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CARE
Corona Accelerated R&D in Europe

WP3 – WP Hits to leads

D3.09 Portfolio report

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Document History

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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. A screening cascade for (phenotypic) hit ID has been implemented and executed. In addition, a coordinated AI-platform and analysis of targets for their druggability is being finalized to facilitate the selection of potential starting points for chemistry. The medicinal chemistry efforts have not yet been initiated as the review and selection of potential starting points from the first wave of hit identification is still ongoing.
In addition to the Hit selection criteria to move forward into Hit to Lead (H2L), WP3 contributors have already prepared for the next steps by defining the initial progression criteria for hits, leads and optimized lead compounds. In addition, a screening cascade for H2L and lead optimization (LO) is proposed, including the flow for the ADMET-PK related assays. The aim is to work towards the predefined target product profiles (TPPs) which have also been discussed within WP3 and are close to finalisation.

Results

1. Screening cascade for hit ID and hit selection criteria

The progression criteria for hit compounds identified via a phenotypic screen (WP1) or target based approach (WP2) to be considered in WP3 for hit-to-lead have been defined taking into account the input from all WP3 parties. Based on various properties including in vitro efficacy, biochemical activity, chemical properties, in vitro toxicity, and chemistry, the potential starting points will be prioritised. A streamlined and efficient drug discovery testing cascade that supports rapid profiling and triaging hits from WP1 and 2 has been established. The Hit ID testing cascade requires open communication and close collaboration with WP1 and WP2 as WP3 relies on WP1 and WP2 activities and resources to generate in vitro and biochemical data in order to be able to (de)select potential starting points for chemistry and guide the chemistry teams to select/optimize the Hits for H2L.

2. Phenotypic hit ID

WP3 has been involved in the follow-up of several screening efforts to identify hit compounds with activity against SARS-Cov-2. Janssen (P2) is performing the follow-up of the screening of ~162 000 compounds in WP1 while CD3 (KULeuven – P11) supports the screen of ~240.000 compounds at KULeuven. This support consists of compound management, compound delivery and analogue selection of initial hits.

Unfortunately the hit rate of the library screen performed in WP1 (Vero-E6 based assay) was up to now very low, even with a low selection threshold of ~20% inhibition. From the phenotypic screen, CD3 (KULeuven – P11) has prioritised 9 hits for dose response confirmation and further characterization. This will be followed up by chemical validation and testing the activity of compounds on other viruses. Screening of the Janssen (P2) library is still ongoing, however, first data sets are being analysed. This will be followed up by hit expansion through development of analogues, identification of potential starting points and broad spectrum testing.

The first 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.

3. Alternative approaches towards identification of hits

WP3 is also involved in the support for the identification of potential starting points through target-based approaches.

Takeda (P3) is performing virtual screening efforts around a number of targets. First screening rounds on the mPro, Methyltransferase (Nsp14&16) and PLpro are finalized and first potential starting points from these activities will be reviewed. Activities around the Helicase are still ongoing.

The University of Dundee (P27, UNIVDUN) is working on mPpro and PLPro together with Exscientia (P7, EXSCI) and synthesis of the first compounds is ongoing. A screen on the methyltransferase (Nsp14) and PLpro is completed and potential hits are currently being evaluated in collaboration with Takeda (P3).

Exscientia (P7) has identified potential starting points for mPro and PLpro based on their AI technology. For the mPro, 2 Hits from the Reframe have been identified as starting points. EXSCI has also defined several other de novo starting points for MPro, which are being investigated in a range of assays by UNIVDUN. One hit from the Reframe library has been identified as potential compound for repurposing for PLpro. Other de novo design activities for the PLpro could be initiated based on the amount and quality of potential starting points.

Ai-biopharma (P35) is putting his efforts in targeting the Polymerase. They have at least one potential starting point for chemistry.

Merck (P33) is performing several virtual screens around mPro, Polymerase and Spike. Compounds from these virtual screens have been selected and are currently being tested in WP2.

Janssen (P2) is performing a virtual screen on the Polymerase.

AiCuris (P36) is performing a virtual screen on the viral nsp3 macrodomain.

Furthermore, WP3 is also coordinating the collection of potential starting points from WP1 and WP2.The first collection and review of potential starting points from WP1 and WP2 is currently ongoing. During a Joint Steering Committee planned in October, it is anticipated that the first starting points with most potential will be prioritized and selected to enter the hit-to-lead trajectory. Later in the project, new selection rounds (JAN-APR 2021) are planned to allow the inclusion of other potential starting points and compound series from other hit identification approaches.

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. Currently there is insufficient information on where and when the resources will be available within the consortium to complete this task. EXSCI will work with CARE partners, including Scifeon, to establish a good picture of programme resources, so that this deliverable can be achieved.

5. Analysis of targets for druggability

EXSCI has completed the work on this deliverable, which is currently being written up as a report by 12th October. The report will rank SARS-CoV2 targets according to their druggability, and provide 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.

6. Progression criteria and TPPs

The progression criteria for lead compounds to enter into lead optimization have been proposed. Besides increased in vitro efficacy and biochemical activity, the DMPK properties and finally in vivo efficacy will be crucial for this lead optimization campaign. Finally, general criteria for an optimized lead/candidate have also been discussed. An additional general drug discovery testing cascade for hit-to-lead and lead optimization has been

put forward. 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 proposes 2 target product profiles, one for prophylactic treatment and one for therapeutic treatment. Although a number of properties still need to be investigated, the overall view of the TPP for WP3 is clear.

Discussion/Conclusion

WP3 has established progression criteria for hits, leads and optimized leads/candidates. A streamlined and efficient drug discovery testing cascade for HitID and hit-to-lead/lead optimization is in place. The selection and prioritization of starting points and hit compounds is supported by validated AI optimisation methods.

The prioritization and selection of potential starting points from the first wave of Hit ID derived from WP1 and WP2 is currently still in progress. The Hit ID campaign is currently ongoing. A large set of potential hit matter from partners of the consortium has already been screened, however, there is still a large set that will be tested in the coming months. As there were limited potential starting points available, WP3 could not initiate the full blown planned H2L campaign at this stage. However, we are aiming to have selected the first set of potential starting points to initiate the chemistry programs by the end of October.