A Translational Bioinformatics Workflow for Rapid Target Discovery and Therapeutic Recommendation in the Setting of Infectious Diseases

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Introduction: Accelerating the discovery of therapeutic interventions for rapidly emerging infectious diseases such as Lassa Fever (LF) and Nipah Virus infection (NiV) is pivotal in the event of an outbreak or public health crisis. These neglected diseases are associated with significantly high mortality rates, and the incentives for pharmaceutical companies to research them are limited. Therefore, novel approaches that can reduce the time from identified drug targets to a clinical candidate are imperative in an outbreak or endemic situations. In this study, we leverage biomedical data and tools to identify drug targets and putative host-pathogen interactions.

Methods: The workflow (Figure 1) involves five distinct modules i) Identification of druggable targets using genomic and proteomic evidence ii) Identification of putative host-pathogen interactions using domain-domain interaction evidence iii) Computational drug repositioning using RepurposeDB (http://repurposedb.dudleylab.org/) and chemogenomic enrichment analyses (CGEA) using host transcriptome data to match drug that can reverse the virus-induced gene signature in human peripheral blood mononuclear cells iv) Druggability and prioritization of proteins with interactant of viral proteins in human proteome v) Functional enrichment and biological interpretation of viral interacting proteins to understand molecular modules associated with host-pathogen interaction.

Results: We compiled a catalog of publicly available data via multiple open-access databases related to two infectious diseases and analyzed using a translational bioinformatics workflow. Using the approach, we identified drug targets and potential therapies using computational drug repositioning. Integrated analytics approach yielded prostaglandin E2 (Alprostadil), Nicardipine, Niclosamide, and Dinoprost Tromethamine, as candidate drugs for LF, while 2 FDA approved drugs, trihexyphenidyl and S-propranolol were identified as candidate drugs for NiV. Confirmatory studies, including adaptive trials and real-world evidences, are required to enable the clinical Drawing on public data sets, and computational methods for rapid drug target selection and therapeutic recommendation may help to reduce disease incidence in the event of an outbreak.

References: