Fluorescence-based high-throughput assay for identifying antivirals to control COVID-19 pandemic

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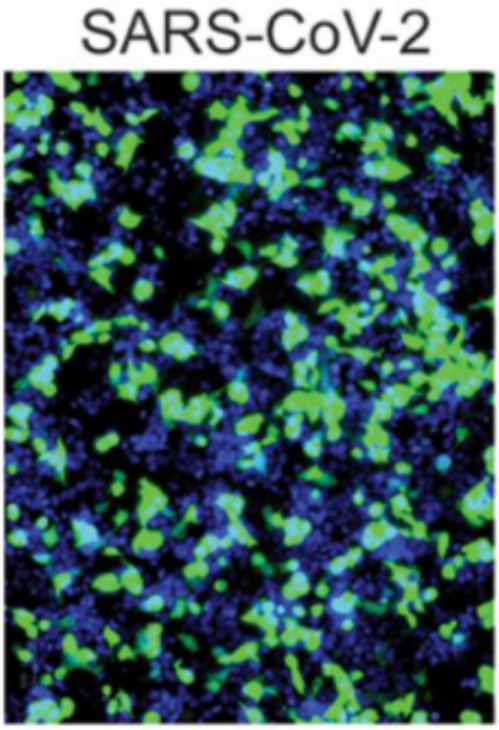
Unmet Need

Current efforts to control COVID-19 are largely focused on behavioral modifications such as social distancing and the use of masks. These approaches attempt to slow the spread of the virus, but meaningful control of the virus will ultimately be the result of a combination of efficacious vaccines and antiviral therapeutics. Thus, the discovery of additional effective SARS-CoV-2 antiviral drugs remains of high importance. Therapeutic development efforts have led to a number of candidate antiviral compounds; however, the clinical benefits have remained limited and a number of newly designed compounds are entering the early stages of testing. The identification and subsequent improvement of novel drugs targeting SARS-CoV-2 will require robust and high-throughput screening approaches.

Technology

Duke inventors have reported an assay intended to help identify novel antivirals to control the COVID-19 pandemic. Specifically, this is a new assay to identify inhibitors of $3CL^{pro}$, the attractive antiviral target that most drug development efforts are directed towards. The reporter is based on a green fluorescent protein (GFP)-derived protein that fluoresces only after cleavage by $3CL^{pro}$. The inventors generated and tested three reporter constructs with distinct cleavage target sequences for activation by the SARS-CoV-2 $3CL^{pro}$ and demonstrated that the reporter with the best signal-to-noise ratio for SARS-CoV-2 is also activable by other coronavirus $3CL^{pro}$ proteins across subgroups (*Betacoronavirus*, *Alphacoronavirus*, and *Gammacoronavirus*) and host species (human, rodent, and bird). Finally, the technology was used to test the inhibition of SARS-CoV-2 $3CL^{pro}$ with a known coronavirus $3CL^{pro}$ inhibitor, GC376 and then validated the correlation between reporter inhibition and inhibition of SARS-CoV-2 replication. Additionally, the inventors screened a library of 1,900 clinically safe drugs and found that mastinib offered broad anti-viral activity and is a strong candidate for clinical trials to treat SARS-CoV-2 infection.



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Other Applications

The reporter is compatible with many CoV 3CL^{pro} proteins, supporting rapid testing of inhibitors against a variety of coronaviruses, present or future, and without synthesis of protease substrates or purification of viral proteins. In addition to applications in drug discovery pipelines, this assay could be deployed to determine targets of antivirals identified via viral screening.

Advantages

- Offers a solution for identifying novel antivirals to control the COVID-19 pandemic
- Allows for antiviral drug screening in human cell culture at biosafety level 2 (BSL2)
- Scalability and use of a fluorescent plate reader support ability to achieve high-throughput screening

Publications

- Drug repurposing screen identifies masitinib as a 3CLpro inhibitor that blocks replication of SARS-CoV-2 in vitro (bioRxiv, 2020)
- Development of a fluorescence based high-throughput SARS-CoV-2 3CLpro reporter assay (Journal of Virology, 2020)

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