DESCRIPTION FOR THE GENERAL PUBLIC

Gene expression is a process in which genetic information coded in DNA is transcribed into RNA and then, using RNA as a template, translated into protein. Proteins malfunction is often the reason of serious diseases. Traditional drugs usually act as a regulators of protein activity. Unfortunately, in case of various diseases such approach is not effective. Therefore, scientists have been undertaking attempts to develop other therapeutic approaches, and one of them is gene therapy. In gene therapy, a drug in the form of genetic information is delivered into cells, where it is used by the cellular machinery to produce protein that acts as a therapeutic agent to treat or prevent disease. At first, it was thought that DNA is the best material to be used in gene therapy. However, a necessary step for expression of DNA is its integration into the genome of the patient. This process is difficult to control and poses a risk of damaging important genes and induction another serious disease. As a consequence, mRNA has recently come into focus as a potential new drug class to deliver genetic information. mRNA is a recipe for preparation of protein in the cytoplasm. In contrast to DNA mRNA does not need to enter into the nucleus to be functional; once it has reached the cytoplasm the mRNA is translated instantly to produce required protein. This makes mRNA a much more safe manner of therapeutic intervention than DNA. However, mRNA in comparison to DNA has one serious disadvantage - it is less stable, both chemically and under cellular conditions. In this project we will search for new methods of RNA stabilization, which at the same time do not disrupt mRNA function in protein biosynthesis. Using advanced nucleotide chemistry methods we are going to prepare substrates for enzymatic modifications of two mRNA ends: mRNA cap structure at 5' end, and polyA tail at 3' end. mRNA ends are essential for proper function of mRNA and protect mRNA from premature degradation. However, in the cell are specialized enzymes responsible for removal of these structures. Slight modifications within the mRNA ends may protect mRNA from degradation and elongate its life-time under cellular conditions. We plan to test if it is possible to modify mRNA using nucleotide analogs to improve its properties important for therapeutic applications. We would like to test the influence of mRNA modifications on efficiency of protein production and enzymatic and cellular mRNA stability. The results of this can be beneficial for further development of mRNA-based gene therapies. Modified, more stable mRNAs can be applied as anticancer vaccines, in regenerative medicine or in gene replacement therapies.