IMI2 Project ID 101005077

CARE – Corona Accelerated R&D in Europe

WP2 – Target-based drug discovery and design

D2.5 A set of emergency/additional molecules

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Document History

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Abstract

One of CARE's aims is to develop a portfolio of novel small molecules to address the current and/or future coronavirus outbreaks. For this purpose, CARE EFPIA companies, SMEs and academic partners screened either public or in-house libraries to identify hits against several coronavirus targets over the first three years of CARE (aside from a phenotypic screening effort). Two approaches were used: virtual screening and high-throughput screening (HTS). It was not possible to identify appropriate hits from this target based approach for the emergency phase of the pandemic. A few potential hits were identified and were selected to be further advanced to meet the preparedness aim of the CARE consortium. Collaborative efforts across CARE have led to the advancement of three antivirals with novel mechanism of action (MOA) and development of potential new antivirals for a well known target. The novel MOA antivirals are currently in lead optimisation and the antivirals against the known target are in in-vivo proof-of-concept.

Results

CARE partners have undertaken a number of virtual screenings of either proprietary or public libraries against SARS-CoV-2 essential enzymes and structural proteins. Targets include, among others, Mpro, nsp14, nsp16, RdRp, RTC, spike protein, and ACE2.

Depending on the target, hundreds to millions of virtual compounds have been screened, with more than one in-house library screened for some of the targets.

These screenings led to the selection of hits that were either bought or synthesized to be further evaluated. Some of the hits were evaluated in cellular assay for inhibition of activity, but none of the hits were further progressed.

From these hits a few lead series have been identified as interesting and are being developed further by partners in CARE using the resources of other work packages.

Conclusions

Finding small molecules with broad activity against coronaviruses for the emergency phase has been challenging because of the low percentage of hits from HTS in both the CARE consortium and efforts globally. This resulted in CARE being unable to deliver any hits for the emergency phase of the pandemic. CARE partners have persisted in their aim to develop broad-spectrum antivirals for the preparedness phase. This has resulted in the identification of a number of potential small molecule antivirals, which are in advanced stages of discovery. CARE now has four ongoing programmes in Work Package 3, three are antivirals with novel mechanism-of-actions and one programme is looking for improved antivirals against a well-characterised target. These molecules are being advanced to meet the preparedness aim of the CARE consortium, with the novel mechanism-of-action antivirals currently in lead optimisation and the antiviral against the known target in in-vivo proof-of-concept.