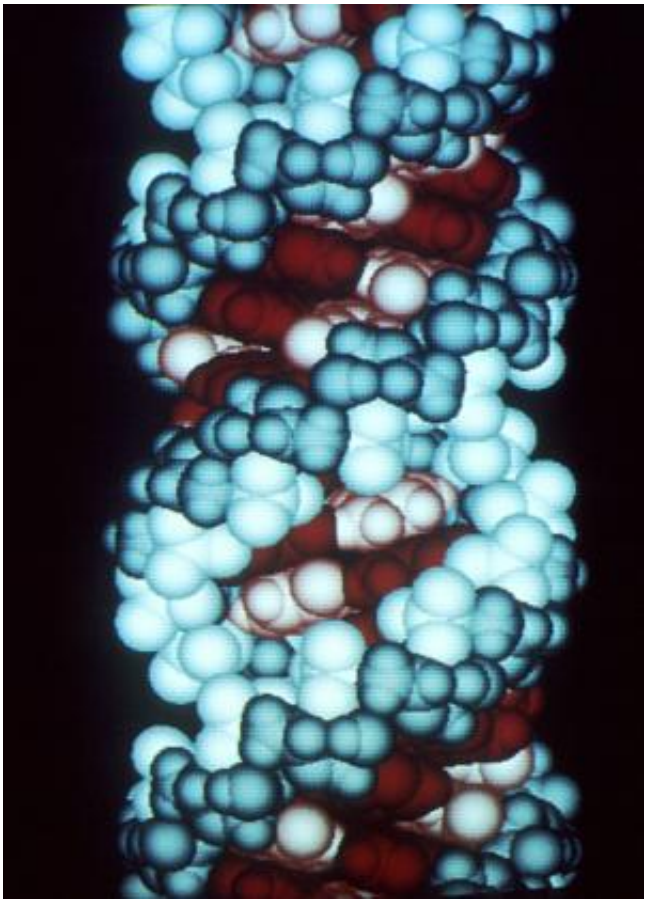
Targeting viral RNA: The basis for next-gen broad spectrum anti-viral drugs

May 10 2021



This is a computer graphic of an RNA molecule. Credit: Richard Feldmann/Wikipedia

A new approach to tackling viruses by targeting the 'control center' in viral RNA could lead to broad spectrum anti-viral drugs and provide a

first line of defense against future pandemics, according to new research at the University of Birmingham.

In a new study, published in *Angewandte Chemie*, researchers have shown how this approach could be effective against the SARS-CoV-2 virus responsible for the COVID-19 pandemic. Earlier modeling and in vitro analysis by the team and published in *Chemical Science* has also shown effectiveness against the HIV virus.

Professor Mike Hannon, from the University of Birmingham's School of Chemistry, is co-lead author of the study. He said: "Although SARS-CoV-2 vaccines have been developed with unprecedented speed, there has still been a 12-month wait for development and approval. Viral pandemics remain a big threat and so broad-spectrum anti-virals are urgently needed to keep diseases like coronaviruses at bay while effective drugs are developed."

The technique proposed by the team uses cylindrically-shaped molecules which can block the function of a particular section at one end of the RNA strand. These RNA sections, known as untranslated RNA, are essential for regulating the replication of the virus.

Untranslated RNA contain junction points and bulges—essentially small holes in the structure– which are normally recognized by proteins or other pieces of RNA—events that are critical for viral replication to occur. The cylindrical molecules are attracted to these holes, and once they slide into them, the RNA closes around them, forming a precise fit, which consequently will interfere with the virus's ability to replicate.

"Our approach offers a very promising new route for anti-viral drug design," says Professor Hannon. "While most drugs in development target the virus's proteins, we have identified molecules capable of tackling the most fundamental part of the virus—its RNA. Experiments

backed up by computer modeling have already shown this to be effective against SARS-CoV-2 and the HIV viruses and we anticipate it will also be effective against a wide range of other viruses, offering an important first step towards a broad spectrum anti-viral drug."

Co-lead author Dr. Pawel Grzechnik, of the University of Birmingham's School of Biosciences, said: "The ongoing COVID-19pandemic has revealed how important is RNA biology to understand molecular processes taking place in our cells, to find ways to suppress pathogens and to make efficient and safe vaccines. RNA only now emerges in the general consciousness of society as the major tool in therapies. We hope to continue our research and further investigate antiviral properties of the cylinders at the University of Birmingham."

Dr. Zania Stamataki, of the University of Birmingham's Institute of Immunology and Immunotherapy and also co-lead author, said: "The SARS-CoV-2 pandemic has stressed the pressing need for the development on new antiviral treatments, particularly for RNA viruses. In Birmingham we have state-of-the-art containment level 3 facilities that allow us to study the full virus life cycle. We have developed models to test the effects of new antiviral therapies, and the supramolecular cylinders show promising results against replicating SARS-CoV-2. The ambition is that these new categories of compounds can be refined and targeted to extend their function against many other viruses that infect humans and animals."

The team will continue to develop the design of the cylindrical molecule to improve its effectiveness and control, and also to fully understand how it works within the virus before testing it in a model organism.

The cylindrical molecules have been the subject of previous research, led by Professor Hannon, which focussed on finding a way to control the way the cylinder interacts with DNA and RNA. This research resulted in

novel compounds that have the potential to be developed into targeted treatments for cancers, viruses and other diseases, and is the subject of a patent application filed by University of Birmingham Enterprise.

More information: Lazaros Melidis et al. Supramolecular cylinders target bulge structures in the 5' UTR of the RNA genome of SARS-CoV-2 and inhibit viral replication, *Angewandte Chemie* (2021). DOI: 10.1002/ange.202104179

Lazaros Melidis et al. Targeting structural features of viral genomes with a nano-sized supramolecular drug, *Chemical Science* (2021). DOI: 10.1039/D1SC00933H

Provided by University of Birmingham