How to screen faster – Efficient identification of active ingredients against SARS-CoV-2 and chemical probes as inhibitors of the 3CL and PL proteases of coronaviruses

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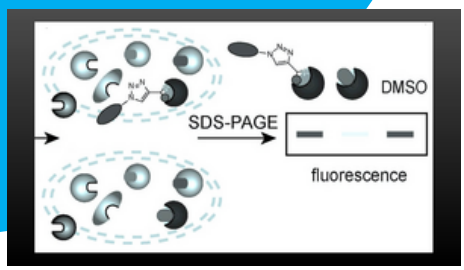
Here, an extremely simple and effective screening method for the identification of cell-compatible drugs against viruses such as SARS-CoV-2, respectively effective inhibitors of their proteases such as 3CL and PL, is presented. The principle can also be transferred to other pathogens.
Furthermore, there are first resulting candidates that could be further developed as active compounds against COVID-19.

- Fast and effective drug screening for antiviral inhibitors without the time-consuming synthesis of libraries
- Realizable as a high-throughput procedure
- Inhibition of proteases before autocatalytic maturation
- Identification of potent enzyme inhibitors with cell permeability
- Suitable for non-proteolytic enzymes
- Small number of off-targets



Application

More effective drug screening and fast, reliable drug candidate selection against viruses such as SARS-CoV-2 and other pathogens with similar proteases.

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Development Status
Screening: TRL6, Active compound: TRL3

Patent Situation
EP 21 772 981.3 pending
US 18/022,644 pending

Reference ID
20/035TLB

Service
Technologie-Lizenz-Büro GmbH manages inventions until they are marketable and offers companies opportunities for license and collaboration agreements. First samples and screening technology can be presented to an interested party. Date of publication: 11th Nov 2020

Background

The search for an effective COVID-19 drug is in global focus facing the prevailing pandemic. Several open reading frames have already been identified in the genome of SARS-CoV-2, which code for proteins that are crucial for the replication of the virus. In order to use these proteins, the polyprotein must be cleaved into the individual functional proteins by the proteases PL^{pro} and $3CL^{pro}$. These proteases are therefore a primary target for drug development.

Problem

Up to now, classical enzyme assays with fluorogenic substrate have been used for the identification of drug candidates. However, this multi-step procedure can only be used for *in vitro* studies – potential candidates must be examined in a subsequent step with regard to important aspects such as a focus on the active site of the enzyme, the reactivity against proteins and their ability to cross cell membranes. In addition, the identification of promising candidates requires the exclusion of numerous off-targets.

Up to now, there is no method that can be performed directly in living cells, considering cell permeability at the same time, and that also allows the identification in complex mixtures. Thus, the conventional method of drug screening is a lengthy process and generally slow, particularly too slow in the case of an acute pandemic.

Solution

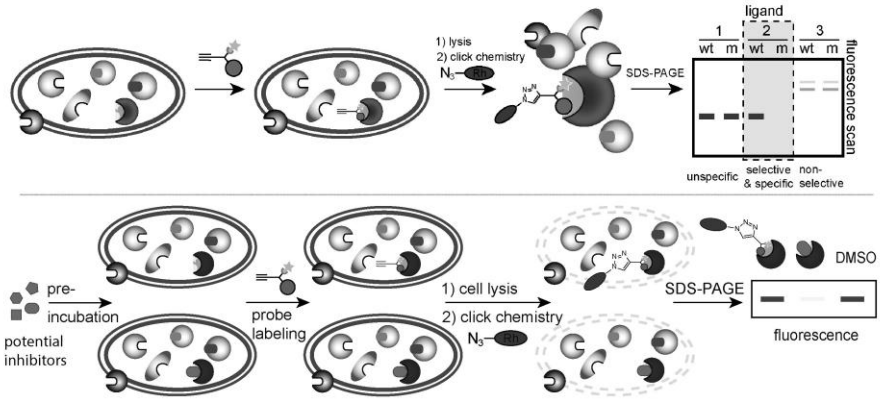
Using a ligand selection strategy, scientists at the University of Konstanz have succeeded in identifying specific molecular probes that bind directly to the active site of the two target proteases of SARS-CoV-2. The method allows to identify competitive inhibitors in living cells directly and also to evaluate enzyme function and activity at the same time.

Moreover, for the first time the inhibition of the target proteases can be reliably detected prior to their autocatalytic maturation. The method can also be used for a high-throughput screening of the enzyme function and activity.

The method can also be used for the identification of further antiviral agents - even beyond SARS viruses - and is ready to be applied immediately.

The scientists have already been able to show that the chemical probes can easily be adapted for specific labeling of the active site and expect that this ligand selection strategy will be useful for a wide range of target proteins in the future.

The approach could significantly advance the development of inhibition assays against proteases prior to their autocatalytic maturation as well as against non-proteolytic enzymes (which cannot be investigated using standard substrate cleavage assays).



Top: Method of selection and screening by probes in wild type and mutant. Down: Inhibitor profiling against proteases [University of Konstanz].

Publication and links

Peñalver, L., Schmid, P., Szamosvári, D., Schildknecht, S., Globisch, C., Sawade, K., Peter, C. and Böttcher, T. (2021),
A Ligand Selection Strategy Identifies Chemical Probes Targeting the Proteases of SARS-CoV-2. Angew. Chem. Int. Ed.
https://doi.org/10.1002/anie.202016113