Collaboration develops new compound with promising activity against SARS-CoV-2 variants

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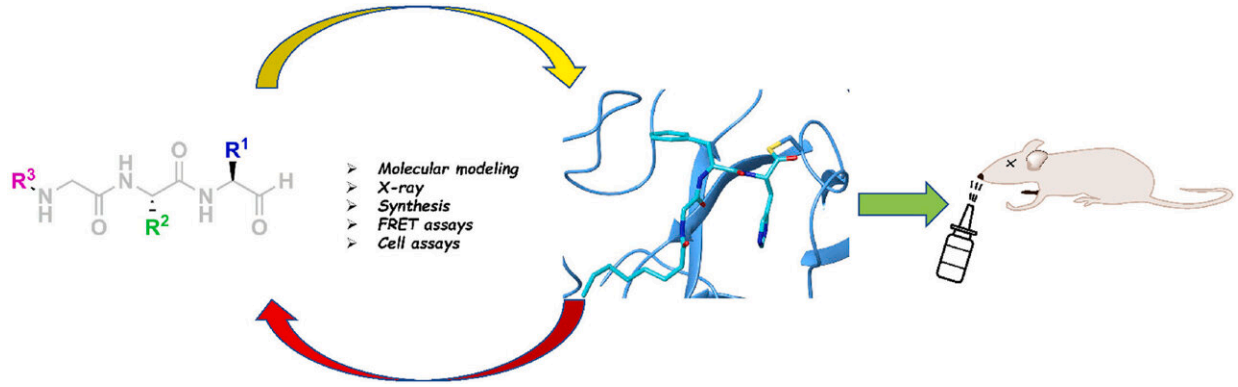

Graphical abstract. Credit: *European Journal of Medicinal Chemistry* (2022). DOI: 10.1016/j.ejmech.2022.114857

A collaboration between the Márquez group at EMBL Grenoble and Italian researchers from the European Biomedical Research Institute of Salerno (EBRIS) has led to the development and characterization of a novel small molecule inhibitor, which shows promising activity against three SARS-CoV-2 variants.

In the *European Journal of Medicinal Chemistry*, the scientists describe a generation of compounds that would act against the main protease of SARS-CoV-2. One of these compounds is currently a clinical candidate

for the development of an intranasal spray against SARS-CoV-2. Moreover, due to the highly conserved amino acid sequence of the active site of targeted enzymes among coronaviruses, this inhibitor could treat infections from different coronavirus species.

The Italian research group, led by Simone Di Micco, began studying SARS-CoV-2 in early 2020. Already interested in the design of new bioactive molecules, they quickly adapted their previous research on celiac disease towards this new direction. While Di Micco's team could use in silico methodology to design new compounds that would target one of the key enzymes of the virus, they didn't have a way to figure out the real-life binding interactions between the molecules and their biological target.

Structural biology is an essential discipline in molecular biology used in drug development. By obtaining the atomic structure of a molecule interacting with its biological target, structural biologists can give important insights about its mode of binding and use this information to design new molecules with improved affinity and specificity.

The fully-automated X-ray crystallography pipelines developed and operated jointly by EMBL Grenoble and ESRF are especially suited for this, as they allow rapid screening of compound libraries and can be used to identify small molecules that bind the biological target.

However, Di Micco's group had no prior expertise in structural biology, nor the equipment to perform the experiments. It was at this point that Di Micco attended a webinar hosted by Instruct-ERIC, a structural biology research infrastructure that supports European researchers by providing them with access to high-end technologies and methods.

Besides delivering high-quality science, EMBL's structural biology services support the external research community across Europe by

offering a range of approaches and infrastructures often based on unique technologies developed at EMBL.

The High-Throughput Crystallization Laboratory (HTX Lab), operated by the Márquez team, is one of the most important facilities for high-throughput nano volume and crystallization screening in Europe.

These pipelines use the CrystalDirect technology for automated crystal harvesting and cryocooling. They combine this approach with the use of EMBL's Crystallographic Information Management System (CRIMS), a web-based software suite providing interfaces for online design and evaluation of crystallographic experiments, with real-time access to results and experimental parameters.

With this system, scientists all over the world can mail in their samples and follow each step from the crystallization to X-ray diffraction experiments and structure solution, obtaining the information needed remotely. "This is what makes HTX Lab different from other laboratories that perform crystallography," said Rahila Rahimova, a postdoctoral fellow in the Márquez Team.

Rahimova, together with research technician Léa Mammri and José Márquez, supported Di Micco with their expertise in structural biology and biophysical methods, and performed X-ray crystallography studies to characterize the molecular interaction between the new compound and the SARS-CoV-2 main protease.

This interdisciplinary collaboration soon yielded results. The structural studies performed at EMBL Grenoble revealed how the compound binds to and inhibits the SARS-CoV-2 main protease, which is essential for the virus life cycle. Moreover, this provided important feedback to the Di Micco group who could then use it to further refine the drug design process. This resulted in a compound with very low cellular toxicity,

reducing the risk of side effects.

"I would like to stress the importance of collaboration in science. In our case, it was also possible to obtain access to EMBL Grenoble facilities, services, equipment, and expertise thanks to ISIDORe," said Di Micco. The Integrated Services For Infectious Disease Outbreak Research (ISIDORe) provides scientists studying infectious disease with access to European facilities, services, equipment, and expertise.

This research also ties into the Infection Biology transversal theme, part of EMBL's 2022-26 Program "Molecules to Ecosystems." This theme aims to contribute to research on infectious diseases and the biology of their mechanisms, diagnostics, and treatment.

The next step for Di Micco is to test this molecule in a clinical trial, since this compound could pave the way towards the development of new treatments against COVID-19. "The infection's highest concentration is in the nose at the beginning: before it goes to the upper airways and then in the lungs. An intranasal spray would simplify the administration of drugs without the assistance of nurses or doctors, or the need to go to the hospital," he said.

More information: Simone Di Micco et al, Rational design of the zonulin inhibitor AT1001 derivatives as potential anti SARS-CoV-2, *European Journal of Medicinal Chemistry* (2022). DOI: 10.1016/j.ejmech.2022.114857

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