**Supplementary Information**

**NOD: A web server to predict New use of Old Drugs to facilitate drug repurposing**

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**Results**

**Table S3: Details of browser compatibility test**

|  |  |  |  |
| --- | --- | --- | --- |
| **S. No.** | **Desktop operating system** | **Internet browser** | **Are all the features of NOD accessible?** |
| 1 | Windows 10 | Google chrome ver. 86.0.x.x | Yes |
| 2 | Windows 10 | Microsoft edge ver. 86.0.x.x | Yes |
| 3 | Windows 10 | Firefox ver. 83.0.x | Yes |
| 4 | Windows 10 | Opera ver. 66 | Yes |
| 5 | Macintosh | Safari ver. 13.1 | Yes |
| 6 | Macintosh | Firefox ver. 82.0.x | Yes |
| 7 | Ubuntu 16.04 | Firefox ver. 82.0.x | Yes |
| 8 | Ubuntu 16.04 | Google chrome ver. 74.0.x | Yes |

**Case study**

A case study with SARS-CoV-2 proteins:

**MODE-1:** The protein sequences of SARS-CoV-2 (the causative agent for Covid-19)corresponding to the reviewed entries in UniProt1 were retrieved and submitted to NOD. 16 SARS-CoV-2 protein sequences had ‘reviewed’ status in the UniProt at the time of conducting this study. These 16 sequences include the proteins like replicase polyprotein 1ab, spike glycoprotein, M protein, nucleoprotein etc. (for details, see Table S4). Such an all-inclusive approach where multiple (or even all) proteins of a pathogen are queried, minimizes the chances of missing any interesting candidate compound that might have the potential to be repurposed against any protein target implicated in the disease of interest. NOD could find reliable homologs for 2 out of the 16 queried SARS-CoV-2 proteins from the DrugBank target sequence database. Subsequently, 20 unique query-target-compound (QTC) associations were generated by NOD, and the entire job was completed in just 285.89 seconds. Fig. S1 shows a step-by-step flow of events on NOD web-interface upon submission of a job under MODE-1 operation. As could be seen in the fifth step of Fig. S1, NOD identified known antiviral agents like remdesivir and GS-441524, which are reported to be effective against coronavirus infections2,3. These compounds are potential candidates that may be probed for repurposing against replicase polyprotein 1a (UniProt accession code: P0DTC1) of SARS-CoV-2 based on its detected homology with replicase polyprotein 1ab (UniProt accession code: P0C6X7) of SARS-CoV. The alignment between the two protein sequences (query and target) spans over almost the entire length (99.9%) of the query protein, ensuring the similarity of the ligand-binding sites between the two proteins. Excitingly, reports from various research groups, including ours, have discussed the potential of remdesivir in treating SARS-CoV-2 infection2,4, and it is currently being probed under various clinical trials to explore it's usage in anti-Covid19 therapy and has also been approved for emergency usage in many countries. The details on clinical trials of remdesivir could be found at [https://www.clinicaltrials.gov/ct2/results?recrs=&cond=&term=remdesivir&cntry=&state=&city=&dist=](https://www.clinicaltrials.gov/ct2/results?recrs=&cond=&term=remdesivir&cntry=&state=#&city=&dist=).

**Fig. S1: A step-by-step flow of events under MODE-1 operation of NOD depicted with screen shots from the example case study on SARS-CoV-2 proteins.** (1) Jobs can be submitted to NOD by hitting the ‘SUBMIT’ button (indicated by a black arrow) after filling up the details in the desired mode available under ‘Run-Options’ page. The details required are: (a) Job Title, (b) E-mail address (where the link to the downloadable result table obtained as output from NOD will be sent), (c) A file containing the protein sequences in ‘.FASTA’ format needs to be uploaded, (d) Adjusting the Query coverage cut-off (if required), and (e) Declaration that the submitted sequences conform to ‘.FASTA’ format (which is the NOD-friendly format). (2) Upon successful job submission, a window opens which informs the user that the responses from NOD will be notified to the provided e-mail address. New jobs can be submitted by clicking on the ‘START OVER’ button (indicated in black arrow) which would take the user to the ‘Run-Options’ page. (3) Once the job is completed, an automated e-mail is sent by the NOD server to the user supplied e-mail ID with a link (indicated with black arrow) to view the responses from NOD. (4) On clicking the link, a HTML file with tabulated data is displayed on the NOD interface. Description on the type of data compiled in each column is provided at the top of the table (highlighted with a red box). The table can be downloaded as a tab-separated file by clicking on the ‘Download Table’ button (indicated with a black arrow). The download-able table contains additional information derived from the DrugBank database (for example, name of the target protein, SMILES code of the shortlisted compounds, etc.). The result tables are automatically deleted from the NOD server after 10 days. (5) A snapshot of the results from the output table has been shown here. The UniProt accession code of the target homologue protein and the DrugBank ID of the candidate molecule are provided as clickable links (highlighted with red box) which can direct the user to the respective databases for more details.

**Table S4: List of SARS-CoV-2 protein sequences submitted to NOD under MODE-1 test operation**

|  |  |  |
| --- | --- | --- |
| **Sl. No.** | **UniProt Code** | **Name of the protein** |
| 1 | P0DTD1 | **Replicase polyprotein 1ab** |
| 2 | P0DTC2 | Spike glycoprotein |
| 3 | P0DTC1 | **Replicase polyprotein 1a** |
| 4 | P0DTC7 | **ORF7a protein** |
| 5 | P0DTC3 | **ORF3a protein** |
| 6 | P0DTC5 | **Membrane protein** |
| 7 | P0DTC9 | **Nucleoprotein** |
| 8 | P0DTD2 | **ORF9b protein** |
| 9 | P0DTC6 | **ORF6 protein** |
| 10 | P0DTC4 | **Envelope small membrane protein** |
| 11 | P0DTC8 | **ORF8 protein** |
| 12 | P0DTD8 | ORF7b protein |
| 13 | P0DTD3 | ORF9c protein |
| 14 | P0DTF1 | ORF3b protein |
| 15 | P0DTG0 | ORF3d protein |
| 16 | P0DTG1 | ORF3c protein |

**MODE-2:** The amino acid sequence of replicase polyprotein 1ab in SARS-CoV-2 (P0DTD1, https://www.uniprot.org/uniprot/P0DTD1) was used as input in MODE-2. The sequence of this protein encodes multiple proteins of the virus, including the proteases which are responsible for cleavage of the polyprotein to functional forms, thereby aiding in the process of viral transcription and replication. One of these proteases is the 3C-like protease, or the main protease, which plays a crucial role in the viral life-cycle and is an important drug target5. The homolog of SARS-CoV-2 replicase polyprotein 1ab as detected by NOD in the DrugBank database, is SARS-CoV replicase polyprotein 1ab with 99.9% alignment coverage for the query sequence.Recently we have reported potential candidates that can be probed for repurposing against the SARS-CoV-2 main protease primarily using computational structure-guided approaches4. Interestingly, some of our earlier reported candidates could also be found in the results generated by NOD that employs a sequence-guided approach followed by 2-D chemical similarity search under its MODE-2 operation. The notable hits are the vinca alkaloids (vinorelbine, vincristine, vindesine, etc.) and known antiviral agent, baloxavir marboxil (Fig.S2).



**Fig. S2: Snapshot of results from SARS-CoV-2 MODE-2 job.** The column highlighted within the red rectangle contains the secondary candidates obtained from similarity search. Several vinca alkaloids (like vinorelbine, vincristine, vindesine etc.) and known antiviral agent are reported by NOD as discussed in the text. Full result for this job could be viewed at http://pauling.mbu.iisc.ac.in/NOD/NOD/webpages/archives.html.

P.S. : Apart from the references cited in the text of the supplementary information, the list below also includes all the references cited in the supplementary tables S1 and S2 (.xlsx files).

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