Target-based drug discovery and design

Work Package 2

CARE
CORONA ACCELERATED R&D IN EUROPE

Leads

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Key Objectives of Work Package 2

To support critical protein and enzyme needs of the consortium by performing

- Gene expression and protein purification
- Target-based *in silico v*irtual screening
  - Support of WP1 results and hit-ID optimisation results
  - Structural studies of Spike proteins and replication enzymes
- Create a protein/enzyme toolbox with enzyme assays in HTS screenable format (made available inside and outside the consortium

CONNECTIONS

with other work packages

Work package 1

Functional testing of emerging compounds from phenotypic screening of WP1

Work package 3

Supporting many WP3 partners with MOA determination in many targets plus target-based screening for HIT-ID and HIT explosion

Collaborative development of Mpro and nsp14 inhibitors

Supporting synthesis of nucleoside analogues for the preparation of triphosphate derivatives tested within WP2

BREAKTHROUGH *moments*

2021 **Completed virtual screening of CoV enzymes and structural** proteins across multiple targets and partners

2021 **Structure based drug design** of key CoV enzymes for five targets

2022 **Comprehensive study of nirmatrelvir** and 13b-K resistance mutations in Mpro and resistance mutations induced by nsp14 inhibitors

2024 Development of SARS-CoV-2 Spike targeting cyclic peptide that inhibits all variants

2024 **Profiling in antiviral experiments** of drug combinations that include nsp14-targeting compounds

DELIVERABLES

Deliverable D2.2
HTS assay for the RTC under a 384-well plate format [31May21]

Deliverable 2.4
A toolbox with at least 8 assays [20Oct23]

Deliverable D2.3
Crystal or cryo-EM structures of the nsp14 and Spike protein [due 31Mar25]

Deliverable 2.5
A set of emergency/ additional molecules [12Feb24]

KEY STATISTICS

70+ Mpro mutants analysed

100+ 100+ antiviral peptides tested

45 Crystal structures determined

Expression plasmids made available to CARE partners covering almost all the high priority drug targets **75+**

200+ Novel nsp14 inhibitors tested in antiviral assays

45 Partner compounds analysed for inhibitory activity against SARS-CoV-2 PLpro

15 Partner compounds analysed for inhibitory activity against SARS-CoV-2 Mpro

Partner Organisations

Aix-Marseille université
Takeda
AiCuris
Ai-biopharma
University of Dundee
SERVIER
The University of Edinburgh
Utrecht University
Leiden University Medical Center
Bill & Melinda Gates foundation
MERCK
abbvie
Pfizer
Universität zu Lübeck
BAYER
Goethe Universität Frankfurt am Main

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