VNP: Interactive Visual Network Pharmacology of Diseases, Targets, and Drugs

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In drug discovery, promiscuous targets, multifactorial diseases, and “dirty” drugs construct complex network relationships. Network pharmacology description and analysis not only give a systems-level understanding of drug action and disease complexity but can also help to improve the efficiency of target selection and drug design. Visual network pharmacology (VNP) is developed to visualize network pharmacology of targets, diseases, and drugs with a graph network by using disease, target or drug names, chemical structures, or protein sequence. To our knowledge, VNP is the first free interactive VNP server that should be very helpful for systems pharmacology research. VNP is freely available at http://cadd.whu.edu.cn/ditad/vnpssearch.

INTRODUCTION

Drug discovery and development is a highly complex, lengthy, and expensive process, which starts from understanding molecular mechanisms of diseases, proceeds through selecting therapeutic targets, and leads to discovering drug leads and optimizing drug candidates.1–4 Diseases are usually multifactorial,5 in which multiple targets are affected and have to be targeted for successful treatment outcomes. Target proteins are always promiscuous6 with small molecular drugs. “Dirty” drugs may bind to many different molecular targets or receptors in the body and so tend to have a wide range of effects and possibly negative side effects.7–11 Several research groups curated different databases for storing information of diseases, targets, and drugs. Online Mendelian Inheritance in Man contains information on all known mendelian disorders and >12,000 genes.12 However, there is a lack of the disease-related target and drug information. DrugBank database combines detailed drug (i.e., chemical, pharmacological, and pharmaceutical) data with comprehensive drug target (i.e., sequence, structure, and pathway) information.13 In DrugBank, the therapeutic indication descriptions (for example, “Used in combination with prednisone for the treatment of metastatic, castration-resistant prostate cancer”) of drugs are listed, which needs further manual curation for specific diseases. BindingDB is a public, Web-accessible database of measured binding affinities, focusing chiefly on the interactions of proteins considered to be drug targets with small, drug-like molecules.14 The disease information of the targets and drugs are not yet provided. Therapeutic Target Database is a database containing information about the known and explored therapeutic proteins and nucleic acid targets, diseases, pathway information, and the corresponding drugs.15 The above-mentioned databases provide valuable resources for drug discovery. Currently, the potentially useful knowledge among diseases, targets, and drugs are still hidden in the text descriptions. CIDEr (multifactorial interaction networks in human diseases) provides a systems biology tool to integrate disease-associated factors focusing on metabolic and neurological diseases.16 Using systems or network4,10,17,18 tools to investigate the structure and dynamics of molecular networks is a novel paradigm of drug discovery.

RESULTS

Disease-Target-Drug Database

Disease-Target-Drug Database (http://cadd.whu.edu.cn/ditad/) stores known connections among diseases, targets, and drugs approved by the US Food and Drug Administration. Each record has a drug target, which is also used as a bridge to link diseases and drugs. Currently, there are >1,000 diseases, >500 protein targets, and >4,000 drugs (including >2,500 herb medicines and 1,500 chemical drugs) curated with tens of thousands of connections among them. The diseases and drugs are curated from the “Pharmacopoeia of People’s Republic of China, version 2010, three columns” (http://en.wikipedia.org/wiki/Pharmacopoeia_of_the_People%27s_Republic_of_China), compiled by the Chinese Pharmacopoeia Commission (http://www.chp.org.cn/cms/about/). The target information is from the Therapeutic Target Database.15 To our knowledge, there are no visual and interactive Web-based tools available elsewhere to explore the network pharmacology complex relationships.

Visual network pharmacology

Visual network pharmacology (VNP) is specially designed to visualize the complex relationships among diseases, targets, and drugs, which mainly contains three functional modules: drug-centric, target-centric, and disease-centric VNP. Users can search the database using disease, target, or drug name strings; chemical structures and substructures; or protein sequence similarity and then obtain an online interactive network view of the retrieved records. In the obtained network view, each node is a disease, target, or drug, and each edge is a known connection between two of them. Three search examples are illustrated: a disease-centric network (Figure 1), retrieved by “Alzheimer’s disease”; a target-centric network (Figure 2), obtained by “Muscarnic
acetylcholine receptor; and a drug-centric network (Figure 3), searched by chemical substructure (7-amino-3-cephem-4-carboxylic acid), in which red triangles, green circles, and yellow rectangles correspond to diseases, drugs, and targets, respectively.

In Figure 1, the input disease string “Alzheimer’s disease” will find >50 proteins and >10 drugs. The graph provides an intuitive view to network the targets and drugs related with Alzheimer’s disease. The connection degrees between targets and drugs are asymmetry, for instance, three drugs connecting to acetylcholinesterase. One drug is linked to alpha-2 adrenergic receptor.

In Figure 2, the query string “Muscarinic acetylcholine receptor” will obtain six targets. These targets are found connecting with >20 diseases and 50 drugs.

In Figure 3, the network view is obtained by chemical substructure “7-amino-3-cephem-4-carboxylic acid,” represented as smiles string NH2C(=O)N2C1SCC=C2C(=O)O.” There are >30 drugs containing the chemical substructure. These drugs are further mapped with six diseases and six targets. Furthermore, after clicking on any node on the graph, users will get a detailed list of the related records.

DISCUSSION
Network pharmacology analysis
In the VNP graphs, diseases are usually multifactorial, in which multiple targets/pathways have to be involved for the successful treatment outcomes and thus multiple drugs are usually developed for the same disease. Second, target proteins are always promiscuous with small molecular drugs and are related with different diseases. Third, some drugs are found interacting with several different molecular targets or receptors in the body, which might be the reason that the drugs have a wide range of effects and possibly negative side effects. Using the VNP, users can easily get a landscape of the related diseases, targets, or drugs in a dynamic and interactive way.

VNP has potential applications such as network analysis of drug combinations and drug repositioning. Hypertension is a typical disease with multiple mechanisms resulting from a complex interaction of genes and environmental factors. VNP provides a convenient tool to get an overview (Supplementary Figure S1) of the drugs and targets for the treatment of hypertension. The treatment of hypertension involves multiple mechanisms and thus several targets. The majority of people require more than one drug to control their hypertension, which includes thiazides, angiotensin-converting enzyme inhibitor, angiotensin receptor block, or calcium channel blocker. Some combinations of drugs might be avoided in practice, such as the use of clonidine, verapamil, or diltiazem together with a beta-blocker. How to select drug combinations for personal treatments is still a very challenging issue waiting for network or systems pharmacology modeling. What should also be noted is that “dirty drug” phenomenon can
be found in this example, that is, the drug omapatrilat can bind to both nephrilysin and angiotensin-converting enzyme. Ropinirole has been originally used in the treatment of Parkinson’s disease and has been further successfully repositioned in the treatment of restless legs syndrome. The drug target of ropinirole is mainly the dopamine receptor. Using VNP, several diseases are related with the dopamine receptor, which includes schizophrenia (Supplementary Figure S2).
Table 1 Comparisons with visualization tools

| Name               | Website                                                                 | Data                                                                 | Online server             | Chemoinformatics and bioinformatics search tools                                                                 |
|--------------------|-------------------------------------------------------------------------|                                                                     |                          |                                                                                                              |
| Arena3D            | http://arena3d.org                                                      | Time-driven phenotypic differences of gene expression data Users' network data | Desktop                  | Sequence similarity clustering claimed                                                                        |
| ArrayXPath         | http://www.snubi.org/software/ArrayXPath                                | Microarray gene expression data                                     | Desktop                  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| AVIS               | http://actin.pharm.mssm.edu/AVIS2                                       | Biological networks                                                | Server provided          | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| BioLayout Express 3D | http://www.biolayout.org                                               | General network graphs                                             | Desktop                  | Chemoinformatics tools (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found |
| Biological-Networks | http://biologicalnetworks.net                                          | Biological networks                                                | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| BioTapestry        | http://www.biotapecstasy.org                                           | Genetic regulatory networks                                         | Desktop                  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| BisoGenet          | http://bio.cigb.edu.cn/bisogenet-cytoscape                             | Molecular interactions information around a set of genes/proteins   | Desktop as a Cytoscape plug-in | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| CellDesigner       | http://www.celldesigner.org                                             | Biochemical networks                                               | Desktop                  | Plug-ins needed to run chemoinformatics (e.g., chemical substructure searching) and                          |
| Cell Illustrator   | http://www.cellillustrator.com                                         | Biological processes and systems                                    | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| CFinder            | http://www.cfinder.org                                                  | General networks                                                   | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| Cytoscape          | http://www.cytoscape.org                                                | General networks                                                   | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| GenePro            | http://wodaklab.org/genepro                                            | Protein and gene interaction networks                               | Desktop as a Cytoscape plug-in | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| GeneWays           | http://anya.igkb.anl.gov/Geneways/Geneways.html                       | Molecular pathway data from the research literature                 | Server provided          | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| GEOMii             | http://sydney.edu.au/engineering/it/visual/valacon/geomi/              | Complex networks                                                   | Desktop                  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| Gephi              | http://gephi.org                                                       | Networks and complex systems                                       | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| Graphviz           | http://www.graphviz.org                                                | Graph visualization                                                | Desktop                  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| Gridlayout         | http://kurata21.bio.kyutech.ac.jp/grid/grid_layout.htm                 | Graph layout                                                       | Desktop                  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| Guess              | http://graphexploration.cond.org/index.html                            | Graphs and networks                                                | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| Hive Plots         | http://www.hiveplot.com                                                | Drawing networks                                                   | Web demo (plug-in needed)| Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |
| Hybridlayout       | http://www.cadlive.jp/ hybridlayout/hybridlayout.html                  | Biochemical network maps                                           | Desktop                  | Chemoinformatics tools (e.g., chemical substructure searching) and bioinformatics tools not yet found         |
| Hyperdraw          | http://www.bioconductor.org/packages/release/bioc/html/hyperdraw.html   | Visualizing hypergraphs                                            | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found |
| IM Browser         | http://proteome.wayne.edu/PMIDb.html                                   | Interaction data                                                   | Web server               | Chemoinformatics tools (e.g., chemical substructure searching) tools not yet found                            |
| IPath              | http://pathways.embl.de                                                | Pathways maps                                                      | Java plug-in needed      | Chemical names mapped; no chemical structure searching functions found                                      |
| JNets              | http://www.manchester.ac.uk/bioinformatics/jnets                      | Protein interaction networks and general networks                   | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) and bioinformatics tools                        |
| KGML-ED            | http://kgml-ed.ipk-gatersleben.de                                      | KEGG Pathway diagrams                                             | Not yet based on server  | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                 |

Table 1 Continued on next page
Table 1 Continued

| Name            | Website                                      | Data                                   | Online server                        | Chemoinformatics and bioinformatics search tools                                                                 |
|-----------------|----------------------------------------------|----------------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------|
| LEDA            | http://www.algorithmic-solutions.com/leda/about/index.htm | Networks or graphs                     | C++ class library                    | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found |
| MAVisto         | http://mavisto.ipk-gatersleben.de            | Motifs in network                      | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| Medusa          | http://coot.embl.de/medusa                   | Graph visualization                    | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| ModuLand        | http://www.linkgroup.hu/modules.php         | Complex networks                       | Desktop as a Cytoscape plug-in       | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| MultiLevel      | https://code.google.com/p/multilevellayout   | Multilevel layout                      | Desktop as a Cytoscape plug-in       | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| NAViGaTOR       | http://ophid.utoronto.ca/navigator           | Protein–protein interaction networks   | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| NetMiner        | http://www.netminer.com/index.php            | Social network and general networks    | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found |
| Network          | http://mbc.cns.iu.edu                         | General networks                       | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools (e.g., sequence analysis) not yet found |
| Workbench       |                                               |                                        | Not yet based on server              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| Ondex           | http://www.ondex.org                         | Networks or graphs                     | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| Osprey          | http://biodata.mshri.on.ca/osprey/service/   | Complex interaction networks           | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| Pajek           | http://pajek.imfm.si/doku.php                | Network analysis and visualization     | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| PathDraw        | http://rospath.ewha.ac.kr/toolbox/PathwayViewerFrm.jsp | Pathway visualization and manipulation | Desktop as a Cytoscape plug-in       | Chemoinformatics (e.g., chemical substructure searching) and bioinformatics tools not yet found                |
| Pathway Tools   | http://bioinformatics.ai.sri.com/ptools      | Biological networks                    | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| PATIKA          | http://www.patica.org                        | Pathway analysis                       | Server provided                      | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| PaVESy          | http://pavesy.mpimp-golm.mpg.de/PaVESy.htm  | Pathway visualization and editing       | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| PhyloGramer     | http://www.atgc.org/PhyloGramer              | Evolutionary relationships within families of genes or proteins | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| PIMWalker       | http://pimr.hybrigenics.com                  | Hybrigenics’ public interaction data   | Server provided                      | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| PIVOT           | http://acgt.cs.tau.ac.il/pivot               | Protein–protein interactions           | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| PolarMapper     | http://kdbio.inesc-id.pt/software/polarmapper | Protein interaction networks           | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| Protein-NetVis  | http://graphics.cs.brown.edu/research/sciviz/proteins/home.htm | Protein networks                      | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| ProteoLens      | http://bioinformatics.iupui.edu/proteolens  | Biological network                    | Desktop                              | Chemoinformatics (e.g., chemical substructure searching) and sequence analysis not yet found                  |
| RedeR           | http://bioconductor.org/packages/release/bioc/html/RedeR.html | Nested networks                       | Desktop                              | Chemoinformatics and sequence analysis tools not yet found                                                 |
| RING            | http://protein.bio.unipd.it/tring            | Protein residue interaction networks    | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
| SoNIA           | http://www.stanford.edu/group/sonia          | Networks data                          | Desktop                              | Chemoinformatics tools (e.g., chemical substructure searching) not yet found                                |
After searching literatures, ropinirole is found to be an effective adjunctive treatment for schizophrenia.20 Through the drug target (via VNP searching) as a bridge, it is possible to find potential new indications of an old drug. However, ropinirole can also cause nausea, dizziness, hallucinations, orthostatic hypotension, sudden sleep attacks, hypersexuality, punding, and compulsive gambling.21 How to distinguish side effects and drug repositioning is another challenge of network or systems pharmacology modeling techniques.

In drug discovery cases, fully understanding the complex network relationships among diseases, targets, and drugs still remains a big challenge, yet it is essential for understanding multiple mechanisms of diseases, selecting important therapeutic targets, reducing side effects, and discovering new therapeutic indications of old drugs.22

Method comparisons
A comprehensive comparison is carried out to compare network pharmacology visualization tools and disease-related data, as shown in Tables 1 and 2 respectively. The software comparison table (Table 1) includes (i) data, (ii) online server; and (iii) chemoinformatics and bioinformatics search tools. The table on data comparisons (Table 2) is composed of (i) data different from that in VNP and (ii) the detail regarding whether there is a network pharmacology server visualizing the data. From the comparisons, the technical novelty of VNP is highlighted as the first network pharmacology server combined with bioinformatics and chemoinformatics tools for network analysis of multifactorial diseases, promiscuous target proteins, and “dirty” drugs.

METHODS

Substructure searching
Chemoinformatics is the application of computer and informational techniques to a range of problems in the field of chemistry, in which a key tool is to find a mapping for a query to a target molecule. Our group implemented chemoinformatics tools to search substructure in biochemical reaction database.23

Sequence similarity searching
In this work, we applied protein Smith–Waterman similarity methods24–26 to compare a query biological sequence with different target protein sequences. The software package is downloaded from the FASTA (a protein sequence similarity software) team at Virginia University (http://fasta.bioch.virginia.edu/fasta_www2/fasta_list2.shtml).

Graph visualization
In this work, the diseases, targets, and drugs are treated as graph nodes, and the connections among them are regarded as graph edges. Our purpose is to position the nodes of a graph in two-dimensional space so that all the edges are of more or less equal length and there are as few crossing edges as possible, by assigning forces among the set of edges and the set of nodes, based on their relative positions, and then using these forces either to simulate the motion of the edges and nodes or to minimize their energy.27 A Fruchterman–Reingold force-directed graph-drawing algorithm is implemented to assign forces among the sets of edges and nodes (diseases, targets, and drugs) of a graph drawing.

Web server
On the Web server side, Apache, Python, Django, C++, JavaScript, and Ajax tools are used to integrate the related chemoinformatics, bioinformatics, graph layout, and visualization tools.

Acknowledgments. This study was supported by grants from the National Natural Science Foundation of China, the Ministry of Science and Technology of China (973 and 863 Programs), the program for New Century Excellent Talents in Universities, and the National Mega Project on Major Drug Development.
Table 2 Comparisons with disease-related networks

| Type of related data (types of network nodes) | Name and additional description, website | Reference | Data different from VNP | Network pharmacology server |
|---------------------------------------------|------------------------------------------|-----------|------------------------|-----------------------------|
| **Disease**                                 | Human disease network (Cytoscape plug-in DisGeNET: http://ibi.imim.es/DisGeNET/DisGeNETweb.html) | Goh et al., 2007, Feldman et al., 2010, Bauer-Mehren et al., 2010 | Drug and drug-related information missing | No online server |
| **Disease-related genes**                   | Gene-based, interactome-enriched, and scientific publication–based human disease networks | Zhang et al., 2011a | The Orphan Disease Networks | No online server |
| **Interactome**                             | Disease-responsive interactome module-based human disease network (disease correlations based on disease-induced changes in mRNA expression of interactome modules) | Suthram et al., 2010 | Elucidating relationships between diseases using preexisting knowledge of disease genes; and further found some disease correlations also sharing common drugs | No online server |
| **mRNA changes**                            | A Bayesian network-based disease-responsive transcriptome analysis to construct a human disease network | Huang et al., 2010a | Transform public gene expression repositories into an automated disease diagnosis database. | No online server |
| **mRNA changes at the transcriptome level** | iCTNet: a Cytoscape plug-in to construct an integrative network of diseases, associated genes, drugs, and tissues (http://www.cs.queensu.ca/ictnet) | Wang et al., 2011b | Target-related information missing. | Running as desktop software acting as a Cytoscape plug-in. |
| **Drug**                                    | Biomite: an integrated bioentity network with >1 million entities and 8 million edges (http://biomine.cs.helsinki.fi) | Eronen & Toivonen, 2012 | Protein interactions, gene–disease associations, and gene ontology annotations | Online server |
| **Gene ontology terms**                     | PAGED: an integrated bioentity network with >1 million entities from 20 organisms (http://bioinformatics.iupui.edu/PAGED) | Huang et al., 2012b | Focus on human genetics | Users cannot search by using chemical structures. |
| **Expression patterns**                     | An integrated bioentity network | Bell et al., 2011 | Drug–disease information missing | No online server |
| **MicroRNA targets**                        | Metabolic pathway–corrected human disease network | Lee et al., 2008a | Relationships among genetic/epigenetic defects, the metabolic networks, and the disease phenotypes | No online server |
| **Network modules of interactome, transcriptome** | MicroRNA/disease association-based disease network obtained from publication data | Lu et al., 2008 | MicroRNA–disease associations | No online server |

Table 2 Continued on next page
Table 2 Continued

| Type of related data (types of network nodes) | Name and additional description, website | Reference | Data different from VNP | Network pharmacology server |
|---------------------------------------------|------------------------------------------|-----------|------------------------|------------------------------|
| • Patient • Disease • Disease • Environmental factor • Disease-related genes | Disease comorbidity network Rzhetsky et al., 2007 and Hidalgo et al., 2009 | Disease–genetic variation relationships | No online server |
| | Etienne: a database + clustering analysis of environmental + genetic + etiological factors of human diseases Liu et al., 2009 | Associations between disease and environmental factors | No online server |
| | VNP http://cadd.whu.edu.cn/ditad/vnpsearch/ | Diseases-Targets-Drugs network pharmacology relationships | Network pharmacology server provided. Chemical substructure searching and sequence similarity calculation functions embedded. |

The databases compared and the related references are from Table 2 of ref. 4.

Conflict of Interest. The authors declared no conflict of interest.

Author contributions. Q.N.H. wrote the manuscript. Q.N.H., Z-X.D., and J.L. designed the research. Q.N.H., Z.D., W.T., X.Y., and Z-B.M. performed the research and analyzed data.

Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
✓ The complex relationships among “dirty” drugs, promiscuous proteins, and multifactorial diseases are not well visualized and explored using online Web servers.

**WHAT QUESTION DID THIS STUDY ADDRESS?**
✓ This study addressed applications of interactive visual network pharmacology tools to network diseases, targets, and drugs in a dynamics Web-based network graph.

**WHAT THIS STUDY ADDS TO OUR KNOWLEDGE**
✓ This study provides a Web-based benchmark network pharmacology tool to explore complex relationships among diseases, targets, and drugs.

**HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS**
✓ This article will accelerate applications of systems approaches in clinical pharmacology for target selection, drug repositioning, side effect investigations, and so on.

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