TITLE: SARS-CoV-2 mRNA capping machinery – studies on nsp14 and nsp16 methyltransferase activity using high-throughput fluorescence method
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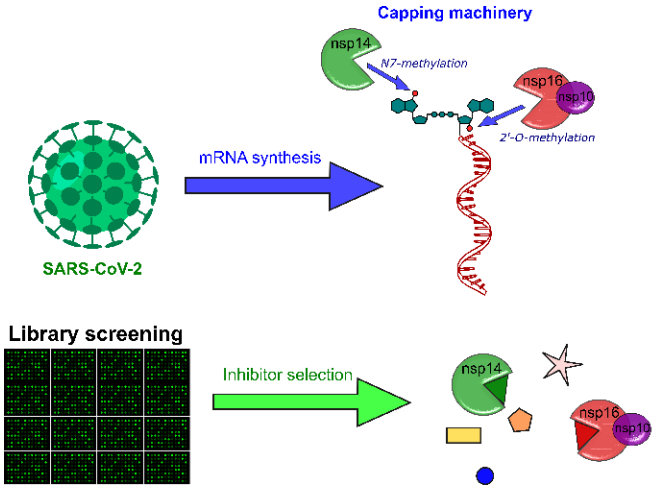

Messenger RNA (mRNA) is a genetic recipe for protein biosynthesis in cells. It is produced in the nucleus in a process called transcription during which the DNA sequence is transcribed into mRNA. Then, mRNA undergoes additional modifications during the maturation process, the first of which is the incorporation of a special structure at the end of 5' mRNA called cap. This structure ensures appropriate durability of mRNAs and effective translation, i.e. protein biosynthesis. Additionally, in higher organisms such as humans, mRNAs are additionally marked (methylated in the appropriate position) to distinguish them from foreign mRNAs. In order to increase the expression of their own proteins and escape the host's immune response, some viruses have developed their own systems to attach cap to their RNA. SARS-CoV2, which is the cause of the ongoing worldwide COVID-19 pandemic, in its genetic material has two enzymes involved in this process (nsp14, nsp16) and one additional regulatory protein (nsp 10).

The aim of the project is to test the nsp14 and nsp16 SARS-CoV2 proteins which are methyltransferases (MTases) involved in cap synthesis at the 5' end of viral RNAs. Their activity is necessary to express viral proteins, multiply the virus and avoid activation of the immune system. The inhibition of these proteins may be a starting point for new therapies against COVID-19 disease. We intend to develop special molecular probes, which will enable us to study the activity of coronavirus methyltransferases (nsp14 and nsp16) and compare them with human counterparts. These probes will allow for a very quick screening for inhibitors of particular enzymes. The best inhibitors will be characterized by biochemical and biophysical methods to inhibit the expression of viral proteins. The involvement of the third viral protein in cap synthesis, nsp10, will also be investigated.

The implementation of the project will allow us to better understand how the virus is able to use natural biological mechanisms to multiply in host cells. Knowledge about the process of cap biosynthesis of the SARS-CoV-2 virus may be the starting point for developing drugs against COVID-19.