In vitro synthesized mRNA has become nowadays an interesting target as innovative drug for delivery of genetic material into unhealthy cells. As compared to DNA, application of RNA has superior safety profile since it cannot be integrated into the host genome and is naturally metabolized, thus its activity is transient. However, efforts should be still focused on prolongation of the lifetime of mRNA and reduction of immunogenicity, particularly for applications other than vaccines. Both these parameters can be modulated by introduction of different modifications into the mRNA. Particularly interesting place to modify is a cap structure located at the 5' end of mRNA; this cap has important roles: it protects the transcript against degrading enzymes and binds to eIF4E protein factor, thus recruiting it to the translating apparatus. mRNA engineered with modified cap analogs, synthesized in our laboratory, is translated several-fold more efficiently than the native one, and is much less susceptible to degradation. mRNAs modified in such way has a possibility to remain long enough that the cell may produce the therapeutic proteins. Drugs based on mRNA can be applied for a broad spectrum of diseases. Our previous discoveries, defined as anti-cancer vaccine, provided the foundation for modern therapeutic approach and are presently in clinical trials carried out by the BioNTech. This is a very innovative therapy personalized for every patient. Such strategy ensures high specificity of action and low toxicity, which offers a hope for successful treatment of increasingly widespread oncologic diseases. If clinical trials succeed the mRNA modified by the altered cap structure, can be used to treat such malignancies as melanoma, and colon, breast, lung, and prostate cancers.

However, the application of mRNA as a carrier in protein replacement therapy, stem cells reprogramming or delivery of nucleases for genome editing remains still a challenge. In this application immunogenicity of RNA, which is its inherent feature, should be kept as low as possible. Otherwise RNA sensors activation trigger innate immune response and interferon expression which negatively may impact the disease treatment. It should be noted that non-immunogenic mRNA with the enhanced stability can be useful for wound healing, treatment of cystic fibrosis or even schizophrenia.

Proposed project will deal with mRNA design which will at once possess modified cap analogs for high efficiency of translation and protection against degrading enzymes together with additional structural elements providing recognition as a 'self' particle. Planned comprehensive research will bring fundamental data about significance of cap structure modification as well as cap related processes like translation, degradation and mRNA recognition. We also will synthetize new cap analogs that would allow mRNA application for still broader spectrum of diseases than the presently tested. It is expected that results that to be obtained would help to improve effectiveness of the anti-cancer vaccine that is currently in clinical tests and in developing new treatments in regenerative medicine and potentially in a variety of other diseases.