Corynebacterium ulcerans interactome reveals hub proteins as potential drug targets

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Background

Corynebacterium ulcerans is a gram positive non-toxigenic bacteria capable of becoming toxigenic by producing a diphtheria toxin similar to *C. diphtheriae*'s. Among the bacteria that cause diphtheria in humans, *C. ulcerans* is considered to have the highest mutagenic potential for its wide range of reservoirs. Recently, cases of diphtheria caused by *C. ulcerans* were reported even in countries which had compulsory vaccination programs, so to prevent this infectious disease from re-emerging new approaches for the selection of novel drug targets are needed.

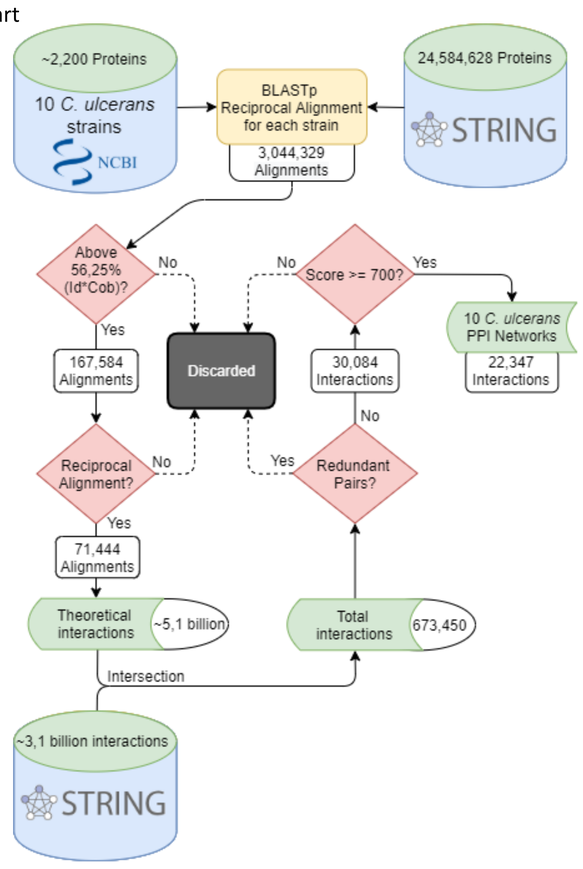
Aim

By making use of the largely deposited protein-protein interactions (PPI) data, we aimed to predict *C. ulcerans*'s PPI Network and identify proteins potentially essential for this organism's life, called hub proteins.

Methodology and Results

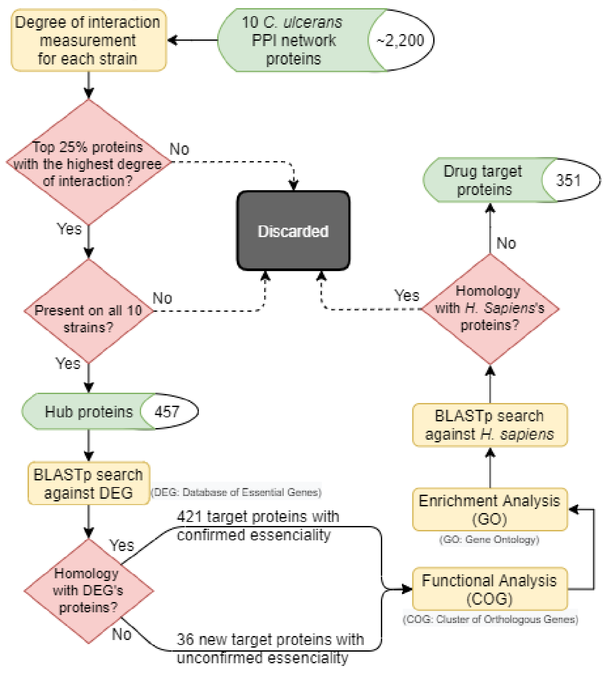
C. ulcerans's PPI Network prediction was based on the interolog mapping method (Fig 1).

Fig 1. *C. ulcerans*'s protein-protein interaction (PPI) network prediction flowchart



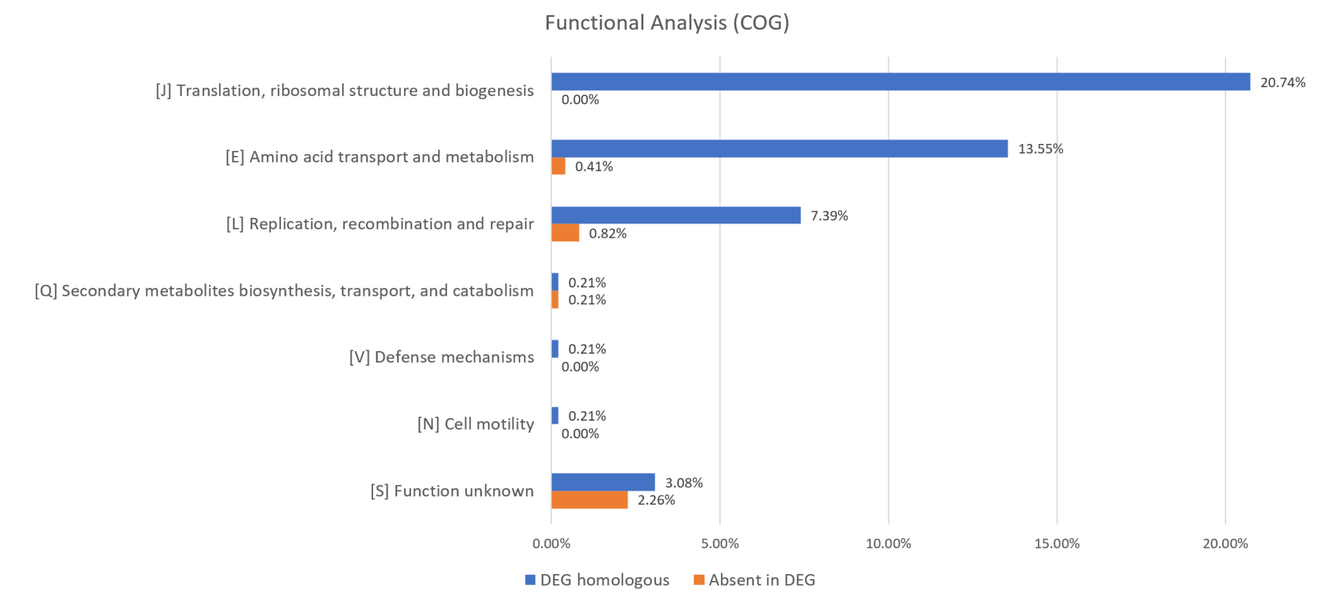
Following the PPI Network prediction was the identification and analysis of *C. ulcerans* hub proteins (Fig 2.)

Fig 2. *C. ulcerans*'s target proteins identification flowchart



Functional and Enrichment Analysis

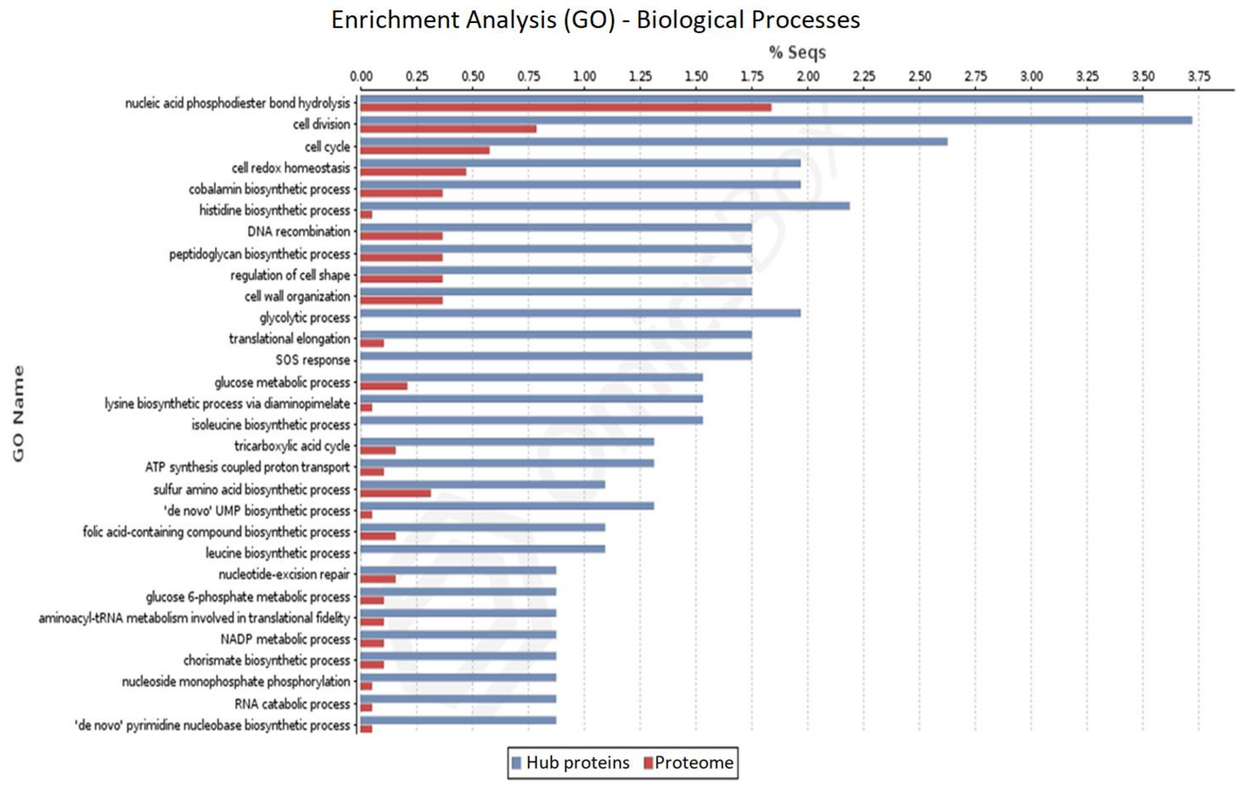
Just like shown in the Fig 2. all the 457 hub proteins went through a functional analysis based on the Cluster of Orthologous Groups (COG), classifying each protein in a specific category according to their function (Graph 1).



Graph 1. *C. ulcerans* hub proteins functional analysis based on the cluster of orthologous groups (COG). Represented in blue are the percentages of DEG homologous proteins classified in that category and in orange proteins absent in DEG.

The most significative categories in the functional analysis were: "J-Translation, ribosomal structure and biogenesis" (20.74%); "E-Amino acid transport and metabolism" (13.96%); and "L-Replication, recombination and repair" (8.21%), all critical for sustaining life.

Lastly, an enrichment analysis was also done to identify the most significant Gene Ontology (GO) terms ($p<0.05$) in the hub proteins when compared to all the *C. ulcerans* proteome. Represented in the (Graph 2) are the biological processes.



Graph 2. *C. ulcerans* hub proteins enrichment analysis of biological processes according to the terms of the Gene Ontology (GO).

Of all the biological processes the most significative categories ($p>0.95$) the "Cell redox homeostasis", "DNA recombination", "Cell wall organization" and "SOS response", corresponding to the essentiality of the hub proteins.

Final Considerations

- Adopting in our methodology an unusual 25% to select proteins with the highest degree of interaction was valid, since the majority of hub proteins aligned against DEG and those who didn't were considered important to *C. ulcerans* after having their functions annotated.
- All the 457 hub proteins identified and analyzed are in fact potentially essential to *C. ulcerans*, since they were categorized in important functional groups and biological processes, and that makes the 351 non-host homologous good drug targets.
- With the 351 (76.8%) non-host homologous *C. ulcerans* hub proteins we suggest their use to evaluate their affinity with different drugs, just as our group did with inedited synthetic derivatives of tetrahydroisoquinoline alkaloids in tests in silico.

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