Rapid Therapeutic Recommendations in the Context of a Global Public Health Crisis using Translational Bioinformatics Approaches: A proof-of-concept study using Nipah Virus Infection

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Abstract

We live in a world of emerging new diseases and old diseases resurging in more aggressive forms. Drug development by pharmaceutical companies is a market-driven and costly endeavor, and thus it is often a challenge when drugs are needed for diseases endemic only to certain regions or which affect only a few patients. However, biomedical open data is accessible and reusable for reanalysis and generation of a new hypotheses and discovery. In this study, we leverage biomedical data and tools to analyze available data on Nipah Virus (NiV) infection. NiV infection is an emerging zoonosis that is transmissible to humans and is associated with high mortality rates. In this study, explored the application of computational drug repositioning and chemogenomic enrichment analyses using host transcriptome data to match drugs that could reverse the virus-induced gene signature. We performed analyses using two gene signatures: i) A previously published gene signature (n=34), and ii) a gene signature generated using the characteristic direction method (n= 5,533). Our predictive framework suggests that several drugs including FDA approved therapies like beclometasone, trihexyphenidyl, S-propranolol etc. could modulate the NiV infection induced gene signatures in endothelial cells. A target specific analysis of CXCL10 also suggests the potential application of Eldelumab, an investigative therapy for Crohn's disease and ulcerative colitis, as a putative candidate for drug repositioning. To conclude, we also discuss challenges and opportunities in clinical trials (n-of-1 and adaptive trials) for repositioned drugs. Further follow-up studies including biochemical assays and clinical trials are required to identify effective therapies for clinical use. Our proof-of-concept study highlights that translational bioinformatics methods including gene expression analyses and computational drug repositioning could augment epidemiological investigations in the context of an emerging disease with no effective treatment.

Introduction:

Nipah Virus (NiV) is a member of *Paramyxoviridae* family of enveloped, Negative-sense single-stranded RNA viruses. NiV is a member of Henipavirus genus – other Henipaviruses include *Cedar henipavirus*, *Ghanaian bat henipavirus*, *Hendra henipavirus* and *Mojiang henipavirus* [1-9]. NiV infection is considered as an emerging infectious disease threat by the World Health Organization (WHO) (See: http, //www.who.int/csr/disease/nipah/en/) [10, 11]. NiV infection was first reported and the virus was isolated during an outbreak in Malaysia and Singapore in the late 1990s [12-14]. NiV infection reemerged in 2018 in Kozhikode, a coastal city in Kerala, India. The Kerala reemergence is associated with high mortality rate (above 80% of identified cases, personal communication) (See: http, //www.bbc.com/news/world-asia-india-44193145). At present there are no approved therapies or vaccines against NiV. In this study, we explore the application of translational bioinformatics databases, tools and methods like computational drug repositioning to predict potential FDA-approved, therapies using publicly available datasets. Follow-up studies, including experimental assays and clinical trials are required before using repositioned candidate drugs for clinical use.

Clinical manifestations of NiV infection:

NiV infection is characterized by a combination of neurological, respiratory and cardiovascular complications. These include but are not limited to: high fever, seizures, encephalitis, meningitis, tremor, ptosis, dysarthria, dysphasia, respiratory tract lesions, severe acute respiratory distress syndrome (ARDS), tachycardia, myocarditis, vomiting, hypertension, and segmental myoclonus along with or without other clinical features [15-

23]. The incubation period for the NiV infection is 4 to 14 days with a combination of clinical symptoms, although some infected patients may remain asymptomatic [24, 25].

Genome, proteome and host-virus interaction studies:

The genome sequence of the NiV was reported with 18246 nucleotides that encode viral proteins (See: http, //www.uniprot.org/uniprot/?query=proteome, UP000128950) including the nucleocapsid protein, phosphoprotein, matrix protein, fusion protein, glycoprotein and RNA polymerase [26]. Mechanistic studies suggest several viral proteins function to target host proteins, for example phosphoproteins P/V/W/C interact and inactivate the transcription factor *STAT1* by inhibiting interferon-induced tyrosine phosphorylation [27-35]. Functional genomics studies have shown that micoRNAs like mir-181 could also play a key role in the NiV infection. Mir-181 is a key modulator of human immune function and neuroinfllammation and may play role in neurovirulence of NiV including blood-brain barrier disruption [36-40]. NiV M proteins also target *ANP32B*, an anti-apoptotic, phosphoprotein [41]. *APAF1* an apoptosis regulator has also shown role in the pathogenicity of NiV [42]. Functional receptors of NiV include tyrosine kinases like Ephrin-B2 and ephrin-B3 [43, 44]. Several comparative genome analyses are also reported for the viral genome and zoonotic reservoirs like bats [45-52].

Candidate therapies and vaccines targeting NiV:

Several antibody, drug and vaccine discovery efforts to target NiV infection are in progress for NiV [53-57]. Multiple vaccine development projects against NiV based on viral epitopes and host-virus interaction mechanisms are currently available for livestock animals [32,

58-98]. Notably, vaccine candidates like human monoclonal antibody m102.4 has found to be effective in pre-clinical studies [71]. Pre-clinical immunotherapy studies demonstrate that monoclonal antibodies might be beneficial (anti-G and anti-F MAbs) as agents against NiV infection. Small molecules that activate *IRF3* and modulate *RIG-I*-like receptors pathways [56] were also investigated as potential strategies to target NiV infection [54]. Drugs like ribavirin (a broad spectrum antiviral effective against both RNA and DNA viruses) have been shown to be associated with lower mortality rates, but lack conclusive evidence from randomized controlled clinical trials [53, 99-103]. Evidence from a recent studies suggests that Favipiravir (T-705), an investigational treatment for influenza may prevent NiV infection in a hamster model [104]. Efforts are also underway to develop nucleic acids therapeutics against NiV infection [105]. Most of these therapies need full cycles of clinical trials or additional evidences including comparative effectiveness to understand optimal contributions to outcomes [53].

Drug repositioning – systematic search for compounds to combat NiV infection:

Drug repositioning (or drug repurposing; See **Figure 1**) is a drug development strategy designed to reduce the time to develop and market a drug for diseases with no approved drugs or diseases that may need better therapy [106, 107]. Rare, orphan, endemic or neglected diseases may not be ideal areas of research and development for pharmaceutical companies. However, drug repositioning offers an alternate path in such settings. For example, National Institute of Health's – National Center for Advancing Translational Sciences recommends that 7,000 rare and neglected diseases that currently lack effective treatments could benefit from drug repositioning compared to traditional drug discovery

that costs billions of dollars and may take more than a decade to deliver a drug to the market. Multiple reports on computational, pre-clinical, off-validation, and other mode-of-success for drug repositioning are available in biomedical literature. But there was no comprehensive, integrative analysis of reported repositioned drugs, their indications, repositioned drug targets, or chemical properties of repositioned drugs. Recently, we compiled drug repositioning investigations from literature and other public data repositories and developed, the first comprehensive resource of drug repurposing (See RepurposeDB: A reference database of drug repositioning investigations - http, //repurposedb.dudleylab.org/). By integrating large-scale data on drugs, indication, side effects, and mechanism of actions, the computational drug repositioning process can be automated. Predictive data can be used for prioritizing candidate drugs for downstream studies including biochemical validation and clinical trials. Thus, computational drug repositioning offers a predictive framework for accelerated therapeutic recommendation in scenarios that requires immediate therapeutic stratification [106-114].

Rationale for Computational Drug Repositioning to identify therapeutic indications for NiV infection:

In the absence of an effective antiviral agent or prophylactic vaccine for NiV in human, it is imperative to develop better therapeutic agents to address such infectious disease threats. However, pharmaceutical companies have limited commercial prospects in developing drugs for rare, orphan, or neglected infectious diseases endemic diseases (**Figure 2)**. Data-driven methods that combine computational and experimental approaches could complement, improve or reduce the cost of drug discovery. For example, during the first

decade (1998-2008) of the NiV cases reported since its identification, the disease has an average case fatality rate of 52% over a total of 477 positively identified cases (using RT-PCR assays). (See: http, //www.who.int/blueprint/priority-diseases/key-action/nipah/en/). In this context, leveraging drug repositioning may be beneficial. Drug repositioning could bring therapies to market in approximately half the budget and time required by traditional drug development cycle. Conducting drug repositioning analyses using publicly available translational bioinformatics tools, databases and methods may aid in such discovery to address public health crises and accelerate the path to discovery of new therapies. The American Medical Informatics Association defines "Translational Bioinformatics" as "the development of storage, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data, and genomic data, into proactive, predictive, preventive, and participatory health"[115, 116]. In this study we show the application of a translational bioinformatics approach "computational drug repositioning" to find potential therapies to target NiV using publicly available datasets and tools. Therapeutic options to target this epidemiological threat is limited and drug repositioning will be a viable therapeutic identification strategy. However, since late '90s biomedical researchers have generated and deposited a variety of biomolecular data related to NiV in publicly accessible biomolecular databases.

Methods:

Figure 3 illustrates the methodology workflow used in the present study. Methods include the following components: Aggregating NiV infection gene signature data for drug

repositioning and Computational drug repositioning using NiV gene signatures followed by filtering and interpretation.

Aggregating NiV infection gene signature data for drug repositioning:

A critical requirement of computational drug repositioning is the availability of gene expression datasets related to the disease of interest. We queried the Gene Expression Omnibus (GEO) [117] to collect NiV related gene expression data. We used published gene signature and used the published signature and a computed signature from the raw data (GEO accession code GSE33133). The samples were originally hybridized and analyzed using Codelink Uniset Human Whole Genome bioarrays and differential expression was originally computed using the Gene Spring v7.0 suite from Agilent [118]. After obtaining gene expression signatures differing between NiV-infected and control cells, we used Chemogenomic enrichment analyses (CGEA) method and evaluated drugs reported to reverse expression differences between NiV and control cells at an FDR-significance level of 0.10. We tested the gene signature against the signature of 1309 compounds, 743 of which have approval status in one or more global pharmaceutical markets as indicated in DrugBank See: https, //www.drugbank.ca/drugs).

Computational drug repositioning using NiV gene signatures:

To leverage CGEA method, we first used the signature induced by NiV on endothelial cell lines, in the form of "upregulated" and "downregulated" gene identifiers. The input query of gene lists is matched to compounds, and the "connectivity" between the gene signature and compound is scored after various filtering steps against the available drug-induced

signatures compiled from various reference databases. References resources like RepurposeDB (http, //repurposedb.dudleylab.org/), Connectivity Map (Cmap: https, //portals.broadinstitute.org/cmap/), Genomics of Drug Sensitivity in Cancer (GDSC: http, //www.cancerrxgene.org/) or Cancer Cell Line Encyclopedia (CCLE: https, //portals.broadinstitute.org/ccle) are used to identify compounds that concordantly modulate the query signature in a direction "towards" or "away" from the input query. A Gaussian mixture model is used to derive the "connectivity score," and statistical significance is estimated using the Kolmogorov-Smirnov test with the Benjamini-Hochberg method for control of false discovery rate. CGEA produces an output of a ranked list of candidate compounds that may potentially modulate a biological state of interest. Depending on the query signature and reference databases, many candidate compounds will often be extracted – such lists can be trimmed and prioritized for most likely candidates using annotations from reference databases (for example RepurposeDB, KEGG drugs, DrugBank, etc.) and also using specific characteristics including mechanism of action, side effects, chemical properties or biological targets. Detailed account of related methods to match gene signature to corresponding drugs are explained elsewhere [111, 112, 114].

Results:

Compiling data sets for computational drug repositioning:

Gene expression data was compiled from GEO (Samples retrieved on 20th May 2018 https, //www.ncbi.nlm.nih.gov/gds/?term=nipah%20virus). The data represents total of six

samples (2 NiV infected (isolate UMMC1, Genebank AY029767) HUVEC cell lines with multiplicity of infection; 2 cell lines infected with recombinant viruses lacking the expression of accessory NiV C protein (NiVΔC) and 2 mock-infected HUVEC cells. Pathology studies indicate that the endothelium of central nervous system was susceptible to NiV infection and may thus represent a representative model system to study NiV infection using molecular level data [119].

i) *Published gene signature:* Published gene signature consists of 34 genes (upregulated genes: *n*=31; downregulated genes: *n*=3).

ii) *Characteristic direction-based gene signature:* Upregulated genes: *n*=2664; Downregulated genes: *n*=2869.

Eight upregulated genes were shared across both signatures (*IFIT1, IFI44L, OASL, CXCL10, IFIT2, OAS2, OAS1, IFI44*) and one gene was common across down regulated genes (*TAF4B*). Both gene lists were used independently to perform drug matching using CGEA approach using a library of drugs were annotated in conjunction with RepurposeDB. In the interpretation step, we primarily focus on the approved subset of compounds to extent the feasibility of launching immediate clinical trials. Briefly the gene set-drug matching data was compiled and annotated using data from the Connectivity Map, Anatomical Therapeutic Chemical (ATC) Classification System, PubChem, SIDER, Offsides and Drug Bank. Results compiled from CGEA consist of compound information including chemoinformatics signatures, drug target information, indications, mechanism of action and side effects.

Computational Drug Repositioning using Gene Expression Signature Identifies Potential, FDA approved Therapies for Nipah Virus:

Following sections summarize a subset of compounds predicted using computational drug repositioning. These drugs are not ready for clinical use and need extensive testing and clinical trials before use at the point of care.

Published gene signature:

Seven compounds have shown to optimally perturb the published gene signature (trihexyphenidyl, 5186223, convolamine, 5186324, tiletamine, S-propranolol). Two of these drugs are FDA approved for different indications, trihexyphenidyl (Score= -0.47, *P*= 0.0006; parkinsonian disorders, drug-induced extrapyramidal movement disorders and antispasmodic drugs. See: https, //www.drugbank.ca/drugs/DB00376); S-propranolol (Score= -0.44, *P*= 0.002) indications in acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety; See: https, //www.drugbank.ca/drugs/DB00571). **Table 1** lists drugs capable of perturbing published gene signature with FDR <=0.10 (See: Supplementary Material for full list of compounds and annotations).

Characteristic direction-based gene signature:

Nine compounds have shown to optimally perturb Characteristic direction-based gene signature (5666823, 2-deoxy-D-glucose, oligomycin, pirinixic acid, clofilium tosylate, cantharidin, 0173570-0000 and beclometasone). Among these compounds, beclometasone

(Score= -0.05, *P*= 0.001; See: https, //www.drugbank.ca/drugs/DB00394) is an approved, anti-inflammatory small molecule with indications for asthma and allergic rhinitis (seasonal and perennial). It is currently an investigational compound for indications including Crohn's disease and graft-versus-host disease. Table 2 lists drugs capable of perturbing characteristic direction gene signature with FDR <=0.10 (Also See Supplementary Material for full list of compounds and annotations).

Antiviral candidate drugs from repositioning:

Seven antiviral agents were available in our dataset. The following is the most effective to least effective order in published gene signature (ribavirin, vidarabine, moroxydine, zidovudine, saquinavir, zalcitabine, ganciclovir). While several of them had scores indicating activity but were not significant after FDR corrections. Ribavirin had the lowest score indicating most potent activity. Following was the order of activity in characteristic direction based gene signature: saquinavir, ganciclovir, moroxydine, vidarabine, zalcitabine, zidovudine, ribavirin. Ribavirin was the least effective – this is an example how the genes themselves, number of genes, and signature directionality of genes could influence the ranking of compounds. We also noted that moroxydine had optimal direction of score in both gene sets but were not statistically significant. Moroxydine is an antiviral agent structurally similar to ribavirin [120]. Conserved structural moieties often indicate similar chemical activities. Additional studies are required to elucidate the role of moroxydine as an anti-NiV agent.

Targeting CXCL10 – a hallmark of NiV infection in humans:

C-X-C motif chemokine (with synonyms C7; IFI10; INP10; IP-10; crg-2; mob-1; SCYB10; gIP-10) is an antimicrobial gene that encodes a chemokine of the CXC subfamily and ligand for the receptor CXCR3. CXCL10 was a gene expressed across both signatures (**Figure 4(a)**) and has a broad expression across 14 different tissue types including appendix and lymph node [121]. CXCL10 is involved in multiple inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis) that affect different systems of human physiology (See: https://www.ncbi.nlm.nih.gov/gene?db=gene&report=generif&term=3627) [121, 122]. CXCL10 also plays a key roles in several infectious diseases including chronic hepatitis B, tuberculosis etc. [122]. While no small molecules could target CXCL10, a fully human antibody (Eldelumab) that targets CXCL10 is reported. The molecule is currently under investigation for Ulcerative colitis [123, 124]. CXCL10 is a modulator of cytokine interaction networks and implicated in pathways including Chemokine Signalling pathway, TNF signalling pathway, Toll-like receptor signaling pathway, NOD-like receptor signalling pathway, NF-kappa B signalling pathway, RIG-I-like receptor signalling pathway. CXCL10 is also a member of disease pathways including rheumatoid arthritis, legionellosis, helicobacter pylori infection, salmonella infection, influenza A, and pertussis (**Figure 4(b)**).

Discussion:

Precision medicine aims to leverage molecular profiling data to recommend medications based on an individual patient's risk profile, existing medications, comorbidities, and non-clinical factors like diet and environmental exposure [125]. Precision medicine approaches that leverage mutation profiles to recommend therapies are emerging as a standard of care

in oncology and potentially expanding to other therapeutic domains including cardiology [126]. Our current study provides, a hypothesis generating, proof-of-concept study to leverage such molecular profile drug stratification approach as an aid to augment in the setting of a global public health crises, namely infectious diseases. Pharmaceutical companies have limited interest in budgeting drug discovery for niche markets and therapies with limited market value. Computational drug repositioning with modern clinical trial designs offer a comprehensive approach to address such challenges. In this work, we applied open access biomedical data, bioinformatics tools and methods to compile and interpret complex data to prioritize potential targets and recommend therapies for NiV, an emerging infectious disease. While we identified several indications, these drugs are not ready for immediate clinical use for NiV and need further experimental and clinical studies before use. In addition to pharmacological and biochemical annotations based filtering, the drugs can be filtered for approval status, availability, and cost as drug distribution varies across global markets. However, such filtering has not been considered in the study and drugs approved and available in the United States of America may or may not available with an approval in other countries or vice versa. In this study, we have only explored computational drug repositioning; other strategies including target-driven drug discovery is another strategy that may help to find a therapy for NiV infection. Several, well characterized host-pathogen interaction suggests targets including STAT1, Ephrins and ANP32B could be suitable for structure-based drug discovery and need further studies. Designing RNA interference molecules [105, 127] or peptide drugs to target these interactions may be useful to develop anti-NiV therapies [28, 32, 52, 78, 81, 82, 84, 89, 97, 128-168].

From data to drugs with clinical evidence: Adaptive and n-of-1 clinical trials in the context of repositioned drugs targeting NiV:

While several clinical trial design methods have been reported in the medical literature, randomized controlled trials (RCT) are considered to be the gold standard for gathering evidence for clinical use (See Kullo et.al and Jouni et.al; also see: https://clinicaltrials.gov/ct2/show/NCT01936675 for a clinical trial that assessed how genetic information might improve assessment of heart attack risk [169, 170]) . However, clinical trial designs are evolving. Several new clinical trial design methods have been introduced over the last few decades (adaptive trial and n-of-1 trial)[171, 172]. These trials were primarily designed to augment RCT methods to develop evidence for personalized clinical modalities and interventions in the setting of precision medicine.

An adaptive trial is a clinical trial to evaluate the efficacy of a medical device or intervention by observing patient outcomes within a pre-defined schedule; the trial could be "adapted" to the observations from the intermediate endpoints. For example, given three therapies (A, B, and C) and a placebo (P), an adaptive trial can be designed with two intermediate endpoints (EP_1 and EP_2) and the end stage of a phase III trial. Therapies that meet EP_1 (B and C) will proceed to EP_2. If only one therapy is effective at EP_2; only this therapy and placebo will proceed to the final phase of the trial. Adaptive trials are currently being evaluated as a trial design for various infectious diseases including HIV and Ebola [173-177].

The n-of-1 trial involves measuring a single patient repeatedly over time, while introducing different therapies (these could be multiple active therapies [178] or comparing therapy to placebo) [179]. In addition to individual-level analyses to understand therapeutic effectiveness for a particular patient, several N-of-1 trials can be statistically aggregated to understand differences in effectiveness across patients, or provide population-level estimates [180]. Despite their benefits and alignment with personalized medicine approaches, N-of-1s present challenges in the context of NiV infection. However, NiV infection is associated with high mortality rate and complex outcomes including myocarditis, neurological complications and ARDS. These symptoms often appear as a singular presentation, and present in patients in different combinations; this makes it difficult to capture end points in a continuous fashion. Delineating the clinical symptoms, as endpoints would be key to developing a trial design strategy. A trial design that can accommodate features like survival analyses with time-to-event, as an outcome should also be explored. Furthermore, the strongest form of *n*-of-1 trials not only requires a baseline phase (without treatment) and treatment phase (where you introduce the drug) but also requires treatment withdrawal and washout periods to observe the effect before reintroducing the treatment. If a positive effect of the drug is observed, withdrawal may not be possible on ethical grounds, and washout periods without any treatments may also harm patient safety. Given these scenarios, other forms of single-subject designs that do not require treatment withdrawal (such as multiple baseline designs, or a baseline phase (such as alternating treatment designs could be considered. To improve confidence in results from these trial designs, randomization could be incorporated [172, 181, 182]. To summarize, we do not endorse one method over the other but discussed various options of

clinical trial design which follow personalized medicine approaches, and should be explored for infectious disease and multiple therapeutic options in the context of drug repositioning candidates.

Limitations:

Our research study has several limitations. Our data is based on infection induced in HUVEC cells. HUVEC cells may reflect differential gene expression from an affected tissue in a disease of interest. In the absence of patient derived genomic or transcriptomic data sets, the drug lists are less reliable for human testing without any additional experimental evidences. We have very low sample size and the gene signature may fluctuate to a higher or lower number of genes based on the sample size, statistical tests, and multiple testing correction methods. The sample size does not meet the biological replication criteria of a minimum of three samples. Our drug repositioning algorithms are predictive in nature and do not endorse immediate clinical use without further pre-clinical and clinical studies. Off-label prescription and recommendations would need additional comparative effectiveness trials for these drugs. Also, as a research study, the list of drugs compiled in the results section needs further evaluation in preclinical validation models and needs to be tested in patient cohorts using different clinical trial modalities including comparative effectiveness trials. Various factors drive the success of statistical validity of the predictive frameworks including availability and quality of data, choice of analytical algorithm, orthogonal evidence, and statistical methods that accounts for a large number of data points. We restrict the results, interpretation and discussions on drugs that are in DrugBank; however, other compounds may have superior anti-NiV activity. These compounds would need

extensive, multi-year trials, and toxicity profiling before clinical testing and should not be used in clinical setting based on the predictive evidences.

Future work:

The gene signature used in this study is based on HUVEC cells, a cell line model for endothelial cells. This could be considered as a surrogate for infection as genes has been shown to express in a robust fashion across multiple tissues in the setting of human diseases. However, a cell line is identical as how infection express in the setting of the human body with multiple cell lines, tissues, organ systems. Also, the cell lines are a simplified representation of complex human disease physiology, where many patients could have several comorbidities and perturbed multiple factors including medications, environment, diet etc. These factors are not considered in the context of our study. Further, an ideal gene signature could be derived by comparing transcriptome extracted from whole blood of patients with NiV infection and age, gender-matched controls with no infection [183]. For example, we have performed similar analyses in diseases like peripheral arterial diseases and later used for drug repositioning investigations [106]. Further follow-up studies including biochemical testing and clinical trials such as adaptive and N-of-1 approaches are also needed.

Conclusions:

Drug repositioning could be a drug identification strategy in the absence of a ready to prescribe, FDA-approved therapies, in the context of an emerging virus with a high

mortality rate in a short turnaround time. In this proof of concept study, we explored the application of computational drug repositioning and chemogenomic enrichment analyses using host-virus transcriptome data. Specifically, we performed computational drug matching searches to find drugs that can reverse the virus induced gene signature on an endothelial cell line in the setting of NiV infection. Briefly, translational bioinformatics approaches with epidemiology efforts may help to accelerate the discovery of affordable therapeutic options for public health crises including emergence of infectious diseases.

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Conflicts of interest:

JTD has received consulting fees or honoraria from Janssen Pharmaceuticals, GlaxoSmithKline, AstraZeneca and Hoffman-La Roche. JTD is a scientific advisor to LAM Therapeutics and holds equity in NuMedii, Ayasdi and Ontomics. KS has received consulting fees or honoraria from Philips Healthcare, McKinsey & Company, Google, LEK Consulting, Kencore Health and Parthenon-EY. All other authors declare no competing interests.

Figures:

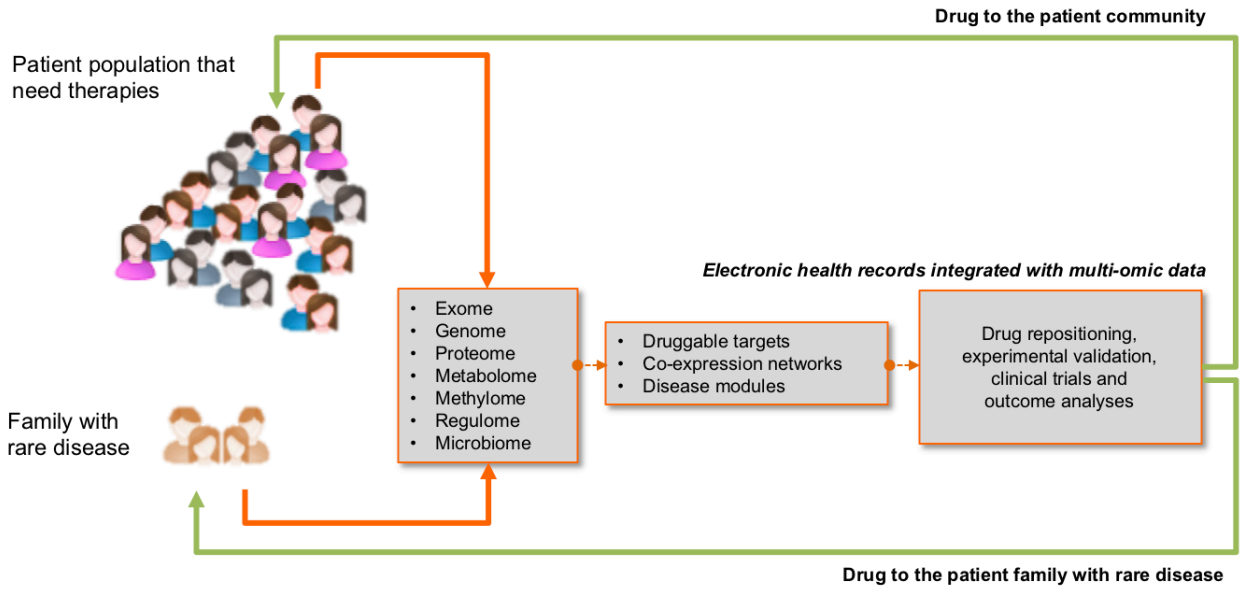

Figure 1: Concept of molecular-profiling based drug repositioning. Adaptation from an earlier version of a figure published in Shameer et.al, 2015 [107]

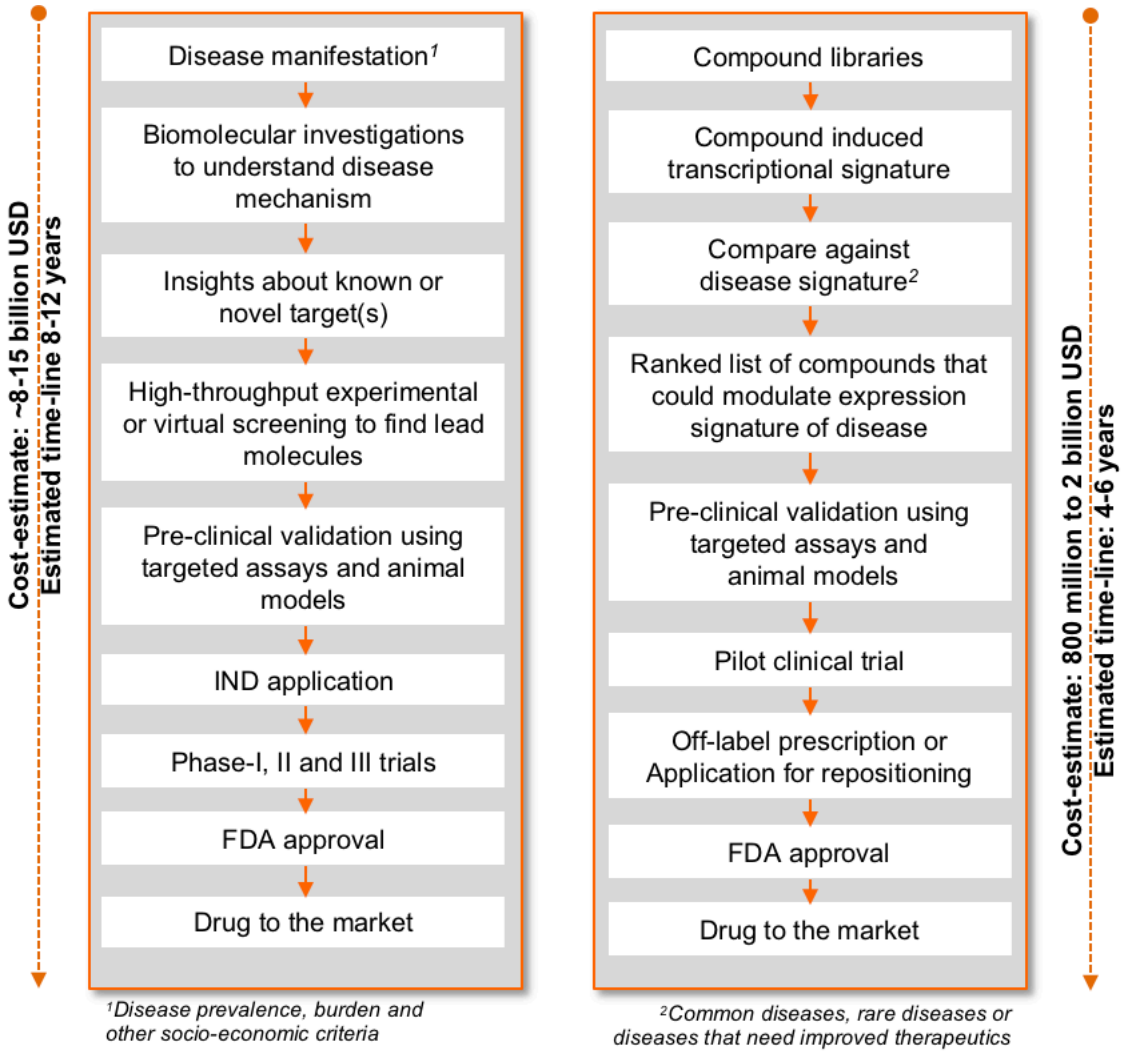

Figure 2: From medicine to markets: comparison of traditional drug discovery and drug repositioning. Steps in pipelines, cost-estimate and time-line from initial findings to the market from *Tobnick,* 2009 [184]. An earlier version of this figure was published in Shameer et.al, 2015 [107]

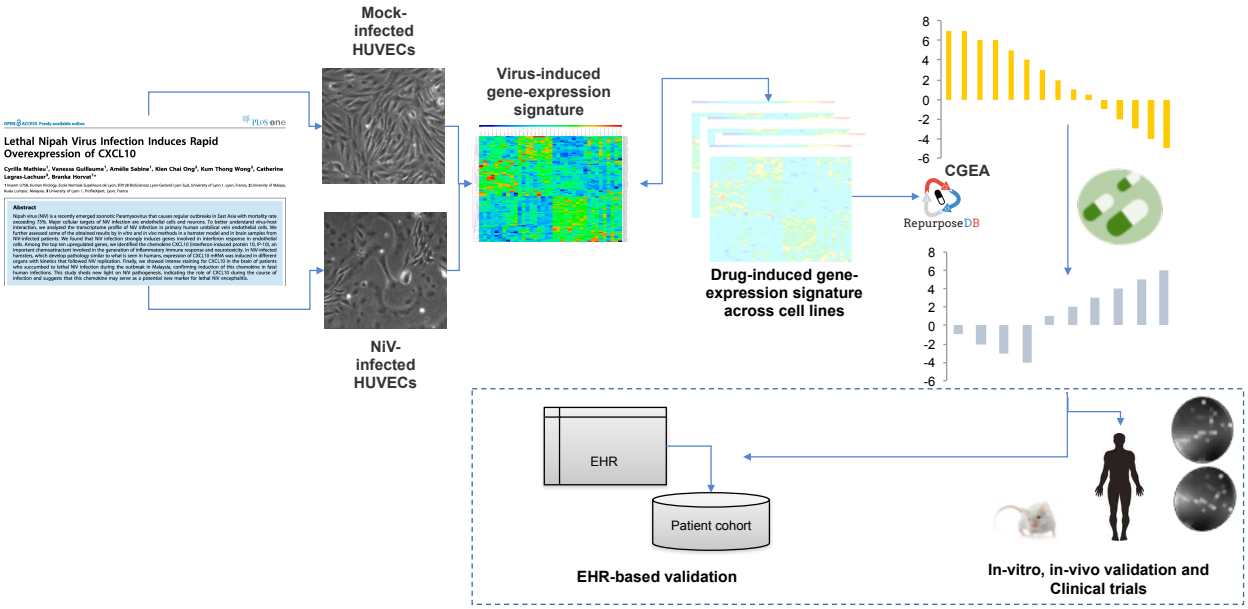

Figure 3: Computational drug repositioning workflow. Steps included in the dashed box illustrate potential future directions for the project.

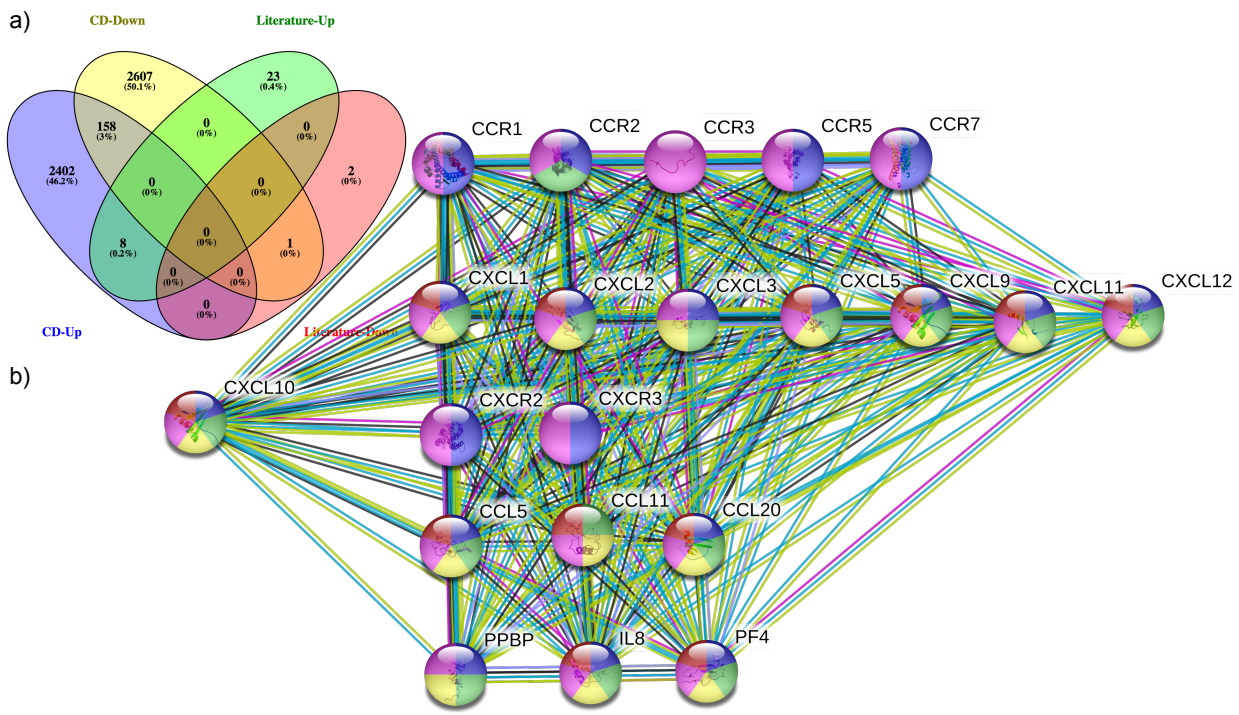

Figure 4: a) Overlap between signatures and direction of expression **b)** First degree interactome of CXCL10. Colors indicates various biochemical functional roles inferred from gene set enrichment analyses of interacting partners (PPI enrichment *P*=< 1.0e-16) of CXCL10 (blue: cell chemotaxis (biological process, *n*=19, FDR= 3.03e-35; green: chemokine receptor binding (molecular function, *n*=15, FDR=1.42e-32; yellow: extracellular space (cellular component, *n*=14; FDR= 6.4e-10); magenta: Cytokine-cytokine receptor interaction (KEGG pathways, *n*=21; FDR=9.72e-39); red: Small cytokines (intecrine/chemokine), interleukin-8 like (Pfam domains, *n*=12, FDR= 5.06e-29).

Table 1: Drugs predicted to perturb the published gene signature

Compound	DrugBank	Drug targets	*P-value*	ATC - Level 4 Description
trihexyphenidyl	DB00376	CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, LKHA4, NPSR1, ACHA7, NMDE2, CP1A2, ESR2	0.000691232	Tertiary amines
5186223	NA	NA	0.002052864	NA
convolamine	NA	NA	0.002079922	NA
5186324	NA	NA	0.002248003	NA
tiletamine	NA	NA	0.002337679	NA
S-propranolol	DB00571	NA	0.002620816	Beta blocking agents, non-selective
moxonidine	NA	ADA2B, ADA2A, ADA1B, ADA1D, ADA2C	0.002583078	Imidazoline receptor agonists
spironolactone	DB00421	NR3C2, AR, MCR, PRGR	0.002394345	Aldosterone antagonists
chrysin	NA	AHR, ESR2, CP1A2, PPBI	0.002348368	NA
piperlongumine	NA	NA	0.001862791	NA
trimetazidine	NA	NA	0.001819088	Other cardiac preparations
lymecycline	DB00256	rpsI, rpsD	0.001597275	Tetracyclines
bephenium hydroxynaphthoate	NA	LKHA4, ERR3, SCN2B, SCN4B, SCN3B, SCN1B, SCN4A, SCN7A, ESR2	0.001460509	Other antinematodals
testosterone	DB01420	AR, ESR2, ESR1, GPBAR, MCR, PRGR, ERR1, GBRB2	0.001143979	3-oxoandrosten (4) derivatives
clioquinol	DB04815	HS90A, HS90B	0.000991944	Quinoline derivatives
fluorocurarine	NA	NA	0.000973587	NA
acetylsalicylsalicylic acid	NA	NA	0.000710032	NA
selegiline	DB01037	MAOB, MAOA, TAAR1	0.000659896	Monoamine oxidase B inhibitors
hydrocortisone	DB00741	NR3C1, ANXA1	0.000490543	Corticosteroids for local oral treatment
triflusal	DB08814	PTGS1, NFKB1, NOS2, PDE10A, PPARD, PPARA, ADRB3, PPARG, ADRB1, PE2R4, PDK1, PDK3, PDK4, PDK2, GRIA2, LCK, RARB, LT4R2, RXRA	0.00047414	Platelet aggregation inhibitors excl. heparin
progesterone	DB00396	PGR, ESR1, NR3C2, CYP17A1, GBRB2, GBRG2, GBRA1, MCR, GPBAR, PRGR, ESR2	0.000431712	Pregnen (4) derivatives
estriol	DB04573	ESR1, ESR2, DHB1, STS, ERR1	0.000425278	Natural and semisynthetic estrogens, plain

norethisterone	DB00717	PGR, PRGR, GCR, DHB1, ESR2	0.00042434	Progestogens
fluvastatin	DB01095	HMGCR, PD2R2	0.000284433	HMG CoA reductase inhibitors
carbachol	DB00411	CHRM1, CHRM2, CHRNA2, ACM5	0.000243507	Choline esters
amoxicillin	DB01060	pbpA, ITA4	0.000234992	Penicillins with extended spectrum
aminophenazone	DB01424	FPR2, UBE2N	0.000219395	Pyrazolones
oxybutynin	DB01062	CHRM3, CHRM2, CHRM1, ACM4, ACM5, ACM2, NR1H2, ACM1, NR1H3, ACM3	0.000152607	Urinary antispasmodics
clorgiline	DB04017	MAOA, S1PR4, TTHY, PPARA, PD2R2	0.000147984	NA
sulconazole	NA	THAS, CP2CJ, HS90A, CP3A4, GRM6	0.00010348	Imidazole and triazole derivatives
DL-thiorphan	DB08626	MME, CSK, FPR1, ACE, C3AR, HXK4, FFAR1, PPARA, CP1A2, CAN1, PPARG, ITB7, PAR4, BRS3, TAAR1	4.23592E-05	NA
fluspirilene	DB04842	DRD2, HTR2A, CACNG1, SC6A9, SC6A5, OPRX, KCNH2, CCR5, CCR1, MDR1	1.95975E-05	Diphenylbutylpiperidine derivatives
benfluorex	NA	CCR2, CAC1B, ADRB3, MRGX2, ADRB2, PE2R4, GLR, ADRB1, PPARA, SCN1A, SCN3A, PPARD, FOLH1, CP2D6, MRGX1, CAN1, ITB7, IDE, TA2R, C5AR, SCN2A	1.65629E-05	Other blood glucose lowering drugs, excl. insulins
felodipine	DB01023	PDE1A, NR3C2, TNNC2, TNNC1, CACNA1C, CACNA2D1, CACNB2, CACNA1D, CACNA1S, CACNA1H, CACNA2D2, CALM1, PDE1B, MCR, CAC1F, BCL2, PTAFR, GRM6, KIF11, B2CL1, CP2C9	5.06629E-06	Dihydropyridine derivatives
isocorydine	NA	TBB8, TBB4A, TBB3, TBB4B, TBB1, CASP3, TBA4A, TBB5, MITF	2.59919E-05	NA
terfenadine	DB00342	HRH1, KCNH2, CHRM3, 5HT1A, MDR1, CAC1B, CP2CJ	3.69174E-08	Other antihistamines for systemic use

Table 2. Drugs predicted to perturb the gene signature derived using characteristic direction method

Compound	DrugBank	Drug targets	*P-value*	ATC - Level 4 Description
5666823	NA	NA	7.19778E-07	NA
2-deoxy-D-glucose	NA	NA	1.67113E-06	NA
oligomycin	NA	NA	0.000141432	NA
pirinixic acid	NA	G6PD, MK12, MK13, MK11, HKDC1, MK14	0.000453719	NA
clofilium tosylate	NA	NA	0.000953984	NA
cantharidin	NA	CP3A4	0.001074699	NA
0173570-0000	NA	NA	0.001139279	NA
beclometasone	DB00394	NR3C1, GCR, MCR	0.001582953	Corticosteroids acting locally
pyrimethamine	DB00205	DHFR, GHSR, ADK, DPP4, IL8, NCOA3, NCOA1	0.00203903	Diaminopyrimidines
econazole	DB01127	ERG11, THAS, HS90A, CP2CJ, GRM6, CP3A4, CP1A2	0.001284034	Imidazole and triazole derivatives
5707885	NA	NA	0.000883981	NA
piperine	NA	ICAM1, ITB2, ITAL, TRPV1, LIPS, TF65, NFKB1, TNR1A	0.000786973	NA
erastin	NA	NK3R, 5HT1B, ADA17, PGFRB, 5HT1D, CXCR3	0.000724138	NA
enoxacin	DB00467	gyrA, parC, TOP2A, CCKAR	0.000561049	Fluoroquinolones
zaprinast	NA	NALP1, Q9BXH2, GPR35	0.000481622	NA
ursolic acid	NA	NR1H4, GPBAR	0.000341174	NA
4-hydroxyphenazone	NA	NA	0.000253656	NA
depudecin	NA	NA	0.000161151	NA
tanespimycin	NA	HS90A, HS90B	0.000149617	NA
cicloheximide	NA	HS90A, XBP1	0.000121825	NA
etoposide	DB00773	TOP2A, NCOA3, NCOA1	9.4644E-05	Podophyllotoxin derivatives
lomustine	DB01206	dna, STMN4	5.53339E-05	Nitrosoureas
disulfiram	DB00822	ALDH2, DBH	4.36826E-05	Drugs used in alcohol

				dependence
mycophenolic acid	DB01024	IMPDH1, IMPDH2	2.63107E-05	Selective immunosuppressants
emetine	NA	5HT2A, 5HT2C	6.77249E-07	Other agents against amoebiasis and other protozoal diseases
phenanthridinone	NA	NA	4.64374E-13	NA
5151277	NA	NA	5.89097E-16	NA

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