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CARE - Corona Accelerated R&D in Europe

WP3 – WP Hits to leads

D3.11 Portfolio report

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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 is 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 have been implemented for each target for which active chemistry is ongoing, including for compounds that have been identified in phenotypic screens. These drug discovery cascades will contribute to the design of a coordinated AI-platform for each target.
Hit to lead programs are ongoing on Nsp14, and 3 hit series identified by phenotypic screening. Hit selection on Plpro and Nsp12 is pending and chemistry on these targets is expected to be initiated before end 2021. Additional hits identified through target based, virtual and/or phenotypic screens within and outside the CARE consortium are being validated in the CARE consortium potentially delivering interesting starting points to be taken up in hit to lead programs by the end of 2021.
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 KULeuven 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 KULeuven 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**; KULeuven - P11, Janssen P2**) were very low. From these hit identification campaigns **Janssen (P2)** confirmed 1 hit series on which active chemistry is ongoing. Compounds from this series demonstrate broad spectrum coronavirus activity with double digit nM cell based potency. Medicinal chemistry efforts are direct towards improvement of potency and ADME/PK properties;

aiming for i*n vivo* proof of concept studies by end 2021. Target deconvolution studies are ongoing to identify the MOA. **KULeuven (P11)** has currently active chemistry on 2 confirmed hit series within the CARE consortium (transferred from SCORE). One series has broad spectrum activity against SARS-CoV-2 and SARS-CoV-1. The other series, with double digit nM cell based activity, has been demonstrated to be SARS-CoV-2 selective. An amendment was added to the TPP (agreement CARE consortium) to allow active development of a SARS-CoV-2 selective compound series if equipotent activity against variants of concern can be reached. The medicinal chemistry program is focussed on optimization of antiviral potency and improvement of ADME/PK properties. All efforts are focussed towards a first *in vivo* proof of concept study by the end of 2021. MOA studies for these compound series are ongoing in collaboration with partners from WP1 and WP2. So far, compounds from both series are inactive in polymerase, mPro, Nsp14n, Plpro and cathepsins/TMPRSS2 related biochemical assays. Resistance studies are ongoing to try to deconvolute the target. KULeuven stopped chemistry around one chemical series. This particular compound series had a very narrow SAR and demonstrated high cytotoxicity in cellular assays. This compounds series is considered as a finalized data package. The data will therefore be summarized in a scientific paper (in preparation) and made available to the scientific community.

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. Hit compounds identified by a phenotypic screen of **BI (P26)** could unfortunately not be confirmed after a range of target and cell based assays performed by WP1 and WP2. However, confirmation studies on hit compounds identified by **Servier (P37)** delivered a potential starting point for chemistry which will be taken up in the program of KULeuven in the coming months once the bilateral agreement is in place.

Additional phenotypic screens are planned/ongoing by **Janssen (P2), KULeuven (P11)** and potentially **Pfizer (P32)**

3. Target driven approaches Hit to lead - hit ID

3.1 Hit to lead

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 **Takeda (P3)** focusses on Nsp14 and PLpro. Unfortunately, the efforts on PLpro have encountered some delay due to issues with the initial screening assay. Therefore the validation of identified hits was on hold. However, an alternative assay is now validated and hit validation of compounds identified in a first HTS (MALDI-TOF based assay) and a large set of analogs are under evaluation. A new screen of 120K compounds is ongoing. In addition, plate based chemistry around a compound identified in literature GRL-0617 has been initiated. Full hit to lead chemistry programs around PLpro are expected by end 2021. For Nsp14 an active chemistry program is ongoing for lead series C. Chemistry focuses on increasing target and cell based potency as well as ADME/PK properties. An additional backup series potentially acting via a covalent mechanism is under evaluation. Furthermore, a methyl transferase focused compound library (~7K compound) provided by Takeda has been screened. Follow up studies are ongoing aiming to identify additional hit matter for chemistry. Crystallography efforts are ongoing to help drive the chemistry forward.

The second team (**Lead Nuvisan (P14),** supported by **Takeda (P3), Merck (P33), GHDDI (P30))** was dedicated to all efforts around the mPro. So far chemistry was focused on one lead series (peptidomimetic) which was mainly being designed by Exscientia. In vitro DMPK profiling was initiated. Exscientia will work on this compound series outside of the CARE consortium. **Bayer (P25**) performed an HTS on mPro. Preliminary data indicate that potential starting points for chemistry have been identified and that these starting points demonstrate good activity in cells. Bayer has decided to work on these identified hit series internally outside of CARE. Therefore, the second chemistry team needs to refocus their efforts to a different target/compound series.

3.2 Hit ID

The identification of potential new starting points is still ongoing. WP3 supports the identification of potential starting points through target based approaches and coordinates the collection of potential starting points from WP1 and WP2 but also outside the CARE consortium. WP3 hopes to finalize the inclusion of new hit matter by end 2021 unless highly attractive series, with improved properties compared to ongoing programs in WP3, are presented to the consortium. This will be discussed in the JSG meetings scheduled every 3 months.

Takeda (P3) performed a virtual screen on mPro. Unfortunately no attractive starting points could be identified. In addition, Takeda is performing virtual screening efforts around helicase and polymerase. Promising starting points from efforts will be reviewed and potentially proposed to WP3 unless they will be developed in consortia out of CARE. However, Takeda will assist WP3 by providing technical and resource support for the other targets if necessary. **Merck (P33)** has performed a virtual screen around mPro. Actives have been selected and evaluated. Unfortunately no hits could be confirmed. **Bayer (P25)** performed a HTS on Spike/ACE2. New identified hits are under discussion in WP3.

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. **University Aix Marseille (P16)** has screened for inhibitors of the polymerase as well and has identified hit compounds. Potential starting points 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 EXSCI'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. Recently an amendment has been added to the TPP to allow progression of potent compound series which are only active on SARS-CoV-2 and variants of concern. Broad spectrum anti-coronavirus activity is still preferred. 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 installed. The hit-to-lead process for mPro was supported by AI optimisation methods. Target product profiles for prophylactic and therapeutic treatment have been finalised.

Hit to lead programs are ongoing for Nsp14 and on 3 compound series identified in a phenotypic screen. The aim of WP3 is to perform *in vivo* proof of concept studies with 2-4 compound series in Q1 of 2022. Chemistry programs for Plpro, polymerase and phenotypic series should be ongoing by December 2021. Potential additional starting points from ongoing hit ID efforts will be reviewed and included in the hit to lead campaigns after careful review.