapeutic anti-PD-L1 antibodies and four anti-PD-1 antibodies are now approved by the U.S. Food and Drug Administration for the treatment of patients suffering from melanoma, lung cancers, breast cancer, and many other cancer types. Thousands of experimental treatment regimes are now tested all over the world, which involve PD-1/PD-L1 blockade alone or in combination with other therapeutic approaches. At the same time, scientists are attempting to discover small molecules that could substitute for therapeutic antibodies in blocking the PD-L1 receptor, as such molecules are often superior to antibodies in respect to the production costs, safety, and efficacy of the treatment.

Recent studies on small molecules targeting PD-L1 protein have defined the unique mechanism of action of these experimental therapeutics. Our previous experience in working with these molecules allows us now to define new approaches for the chemical and functional modification of these drugs aimed at the improvement of their bioactivity. In this project, new photoswitchable molecules will be developed that could be turned ON and OFF with UV/VIS light. Such an approach will limit side effects by applying the treatment only at the tumor site while sparing natural regulatory mechanisms of the immune system in healthy tissues. Additionally, the molecules will be modified with small chemical tags which will improve the targeting of PD-L1 at the early stages of PD-L1 production by a cancer cell. New drug candidates resulting from these approaches will be tested with the use of isolated human cancer cells to verify their anti-cancer potential. Most successful molecules will also be tested on mouse pre-clinical models to ultimately verify their therapeutic potential in a living organism.

Besides the targeting of the PD-1/PD-L1 immune checkpoint, the expression of other known immune receptors will be evaluated in primary samples excised from colorectal cancer (CRC) patients. Colorectal cancer is the third most frequent cancer type worldwide. The cancer is fully curable by surgery at the early, pre-metastatic state, however, due to a long pre-symptomatic period, it is often diagnosed too late for successful eradication by the resection. As a consequence, the design of new treatment strategies, such as immunotherapy, is required to give a cure also to patients with metastatic, non-resectable CRC. Defining the expression patterns of the immune checkpoint molecules will provide rationales for designing strategies of combined treatments involving PD-L1 blockade. The obtained results will contribute to our knowledge concerning the mechanism of colorectal cancer escape from the immune system and will provide the chance for the design of new, targeted strategies for better treatment of CRC patients.