

## Masitinib and Its Role in Inhibiting SARS-CoV-2 Infection

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### Letter to the Editor

A drug used successfully in veterinary medicine to treat mast cell tumors in dogs may be effective against COVID-19 and some other viral diseases in humans, according to laboratory experiments and preclinical studies published in Science 2021 [1]. Coronaviruses also require such enzymes. After entering the cells, their genome is first converted into 2 polyproteins, which must be broken down into smaller units. This task is performed by 2 proteases. This is once the main protease 3CL (also called Mpro or nsp5). The 2nd enzyme is the "papain like" protease, abbreviated PLpro. Drugs that block one of these enzymes could prevent the viruses from replicating in the cells and thus stop the progression of the infection.

Currently, the only active agent against the replication of coronaviruses in cells is remdesivir. It blocks an RNA polymerase that the viruses need to replicate their genetic material to be incorporated into new viruses. Remdesivir is rarely used because it must be administered as an infusion and is effective only in the early stages of infection in mild courses.

A team led by Savas Tay and Nir Drayman of the University of Chicago has been systematically searching for other agents that can stop coronavirus replication in cell cultures in laboratory experiments [1]. They conducted the screening with OC43, one of four coronaviruses that circulate as cold viruses and, unlike SARS-CoV-2, do not cause fatal infections (and therefore can be studied in the lab without safety precautions). The researchers screened a total of 1,900 compounds that are used as drugs in humans or have at least been shown to be safe in clinical trials. They found 108

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compounds that inhibited OC<sub>43</sub> replication. Of these, 30 were tested in a high-security laboratory for their ability to stop SARS-CoV-2 replication in cells. A total of 20 passed this test. Further experiments were conducted to determine whether the compounds were able to inhibit the enzyme 3CL [1]. This test was passed by 8 substances [1].

The most effective was masitinib, which completely inhibited 3CL activity in cells. Masitinib is an orally bioavailable inhibitor of the tyrosine kinase KIT. It is approved for the treatment of mast cell tumors in dogs. In humans, it has been tested in Phase 2 and Phase 3 clinical trials in various diseases (cancer, asthma, Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis) [2-6]. Masitinib is not approved as a drug in human medicine. X-ray crystallography showed that masitinib binds in the active site of the 3CL protease, preventing the enzyme from cleaving the polyprotein of SARS-CoV-2. The study published in Science showed significant results to inhibition of 3CL activity in cells [1].

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