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Modified nucleotides as tools for obtaining therapeutic mRNAs: synthesis, properties and selected applications

mRNA-based therapies such as anti-cancer immunotherapies or gene therapies receive more and more attention as a new potential option of medical treatment. One limiting obstacle for in vivo and therapeutic applications of mRNAs is their instability and insufficient translation in the cellular environment. Therefore, mRNA-based therapies need simple methods of mRNA modification which would improve pharmacokinetic and pharmacodynamic properties of mRNA.

The main goal of this work was a synthesis and application of nonhydrolizable nucleotides derivatives to synthesis of stable and efficiently translated mRNA in vivo. mRNA molecules consist of several important structural elements such as a 5'cap, 5' untranslated region, coding region, 3' untranslated region and polyA tail. This work explores the concepts of logic-driven design and engineering of these elements by chemical methods as one potential method to increase stability and translational capabilities of mRNA.

The research is focused on the synthesis and evaluation of biological properties of novel 5' cap analogs and polyA precursors designed to inhibit decapping and deadenylation and enhance mRNA potential in vivo. A number of original compounds (nucleotides containing appropriate oligophosphate chain modifications) were obtained and divided in four types of molecular tools useful for mRNA stabilization. In addition, a new synthetic method was developed which enabled the synthesis of many biologically important nucleotides containig phosphorothioate, boranophosphate, selenophosphate, imidodiphosphate and methylenebisphosphonate modifications and their combinations. Finally, the influence of new compounds on behavior of mRNA in vitro and in human immature dendritic cells (hiDCs) were examined and the most promising compounds, resistant to enzymatic hydrolysis and enhancing translation of mRNA, were selected. Since increased stability and translatability of mRNA in hiDCs is a desired effect in anti-cancer immunotherapies, the new compounds become potential tools for therapeutic mRNA production.