IMI2 Project ID 101005077

CARE - Corona Accelerated R&D in Europe

WP3 – WP Hits to leads

D3.10 Portfolio report

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Document History

Version	Date	Description
V3.1.	31 MAR 2020	Portfolio report WP3 (12M)

The CARE project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101005077. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and BILL & MELINDA GATES FOUNDATION, GLOBAL HEALTH DRUG DISCOVERY INSTITUTE, UNIVERSITY OF DUNDEE.

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Abstract

The objective of WP3 is to combine the broad expertise of consortium partners in drug discovery in order to identify small molecule candidate drugs to fight coronaviruses.
To effectively deliver drug candidates, WP3 has been interacting closely with WP1 and WP2 to identify and select potential starting points for further development based on clearly defined progression criteria. AI analysis of targets for their druggability has been performed and the results will be applied to prioritize certain targets when necessary. Screening cascades for (phenotypic) hit ID have been implemented and executed. Efficient drug discovery testing cascades are being implemented for each target for which active chemistry is ongoing, including targets that have been identified in phenotypic screens. These drug discovery cascades will contribute to the design of a coordinated AI-platform for each target.
The medicinal chemistry has been initiated so far on Nsp14, mPro and 2 hit series identified by phenotypic screening. Additional starting points identified via virtual screens on targets and phenotypic screens are expected to be included in the coming months.
The aim is to work towards the predefined target product profiles (TPPs).

Results

1. Screening cascade for hit to lead and lead op

The progression criteria for hit compounds identified via a phenotypic screen (WP1) or target based approach (WP2) have been defined based on various properties including *in vitro* efficacy, biochemical activity, chemical properties, *in vitro* toxicity, and chemistry. A streamlined and efficient drug discovery testing cascade that supports rapid profiling and triaging hits from WP1 and 2 has been established.

For each target/phenotypic approach more specific drug development cascades have been defined. These cascades describe (1) the critical path to in vivo efficacy studies, (2) partners in the consortium who can deliver the necessary resources/assays, and (3) cycling times. These screening cascades can be adjusted based on the available resources, starting points and targets/approaches that will be prioritized.

2. Phenotypic hit to lead – hit ID

WP3 has been involved in the follow-up of several screening efforts to identify hit compounds with activity against SARS-Cov-2. Besides supporting their own screening campaign with ~240 000 compounds, the **KU Leuven team (P11)**, is taking the lead in following up on all potential starting points identified in phenotypic screening efforts from other partners within the consortium.

Results obtained from the screening efforts on the Reframe / repurposing side were disappointing. Very few compounds showed reproducible anti-viral activity with acceptable selectivity index. Some compounds, identified by KU Leuven and also already described in literature, were further investigated. Unfortunately, in most cases, activity could not be confirmed.

The hit rate of the large phenotypic screening campaigns (Vero-E6 based assay; KU Leuven P11, **Janssen P2**) were very low. From these hit identification campaigns

Janssen confirmed 1 hit series on which active chemistry is ongoing. KU Leuven (P11) has currently active chemistry on 2 confirmed hit series within the CARE consortium. Chemistry efforts are still at an early stage focussed on SAR exploration and optimization of antiviral potency. First steps in identification of the MOA have been taken, compounds are currently being tested for their potency on different targets in WP2. First results show that compounds from both series are inactive in polymerase, mPro and cathepsins/TMPRSS2 related biochemical assays. The anti-viral activity of these hit series on variants of concern is closely monitored.

Other partners of the consortium have performed phenotypic screens as well using a dedicated small molecule compound library with mixed success. A small phenotypic screen by **Astellas (P24)**, **Novartis (P31)**, and **AiCuris (P36)** did not identify compounds for further follow up. The potential hits from a phenotypic screen from **Enyo Pharma (P28)** could not be confirmed. However, confirmation studies on hit compounds identified by **BI (P26)** and **Servier (P37)** are looking promising with potential new starting points being identified to initiate chemistry on.

Additional phenotypic screens are planned by **Janssen (P2)**, **KU Leuven (P11)** and **Pfizer (P32)**.

3. Target driven approaches Hit to lead - hit ID

3.1 Hit to lead

The first round of screening efforts (e.g. biochemical assays, virtual screen) based on specific targets of the virus led to the identification of potential starting points and validated hit compounds to be prioritized and selected to enter the hit-to-lead trajectory.

To streamline the medicinal chemistry efforts, different teams, organized by target, have been put in place. These teams are empowered to prioritize potential starting points and drive the chemistry efforts for their target. Currently 2 teams are built around 3 targets.

The first team (lead Dundee (P27), supported by Exscientia (P7), Takeda (P3), GHDDI (P30)) focusses on Nsp14 and PLpro. Unfortunately, the efforts on PLpro have encountered some delay due to issues with the screening assay. Alternatives for this assay have been identified to support the project. For Nsp14 chemistry has started on 5 compound series. Early SAR exploration is ongoing and crystallography efforts will be initiated to help drive the chemistry forward.

The second team (Lead Nuvisan (P14), supported by Exscientia (P7), Takeda (P3), Merck (P33), GHDDI (P30)) is dedicated to all efforts around the mPro, So far chemistry is focused on one lead series (peptidomimetic) which was identified by Exscientia. In vitro DMPK profiling has been initiated.

3.2 Hit ID

The identification of potential new starting points for Nsp14, PLpro and mPro are still ongoing as well as for other anti-viral targets. WP3 supports the identification of potential starting points through target based approaches and coordinates the collection of potential starting points from WP1 and WP2. New selection rounds are planned to allow the inclusion of other potential starting points and compound series from other hit identification approaches.

Takeda (P3) is performing virtual screening efforts around a number of targets e.g. mPro, Methyltransferase (Nsp14&16), PLpro, and helicase. Promising starting points from the ongoing mPro efforts will be reviewed and potentially proposed to WP3. Potential starting points identified on the other targets will be mainly developed in consortia out of CARE, however, Takeda will assist WP3 by providing technical and resource support for the other targets if necessary. Potential starting points for mPro can be identified from ongoing screening efforts from other CARE consortium partners. **Bayer (P25)** has performed an HTS screen on mPro, the selection of potential starting points is pending and selected starting points will be included in the medchem efforts of the appropriate chemistry team. **Merck (P33)** has performed a virtual screen around mPro. Actives have been selected and evaluation of the compounds is ongoing.

Currently no chemistry has been initiated on the polymerase yet, although several CARE consortium members have active screening projects on this target. **Ai-biopharma (P35)** is putting his efforts in targeting the polymerase. They have at least one potential starting point for chemistry which will be performed Ai-biopharma internally. **Janssen (P2)** completed a virtual screen on the polymerase. Hit compounds have been selected and further testing in biochemical and cell based assays is ongoing. **Pfizer (P32)** initiated a virtual screen with their proprietary compound collection. Potential starting points that would be identified will be carefully reviewed by WP3 and prioritized and selected to enter the hit-to-lead trajectory when agreed by the JSG of WP3.

4. Coordinated AI-platform

Work is ongoing to define a coordinated process to allow Exscientia's AI platform to accelerate the delivery of candidate small molecules for CARE. This activity requires a workflow to be agreed by the CARE partners and mapped onto the resources (human and technology) available within the 37 CARE partners. This is a challenging task to perform for the complete project. The better option is to perform this tasks per target/approach. A coordinated AI platform for Mpro is currently being installed. The process will then be applied to Nsp14, the phenotypic approach and in the future for other targets for which hit to lead activities would be initiated.

5. Analysis of targets for druggability – Variants of concern

Exscientia has completed the analysis of targets for their druggability. The results have been presented and the report filled. The report ranks SARS-CoV2 targets according to their druggability, and provides recommendations to CARE partners as to which ones would be best to pursue from a chemistry design perspective. Further work has to be done to establish the biological implications of these choices, with regards to eliminating COVID-19 disease, and SARS-Cov2 viral load.

The focus of WP3 is to develop broad spectrum coronavirus antivirals including activity against variants. Exscientia investigated the mutations identified in variants of interest and analyzed if they appear in the targets for which active chemistry is ongoing. So far barely any mutations have been identified in the current targets. This exercise will be continued and performed on newly identified targets and variants of interest.

6. Progression criteria and TPPs

The progression criteria for compounds to enter into a next phase (hit-to-lead, lead optimization towards preclinical candidate) have been finalised. The proposed progression criteria and screening cascades have to be used as guidelines and will of course have to be adapted depending on the specific compounds series in development. In addition to the input from WP1 and 2, the hit-to-lead and lead optimisation campaign will be supported by know-how and resources from WP6.

The prioritization of the assets will be based on the target product profiles. WP3 finalised 2 target product profiles, one for prophylactic treatment and one for therapeutic treatment.

Discussion/Conclusion

WP3 has established progression criteria for hits, leads and optimized leads/candidates. A general streamlined and efficient drug discovery testing cascade for HitID has been established and the screening cascade for specific hit-to-lead/lead optimization are being installed. The hit-to-lead process for mPro is supported by AI optimisation methods. Target product profiles for prophylactic and therapeutic treatment have been finalised.

Medicinal chemistry efforts have been initiated for mPro, Nsp14 and on 2 compound series identified in a phenotypic screen. Potential starting points from ongoing hit ID efforts will be reviewed and included in the hit to lead campaigns after careful review.