Cancer is one of the leading causes of premature deaths in developed countries. Despite significant progress in the field of clinical oncology, in some cases, no form of effective therapy exists. Scientists around the world are constantly working on new strategies for cancer treatment. One of such state-of-the-art methods is targeted therapy, which utilizes drugs targeted at specific molecular processes occurring exclusively in cancer cells.

Cancer cells control many cellular processes in order to uncontrollably divide and grow. One such change is "disabling" the p53 tumor suppressor, known as "the guardian of the genome". The function of p53 is to ensure that mutations or other DNA damage events are properly detected and repaired. When the repair is not possible, p53 stops the defective cells from dividing or pushes them towards apoptosis, which is a safe way of removal of damaged cells.

The activity of p53 is inhibited by MDM2 (*mouse double minute 2*) protein. This inhibition can happen in two ways. First, MDM2 forms a complex with p53, which renders p53 inactive. Then, because of its enzymatic activity, MDM2 can direct p53 towards degradation in the proteasome. Because of its functions, MDM2 is often overproduced in tumor cells, becoming a possible oncoprotein.

MDM2 is a promising target for targeted cancer therapy because its inhibition causes the desired recovery of p53 activity in cancer cells. New small-molecule compounds, which block the binding between MDM2 and p53 are constantly developed. A notable example is **RG7388** (idasanutlin), an active and selective drug created by the Roche company. RG7388 is widely studied as a therapeutic in many human cancer cell lines and mouse models, in which human tumors are transplanted into mice with immunodeficiencies. The promising results of such studies allowed RG7388 to be introduced into clinical trials.

What's interesting, the activity of this compound has not been tested in murine cancer cell models and in syngeneic mouse models, in which tumors are created by injecting murine cells into mice with a fully functional immune system. Our preliminary results suggest that RG7388 is active in murine cancer cell models.

The presented project aims at a detailed characterization of the activity of RG7388 in mouse skin and colon cancer cells and determining its mechanism of action in this model. The next step will include testing the compound on laboratory mice. Murine cancer cells will be injected into mice with functional immune systems, which will allow us to study the effects of the treatment on the immune response. **The therapeutic potential of RG7388 will be additionally verified in combination therapy with immunotherapy against PD-1/PD-L1 immune checkpoint proteins.** This form of therapy has been proved effective and is already available for some patients. The second important aim of this project is to determine whether the combined treatment will result in a better therapeutic effect than the agents used separately.

During the realization of this project, we expect to evaluate the mechanism of action of RG7388 in murine cancer cells, which will widen the current state of knowledge regarding this potential drug. Assessing the effectiveness of proposed combination therapy would determine the effectiveness of such therapy in patients with skin and colon cancers.