Drugst.One - A plug-and-play solution for online systems medicine and network-based drug repurposing

Supplementary information

1. Drugst.One ecosystem

The Drugst.One ecosystem consists of the Drugst.One plugin for developers and a content delivery system (CDS) to distribute it, a website, a backend server, and a Python package (Figure 2). Any communication between Drugst.One components is SSL encrypted using HTTPS. We use GitHub for versioning of plugin and backend as well as code example repositories, all of which can be found here: https://github.com/drugst-one. For the Drugst.One website, the CDN server, CI/CD pipelines and container registries we, for now, use a GitLab instance hosted by the RRZ, the computing center of the University of Hamburg.

1.1 Plugin

The Drugst.One web plugin visualizes and enriches protein-protein interaction (PPI) networks (Figure S1). Given a set of gene or protein identifiers, or small networks, interaction information can be completed automatically from the Drugst.One database and the users of the website can explore the nodes in their network context. With one click, transitive connections between otherwise unconnected proteins within the interactome can be identified or first-neighbor diseases and drugs can be added to the network. Further, tissue-specific expression of the proteins can be highlighted directly in the network.

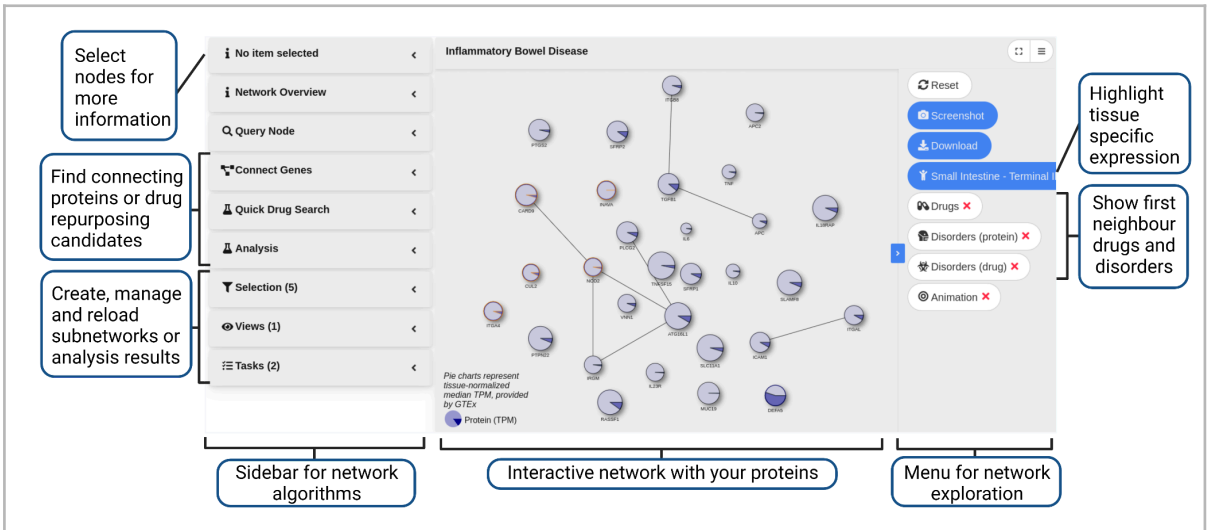

Figure S1: The interface of the Drugst.One plugin consists of a sidebar with network

information and options for drug repurposing algorithms (left), an interactive network visualization (center), and a menu with functions to modify the network (right). Individual components and positions of these elements can be configured. Visualized are the 30 genes from the inflammatory bowel disease use case (section 4 in Supplementary Notes).

Besides exploring the loaded genes or proteins, the plugin can be used to generate drug repurposing hypotheses. Using the explorative functionalities such as highlighting proteins based on their expression in tissues, input proteins for analysis tasks can be selected. Leveraging the power of specialized network algorithms, disease modules can be identified to find additional drug targets within the same genetic context and drug repurposing candidates can be prioritized (Figure S2). Analysis results are stored for future access and can be loaded directly into the interface where a network visualization helps to understand the relation of the result to the input nodes. New analyses can be started on the original network or based on previous analysis results, supporting an iterative approach to a transparent and user-driven drug repurposing.

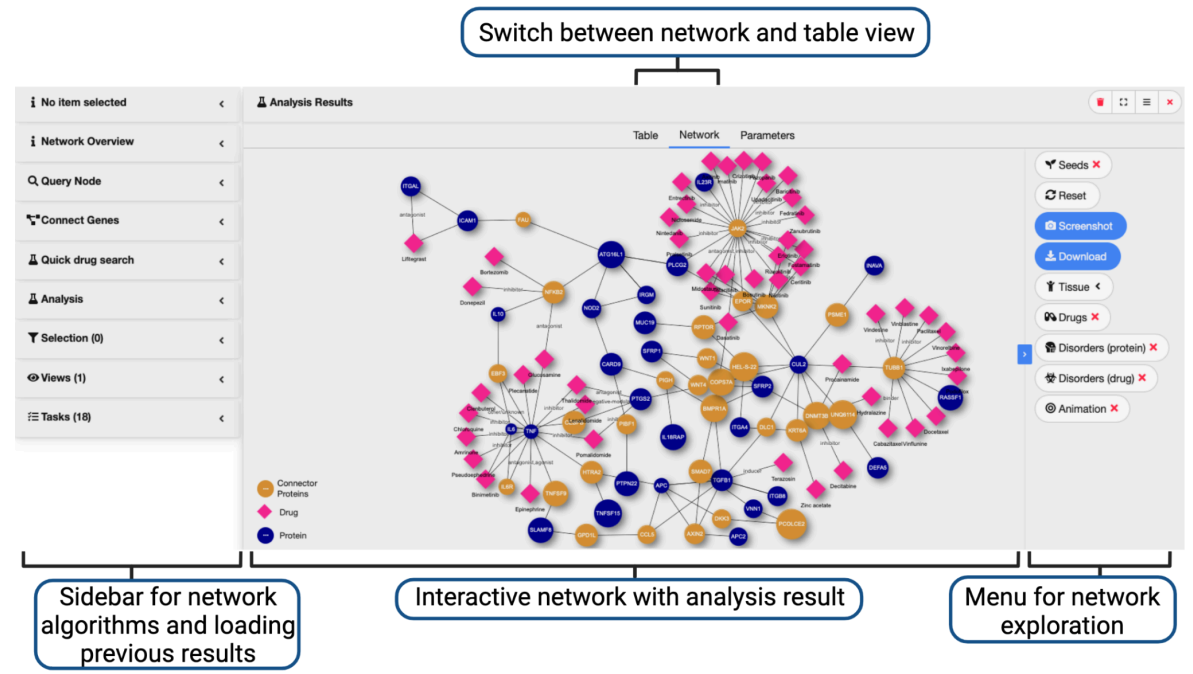

Figure S2: The results of drug target and drug repurposing candidates search for the inflammatory bowel disease use case (Supplements 4) are represented in the Drugst.One plugin as a network. A ‘Quick Drug Search’ was executed on all proteins; hence, a Multi-Steiner tree was used to connect the genes and a harmonic centrality algorithm to identify putative drug candidates.

Despite all these features the plugin remains completely serverless for hosting websites as all computations take place on the Drugst.One servers. The customizable plugin consists of a JavaScript-based web component, which can be fitted to the needs of the host website through JSON-formatted configuration strings. Functions, buttons, colors, and dimensions of the component can be adjusted to seamlessly blend in with the rest of the page. Style encapsulation guarantees no interference with styles from the host webpage. Lastly, the

Drugst.One plugin is lightweight, no heavy libraries will be added to the host's webpage to minimize loading times.

The latest Drugst.One plugin (at submission v1.1.20) is developed in Angular.js 14 with TypeScript 4.4.4 and compiled and packaged with npm 8.15.0 and node 16.17.1 into drugstone.js and drugstone.css files. For network visualization, vis.js (v9.1.6) is used and screenshot support is provided through dom-to-image-cross-origin (v.2.6.7).

1.2 Content delivery system

To enable the easy use and distribution of the plugin, we set up a simple content delivery system (CDS) to account for a large number of simultaneously loaded plugin instances on multiple hosting web pages. The CDS manages the plugin versions by maintaining all builds of previous plugin versions that can be accessed through fixed version identifiers. The latest stable release is tagged ‘latest’ and will be updated upon a new stable release. Unstable development versions can be tested using versions tagged as release candidates (‘-rc’). The most current development version can be accessed through the tag ‘nightly’. A list of all available plugin versions is generated after each build and is available at https://cdn.drugst.one/.

1.3 Website

The Drugst.One website (https://drugst.one/) serves as a documentation and exploration environment for the Drugst.One plugin. Many examples in the documentation and tutorial videos guide users through the individual features of the Drugst.One plugin as well as its integration.
The Drugst.One playground provides a graphical interface to conveniently generate custom “copy-and-paste” code snippets incorporating style and configuration choices made by the user. Further, a standalone version of the Drugst.One plugin is integrated into the website and can be accessed and modified by passing parameters using GET or POST HTTP requests, allowing developers to use the plugin without having to host a web service or incorporate the plugin in a webpage. Additionally, to facilitate and initiate the development of novel web tools presenting biomedical networks, it provides a website application template with the Drugst.One plugin.

1.4 Server

The Drugst.One backend server consists of a Django API (v3.2.19) connected to a PostgreSQL (v14) database in combination with a redis broker and worker (v7.0.11) and a Celery scheduler (v5.2.7). The backend interacts closely with the plugin, instantly returning information to the loaded proteins and adding the interactions between the proteins to create the PPI network. It further handles the asynchronous execution of the network algorithms in the analysis tasks by starting separate jobs on the redis server, allowing it to handle a large number of jobs in parallel or queue them accounting for the workload of Drugst.One instances on multiple websites. Most network algorithms (Supplement 3.2) are implemented

with graph-tool (version 2.55), a performant C++-based network library for Python, and pre-processed network files, resulting in fast execution times of usually less than 30 seconds.

1.5 Python package

Programmatic access is supported using Python 3.6 and newer. The Python package (https://pypi.org/project/drugstone/) can be installed using pip (‘pip install drugstone’) and supports the main functionalities of the plugin, including fetching protein information, PPIs, and conducting drug repurposing analyses. With the Drugst.One python package, a larger number of tasks can be executed in an automated fashion, then form the GUI of the plugin, empowering developers to integrate Dugst.One into custom workflows of their own programs.

2. Integration and customization

The Drugst.One ecosystem is a multi-component platform consisting of a website, the web plugin, a server, a content delivery system (CDS), and a Python package, as depicted in Figure 1 (for details, see Supplementary Notes 1).

The web plugin can be added to any webpage by importing one JavaScript and one stylesheet file from the https://cdn.drugst.one distribution server, and by adding the 'drugst-one' HTML tag to the source code of any system medicine tool's website (Figure S2). Features can be customized to a high degree through JSON configuration strings that are passed as attributes. This includes default states of on/off toggles, the network, and the node and edge groups that define the network style. The plugin is responsive to changes during runtime, allowing developers to add buttons or other controls to the host page, for example switching between networks. For seamless integration of the rendered plugin into any website, styling and coloring are controllable by adding specific CSS variables to the website stylesheet. To assist developers in the integration process, the Drugst.One website provides conclusive documentation of available parameters, features, and styles. It further offers an interactive configuration page at https://drugst.one/playground where configuration options are categorized, and the replication of a configured Drugst.One instance is achieved by simple copy-pasting of the generated code snippets to the developers' websites. This low-code approach allows bioinformatics researchers to provide the community with an interactive mechanism mining web tool within hours or even minutes instead of days. The lightweight Drugst.One JavaScript library connects to the Drugst.One data warehouse server, which handles all the computationally expensive work like data annotation, mapping, and asynchronous algorithm execution.

Alternatively, a standalone integration of Drugst.One is provided at https://drugst.one/standalone, which can be accessed and customized using URLs or POST-based requests. This way, results from any website or even a command line tool can be redirected to Drugst.One through a simple web service request (Supplementary Notes 2). Detailed documentation about all Drugst.One integration options can be found at https://drugst.one/doc.

2.1 Plugin

Developers can add the plugin to their own website using JavaScript. This may help to visualize any results containing a list of proteins or PPIs and to add the Drugst.One functionalities. Integration is done in three steps. Firstly, the Drugst.One libraries need to be loaded with the website by integrating the import statement into the head tag of your website. It is possible to define a specific version identifier to use a static version of the plugin or to use the tag 'latest' to automatically update to the latest stable version upon a new release.

```
<head>
   <script src="https://cdn.drugst.one/latest/drugstone.js"></script>
```

```
   <link rel="stylesheet"
href="https://cdn.drugst.one/latest/styles.css">
</head>
```

Secondly, the Drugst.One component needs to be placed on the website. After loading the Drugst.One libraries, the html tag ‘drugst-one’ becomes available. The position of the tag defines the position of the component on a webpage.

```
<drugst-one id='drugstone-component-id'></drugst-one>
```

Lastly, the component can be configured by passing options as JSON strings to the three attributes ‘groups’, ‘config’, and ‘network’. The ‘network’ parameter can accept lists of nodes and optionally edges to construct the network. Each node and edge in the network is assigned to a node and edge group, respectively, which defines the styles of each member. Additionally, groups are assigned a group name that all its members inherit, e.g. ‘protein’ or ‘drug’. Individual nodes and edges may receive individual styles to highlight them which will override the group styles. Because the network is based on vis.js, all node and edge attributes used in vis.js are applicable, including e.g. directed edge styles. Settings regarding the component itself e.g. to add or remove certain features, or which datasets to use may be passed to the ‘config’ parameter.

```
<drugst-one
groups='{"nodeGroups":{"Protein":{"type":"Protein","color":"#ff881f","fo
nt":{"color":"#ffffff"},"groupName":"Protein","shape":"ellipse"}},
"edgeGroups":{"PPI":{"color":"#111111", "groupName":"PPI"}}}'
   config='{"identifier":"symbol","title":"Breast cancer example
network"}'
   network='{"nodes":[{"id":"BRCA1","label":"BRCA1", "group":
"Protein"}, {"id":"BRCA2","label":"BRCA2", "group": "Protein"}],
"edges": [{"from":"BRCA1", "to":"BRCA2"}]}'>
  </drugst-one>
```

The Drugst.One plugin adapts to any changes of the options immediately, allowing developers to add features like buttons, toggles, or selections to e.g. change or adjust the network at runtime.

Custom styling of the component can be achieved by setting global CSS parameters on the website. Through the prefix ‘drgstn’ it is ensured that CSS variables will not randomly collide with other style variables.

```
:root {
   --drgstn-primary:#347eee;
   --drgstn-secondary:#2e42f2;
   --drgstn-success:#48C774;
```

```
    --drgstn-warning:#ffdd00;
    --drgstn-danger:#ff2744;
    --drgstn-background:#f8f9fa;
    --drgstn-panel:#ffffff;
    --drgstn-info:#61c43d;
    --drgstn-text-primary:#151515;
    --drgstn-text-secondary:#eeeeee;
    --drgstn-border:rgba(0, 0, 0, 0.2);
    --drgstn-tooltip:rgba(74,74,74,0.9);
    --drgstn-panel-secondary:#FFFFFF;
    --drgstn-height:600px;
    --drgstn-font-family:Helvetica Neue, sans-serif;
}
```

2.2 Standalone

In cases where it is not desired or possible to integrate the Drugst.One component to a website, e.g., because a tool has no website, the version hosted at the Drugst.One website is accessible using HTTP requests. When working with small networks and little customization of the plugin is required, it is sufficient to encode the parameters in GET requests.

```
https://drugst.one?nodes=PTEN,TP53&edges=PTEN%20TP53&autofillEdges=false
```

For the GET-based configuration, only selected parameters are available (https://drugst.one/doc#standalone_api).
Drugst.One buttons are provided to facilitate the integration.

```
<link rel="stylesheet"
href="https://cdn.drugst.one/libs/drugstone-buttons/0.0.1/drugstone-buttons.min.css">

<a class="drugstone-button drugstone-grey"
href="https://drugst.one/standalone?nodes=PTEN,TP53,BRCA2&autofillEdges=true&activateNetworkMenuButtonAdjacentDrugs=true&interactionDrugProtein=NeDRex&licensedDatasets=true" target="_blank">Drugst.One</a>
```

To pass more network data or extensive configuration parameters that are otherwise not available or exceed the URL limit of 2048 characters, POST requests can be used. An API endpoint expects the same options as the plugin and returns an identifier with which the network can be loaded using a GET request (i.e. an URL):

```
(Send options to API and GET identifier)
let networkID = post(
   'https://api.drugst.one/create_network',
   {
       network: {nodes: [...], edges: [...]},
       groups: {...}
       config: {...}
   }
)
```

```
(Load configuration in Drugst.One standalone with a network identifier)
https://drugst.one?id=<networkID>
```

Table S1. Systems medicine tools that integrate Drugst.One listed in alphabetical order. Options are ‘Link-out’, referring to a URL based redirect from the tool or website to the Drugst.One standalone page, ‘Plugin’, referring to the integration of the javascript-based plugin into the web tool, and programmatic access using the ‘Python package’. This table contains all collaboration partners that integrated Drugst.One into their projects.

Tool	URL	Tool Description	Integration	Integration status
BiCoN (1)	https://exbio.wzw.tum.de/bicon/	Network-constrained patient stratification through biclustering	Plugin	Done
DOMINO (2)	http://domino.cs.tau.ac.il/	Active module identification with improved empirical validation	Link-out	Done

Tool	URL	Tool Description	Integration	Integration status
G-Browser	https://exbio.wzw.tum.de/genome-browser/	An enhanced genome browser plugin that seamlessly integrates data sources and functions for genetics research.	Plugin	Done
GraphFusion	https://github.com/CarlosJesusGH/GraphFusion	An intuitive web-based graph analytics, fusion, and visualization tool	Plugin	Done
GraphSimViz (3)	https://graphsimviz.net/	Visualization of diseasomes, drugomes, and drug-disease networks	Plugin	Done
HitSeekR (4)	https://exbio.wzw.tum.de/hitseekr/	User-friendly tool for drug (target) identification in high-throughput screening	Plugin	Done
Interactive Enrichment Analysis (5)	https://github.com/gladstone-institutes/Interactive-Enrichment-Analysis/	Enrichment analysis on multiple public datasets	Link-out	In progress
mirDIP (6)	https://ophid.utoronto.ca/mirDIP/	Integrated microRNA-target data integration portal	Plugin	Done
NAViGaTOR (7)	https://ophid.utoronto.ca/navigator/	Network visualization and analysis software	Link-out	In progress
NDEx IQuery (8)	https://www.ndexbio.org/iquery/	Web tool for pathway and network-based gene set analysis	Plugin	Planned
NeEDL - Epistasis Disease Atlas (9)	https://epistasis-disease-atlas.com	Web resource to visualize, investigate, and interpret higher-order genetic interactions of single nucleotide polymorphisms in 18 human heritable diseases.	Link-out	Done
NeEDL - R Shiny App (9)	https://hub.docker.com/r/bigdatainbiomedicine/ne	R shiny app to visualize, investigate, and interpret higher-order genetic interactions of single	Plugin	Done

Tool	URL	Tool Description	Integration	Integration status
	edl	nucleotide polymorphisms on locally computed datasets.		
openPIP (10)	https://github.com/BaderLab/openPIP	Open platform to store and retrieve protein-protein interaction datasets.	Link-out	Done
pathDIP (11)	https://ophid.utoronto.ca/pathDIP	Integrated pathway database and pathway enrichment analysis portal	Plugin	Done
Pathway Figure OCR (12)	https://pfocr.wikipathways.org	Platform for browsing pathway information extracted from published figures.	Link-out	Done
ProHarMeD (13)	https://apps.cosy.bio/proharmed	Closing the gap between (harmonized) proteomics results and mechanotyping / drug repurposing	Plugin	Done
ROBUST-Web (14)	https://robust-web.net/	ROBUST is a disease module identification tool.	Plugin	Done
SCANet (15)	https://pypi.org/project/scanet/	SCANet is an all-in-one package for single-cell profiling covering the whole differential mechanotyping workflow, from inference of trait/cell-type-specific gene co-expression modules to mechanistic drug repurposing candidate prediction.	Python package	Done
Seed Connector Algorithm (16)	https://github.com/bwh784/SCA	Identification of network modules by adding a minimal number of edges between the seed nodes.	Link-out	Done
UnPaSt	https://apps.cosy.bio/unpast	Visualizer and context explorer for unsupervised expression data bicluster results.	Plugin	Done
WikiPathways (17)	https://wikipathways.org	Platform for browsing and visualizing pathways.	Link-out	Done

3. Methods

3.1 Data integration

Table S2. List of association types and source databases stored in the Drugst.One data warehouse. The version refers to the latest state before submission. *Databases with an asterisk are integrated as a part of NeDRexDB.

Source	Version	Layers	Licensed
APID (18)	January 2019	Protein-Protein	no
BioGRID* (19)	2023-07-03	Protein-Protein	no
ChEMBL (20)	27	Protein-Drug	no
CTD* (21)	2023-07-03	Drug-Disorder	no
DGIdb (22)	4.2.0	Protein-Drug	no
DisGeNET*(23)	2023-07-03	Protein-Disorder	no
DrugBank (24)	5.1.8	Drug-Disorder	yes
DrugBank* (24)	2023-07-02	Protein-Drug	yes
DrugCentral* (25)	2023-07-03	Protein-Drug, Drug-Disorder	no
GTEx (26)	v8	Tissue Expression	no
IID* (27)	2023-07-03	Protein-Protein	no
IntAct* (28)	2023-07-03	Protein-Protein	no
NeDRex (29)	2.10.0	Protein-Protein, Protein-Drug, Protein-Disorder, Drug-Disorder	yes
NeDRex (29)	2.10.0	Protein-Protein, Protein-Drug, Protein-Disorder, Drug-Disorder	no
OMIM* (30)	27-12-2022	Protein-Disorder	yes
STRING (31)	11.0	Protein-Protein	no

3.2 Algorithms

Seven network mining algorithms are implemented in Drugst.One for module identification and/or drug prioritization. To keep the plugin lightweight and easy to use, algorithms were deliberately chosen due to their focus on basic network properties like degree centrality and network proximity. Depending on the type of network, e.g. sparsely or densely connected, users can try out different approaches to explore the search space of related drug targets and drug repurposing candidates. While all of the algorithms share some general parameters (Supplement 3.2.1), some of the algorithms may offer additional settings (Supplement 3.2.2 - 3.2.9).

3.2.1 General parameters

For each algorithm the following options exist:

- Result Size. The number of returned nodes (drug targets or drugs)
- Maximum Degree. Option to filter out hub genes. If set to > 0, genes with a network degree in the complete gene-drug interaction network above this threshold will be excluded.
- Hub Penalty. Penalizes genes with a large degree in the network.
- Filter Edges. If set, only the shortest paths to the drug target or drug nodes will be displayed in the resulting network. Otherwise, all found pathways will be shown.

3.2.2 Betweenness centrality

Betweenness is obtained by finding the shortest paths for each pair of nodes in the network and assessing the number of shortest paths that pass through a particular node, such that a measure of the centrality of a node in a network global context is received. Betweenness centrality has been established as a common measurement in network biological applications (32) and is especially practical in finding communities in large networks (33). In Drugst.One, betweenness is based on the shortest paths between the seed nodes only and can be used to find drug targets with maximized connectivity to all seeds.

3.2.3 Harmonic centrality

Harmonic centrality (C_h) measurement can be described as the average shortest distance from each node to all other nodes in a network. This measurement is the equivalent of harmonic centrality for disconnected graphs. Formally speaking, it can be annotated as

$$C_h = \sum_{y \neq x}^{y} \left(\frac{1}{dist(x, y)} \right)$$

where x is a given node and $\frac{1}{dist(x,y)} = 0$ if $dist(x, y) = \infty$ (34). The closer a node is to other nodes, the higher the score. It has already been proven successful in a number of biological network problems for instance with metabolic or PPI networks (35, 36).

3.2.4 Degree centrality

Degree centrality (C_d) measurement is obtained by ranking the nodes in a network based on their degree, which is defined as the number of neighbors a node has divided by the total number of nodes in the network. It can be described as

$$C_d(x) = deg(x)$$

where x is a given node and $deg(x)$ is its degree. While it is a commonly used network analysis technique, it most importantly has been shown useful in the identification of essential proteins in PPI networks (37, 38). Thus, it is a simple approach for classifying the network-related importance of a particular protein. In Drugst.One, it can be used to discover valuable drug targets or drugs, based on the seed selection given by the user. However, ranking by node degree is prone to introduce research bias.

3.2.5 KeyPathwayMiner

KeyPathwayMiner (KPM) is an online tool developed by Alcaraz et al. for pathway enrichment analysis (39). Users can utilize KPM for their drug target search by selecting seed genes from the network and letting KPM find an interaction network of genes spanned by the seed genes. The resulting genes are functionally related to the seed nodes and therefore are suitable drug target candidates. Only one parameter k has to be set by the user, which defines the amount of permitted intermediate nodes that are neither part of the seed nodes nor the common pathway.

- Additional proteins k: Number of intermediate nodes allowed between the seed nodes.

3.2.6 Multi-Steiner tree

The Multi-Steiner tree algorithm (40) approximates the minimum spanning tree connecting the seed nodes in a reasonable time. The implementation is adopted from Ahmed et al. (41). It can be used to create a minimum spanning subnetwork between user-selected seed nodes, which happen to be central interaction partners between the seed nodes and thus represent favorable drug targets. The user can specify the number of Steiner trees computed to approximate a minimum spanning tree, and the tolerance indicating how much the subsequent trees may increase the number of edges a higher number of Steiner trees leads to more variations at the cost of a longer runtime.

3.2.7 Network proximity

As introduced in Sadegh et al. (40) we adopted the modified version of the originally proposed network-based proximity metric proposed by Guney et al. (42).
Network proximity is defined as the average length of shortest paths from target protein nodes of a drug to a set of disease nodes, called seeds. A background distribution is computed by creating a specified number (default 32) of random drug target sets and a

specified number of random seed sets (default 32). Drug target set sizes are chosen to represent the observed drug degrees in the drug-target network, differing from the original bin-based degree-preserving set randomization. The average shortest path between each observed drug-target set and the input seed set is compared to the background distribution to compute a statistical significance score (z-core) using mean and standard deviation of the background.
This algorithm was adopted in Drugst.One such that highest-scoring drugs are returned to the user as candidate drugs.

- Number Random Seed Sets: Default 32. Sets the number of random seed sets generated to establish the background distribution.
- Number Random Drug Target Sets: Default 32. Sets the number of random drug target sets generated to establish the background distribution.

3.2.8 TrustRank

TrustRank (43) is based on the same concepts as the Google PageRank algorithm and harmonic centrality (44, 45). A trust score is propagated through the network starting at the seeds, damping the score based on the distance traveled. The user can set the damping factor in a range from 0-1, with a higher damping factor causing the propagation to either stop at nodes in close proximity or in larger portions of the network. In Drugst.One, TrustRank is used to identify putative drug targets as well as drug candidates.

- Damping Factor: Correlates with the distance a trust score propagates through the network. The larger the factor, the larger the proportion of the network that is considered.

3.2.9 Algorithm applications

Table S3. An overview of all integrated algorithms regarding their availability in drug target and drug search functions.

Name	**Drug target search**	**Drug search**
Betweenness centrality	yes	no
Harmonic centrality	yes	yes
Degree centrality	yes	yes
KeyPathwayMiner	yes	no
Multi-Steiner tree	yes	no
Network proximity	no	yes
TrustRank	yes	yes

3.3 Algorithm Runtime Scaling

To be able to give users some additional guidance for selecting algorithms, we conducted some general runtime scaling behavior analysis for all integrated algorithms. For this, we selected different seed set sizes (10, 25, 50, 100 genes) as input complexity. To have realistic, yet diverse seed sets, we used NeDRexDB and identified 5 diseases for each step that have exactly or a little more genes annotated. We selected different types of diseases (cancerous, neurological, …) to get a rough cross-section through different potential fields of applications including most likely different distribution of the seed genes within the interactome, influencing the running time of algorithms. To assume the worst case, we selected the largest available networks (NeDRex - licensed) and used the Drugst.One Python package to run and time the execution duration. The results are plotted as line graphs, with error areas indicating the variance between the different cases of the same seed set size.

For the drug-target identification step, quite different behaviors can be seen (Fig. S3). Harmonic centrality, Degree centrality, and TrustRank are slightly dependent on the input size, but changes are from ~4s for 10 seeds to ~15s for 100 seeds. KeyPathwayMiner runtime is steady at around 100s for any input size, whereas MuST and Betweenness centrality heavily scale with input size taking up to 10 or 20 minutes at 100 genes. Further, it can be seen that MuST experiences by far the greatest variation in execution speeds which tells us that it heavily depends on how seeds are distributed across the PPI.

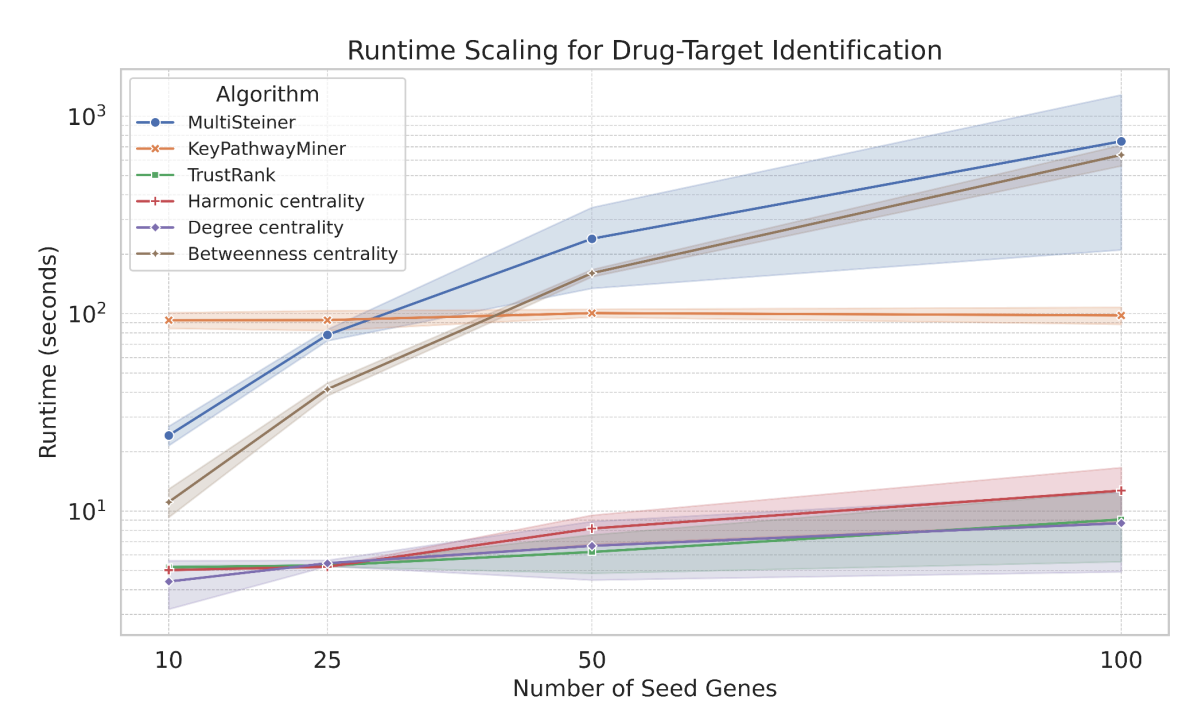

Figure S3: Line graph depicting the running time scaling behavior of all integrated algorithms. The y-axis is in log scale to be able to show and compare all algorithms in one plot, even though some are finished usually below 30s, whereas MuST in the worst case of 100 genes input size will run up to 20 minutes and in general is heavily dependent on gene input size and connectivity.

The scaling behavior of drug ranking given different sizes of seed sets is mainly uneventful and generally independent of input size (Fig. S4). Network proximity always takes around 4-5 minutes to finish whereas the other algorithms, Closeness centrality, Degree centrality, and TrustRank, run only for ~20-30 seconds to return a ranked list.

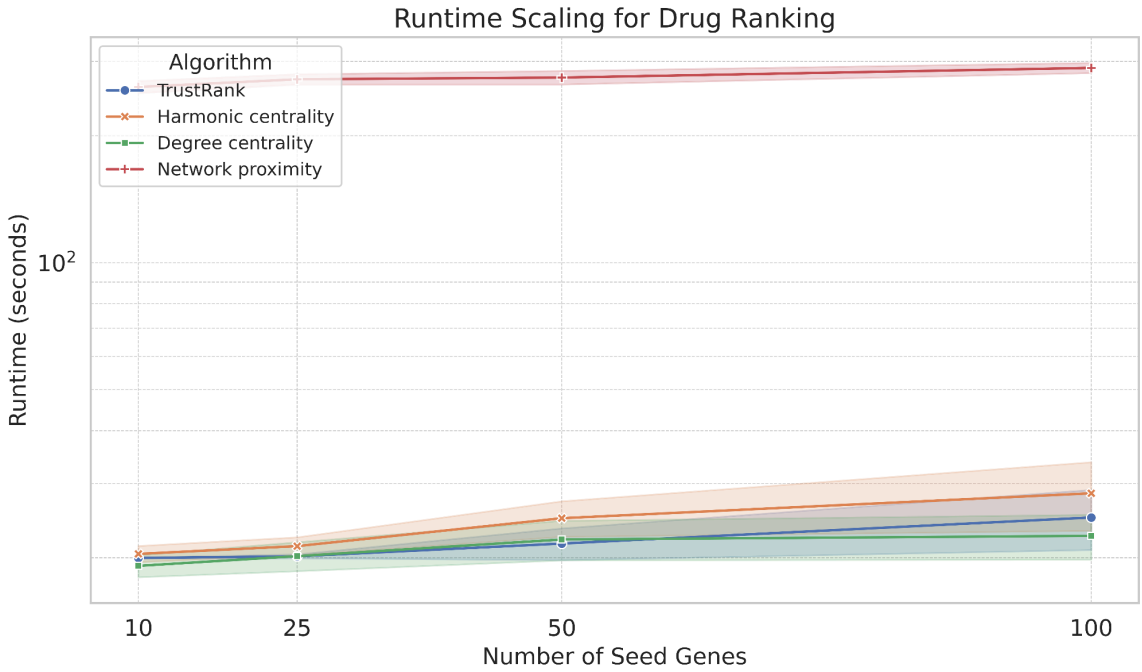

Figure S4: Drug ranking algorithms barely scale with the number of genes used as input. Network proximity has a generally high running time whereas all other methods execute significantly faster.

All seed files, scripts, and results can be found in the following GitHub repository: https://github.com/drugst-one/algo-running-times

4. Use Case: IBD

This use case was created on the weekly updated version of Drugst.One and thus results might differ slightly in the newest Drugst.One database version.

4.1 Repurposing of JAK inhibitors against IBD

A central aspect of Drugst.One is the focus on *in-silico* drug repurposing candidate prediction. To this end, we replicate an exemplary repurposing case study for inflammatory bowel disease (IBD).

Sadegh et al. (29) identified fostamatinib, ruxolitinib, and imatinib for application in IBD by starting from 30 seed genes associated with IBD according to DisGeNET (23) and OMIM (30) (Figure S1, Table S4). Multi-Steiner tree (MuST) (40) was applied to connect the seed genes in the network and the closeness centrality (CC) algorithm was employed to identify drug repurposing candidates (Figure S2).

To reproduce this example case in Drugst.One, we loaded the 30 seed genes associated with IBD into Drugst.One (Table S4). As protein-protein and drug-target interaction datasets the licensed NeDRex versions were used and we executed a ‘Quick Drug Search’, consisting of a ‘Drug target search’ using MuST (trees=5, tolerance=5, hub penalty=0.5) to connect all seeds (Table S5). Drugs were ranked using harmonic centrality, being the closest to CC used in the original paper, and the top 50 drugs were chosen as the most promising candidates. In the referenced paper, the authors identified fostamatinib, ruxolitinib, and imatinib on ranks 1, 5, and 12 respectively as drugs that have literature support for being relevant for IBD. With Drugst.One, the same drugs are found at ranks 4, 4, and 9, (Table S6). The difference might stem from small variations in the interactome and drug-target data or the use of harmonic centrality instead of closeness centrality. The drugs target *JAK2*, a gene added by MuST, with ruxolitinib and fostamatinib being known JAK inhibitors (JAKi), and their potential for IBD treatment is currently under investigation (46). Further, they inhibit *MKNK2*, another gene identified by MuST and investigated for its role in different types of colitis (47). JAKis interact with *MAPK*, a gene well-known for its role in IBD (48, 49), with which the observed effect of a dysregulated *MKNK2* might be explained. Tofacitinib, another JAKi and ranked second by HC, has the same targets as fostamatinib and ruxolitinib and is subject to studies investigating beneficial effects in IBD (50, 51).
Dasatinib, the tyrosine kinase inhibitor on rank one (Table S6), is known to induce ulcerative colitis, part of the IBD umbrella, in some patients (52, 53). Even though this drug does not have the desired effect, it is directly associated with the targeted disease and its pathways and may lead to the identification of impactful targets.
Rank two is shared by three immunomodulatory drugs thalidomide, pomalidomide and lenalidomide, as well as glucosamine. Thalidomide has known indications for ulcerative colitis, a subtype of IBD, while also lenalidomide and pomalidomide showed protective effects against IBD in mouse models (54). Lopez-Millan et al. identified lenalidomide as the more potent option, suggesting its usage as a therapeutic drug against inflammatory diseases. There is evidence of beneficial effects of these immunomodulators in human IBD, but their use in clinical practice is under discussion due to severe adverse side effects (55, 56).

Binimetinib is ranked third, which is mainly used as an anti-cancer drug. In this application, inflammatory colitis was observed as an adverse side effect (57), hinting towards a cause-effect relationship that can be studied further to research the mechanistic origins of IBD.
On rank four, together with ruxolitinib and fostamatinib, other inhibitors with the same targets (*MKNK2* and *JAK2*) are found, namely tofacitinib (FDA-approved for ulcerative colitis), sunitinib, midostaurin, erlotinib, and ceritinib.
On ranks two to five, tumor necrosis factor-α (*TNF*) inhibitors are found. *TNF* is a known target to treat IBD (58, 59) and thus effects of the drugs chloroquine on ulcerative colitis (60) and plecanatide on colitis symptoms in mice (61, 62). Further, epinephrine, pseudoephedrine, and clenbuterol share rank five, all have *TNF*-inhibiting effects (63–65) and appear to have general anti-inflammatory effects (66), most likely induced by downregulated or inhibited *IL-6* expression (65, 67).
Rank six terazosin, a drug inhibiting *TGFB1*, whose dysregulation is closely linked to IBD (68).
In summary, with Drugst.One we were not only able to re-identify three promising repurposing candidates from a previous study for IBD, but show that the first 5 ranks (that includes 20 drugs) contain valid candidates or already approved drugs for IBD treatment, including hypotheses about their molecular relationship with IBD.

The following 30 seeds are IBD-associated genes that were used by Sadegh et al. (29) to build their use case.

Table S4. List of the 30 IBD-associated genes used by Sadegh et al. (29) in their drug repurposing case study. This list serves as input for an example use case highlighting the potential of Drugst.One.
The parameters that can be used to replicate the use case, may be found in Table S5.

ATG16L1	ICAM1	TNF	SFRP2	APC2
IL10	CUL2	SFRP1	TNFSF15	ITGA4
DEFA5	MUC19	SLAMF8	APC	IL6
INAVA	CARD9	ITGB8	IL23R	NOD2
RASSF1	SLC11A1	IL18RAP	TGFB1	IRGM
PLCG2	PTPN22	PTGS2	VNN1	ITGAL

Table S5. The Drug-Protein, as well as the Protein-Protein datasets, used for the IBD drug repurposing use case, were set to the most complete one (NeDRex - licensed). For reproducibility, the exact parameters used in drug target and drug identification steps are listed.

Drugst.One	
Protein-Protein interaction dataset	NeDRex (licensed)
Drug-Protein (target) interaction dataset	NeDRex (licensed)
Drug target search	
Algorithm	MuST
Number of Steiner trees	5 (default)
Tolerance for trees	5
Hub penalty	0.5
Drug search	
Algorithm	Harmonic centrality
Result size	50

Table S6. The top 50 drugs resulting from the 'Quick Drug Search' in the IBD drug repurposing use case. The search was conducted on the NeDRex dataset (licensed). Listed are the drugs with their respective score (normalized) as returned by algorithm as well as the assigned rank.

Drug	Score	Rank
Dasatinib	1	1
Lenalidomide	0.9882636549013167	2
Thalidomide	0.9882636549013167	2
Glucosamine	0.9882636549013167	2
Pomalidomide	0.9882636549013167	2
Binimetinib	0.9824981860163579	3
Erlotinib	0.9600936780691096	4
Sunitinib	0.9600936780691096	4
Ruxolitinib	0.9600936780691096	4
Tofacitinib	0.9600936780691096	4
Midostaurin	0.9600936780691096	4
Fostamatinib	0.9600936780691096	4
Ceritinib	0.9600936780691096	4
Chloroquine	0.9600936780691095	5
Epinephrine	0.9600936780691095	5
Clenbuterol	0.9600936780691095	5
Pseudoephedrine	0.9600936780691095	5
Amrinone	0.9600936780691095	5
Plecanatide	0.9600936780691095	5
Terazosin	0.9492702822172273	6
Bortezomib	0.9334851363762997	7
Donepezil	0.9334851363762997	7
Lifitegrast	0.9283394387790588	8
Pralsetinib	0.9232501599628847	9
Nilotinib	0.9232501599628847	9
Niclosamide	0.9232501599628847	9
Fedratinib	0.9232501599628847	9
Imatinib	0.9232501599628847	9
Bosutinib	0.9232501599628847	9
Crizotinib	0.9232501599628847	9
Nintedanib	0.9232501599628847	9
Upadacitinib	0.9232501599628847	9

Entrectinib	0.9232501599628847	9
Pazopanib	0.9232501599628847	9
Zanubrutinib	0.9232501599628847	9
Axitinib	0.9232501599628847	9
Baricitinib	0.9232501599628847	9
Procainamide	0.9083117074801125	10
Decitabine	0.9083117074801125	10
Hydralazine	0.9083117074801125	10
Zinc acetate	0.9083117074801123	11
Vinflunine	0.8986184380435127	12
Ixabepilone	0.8986184380435127	12
Vinblastine	0.8986184380435127	12
Podofilox	0.8986184380435127	12
Paclitaxel	0.8986184380435127	12
Docetaxel	0.8986184380435127	12
Cabazitaxel	0.8986184380435127	12
Vindesine	0.8986184380435127	12
Vinorelbine	0.8986184380435127	12

4.2 Drug candidate identification and mechanism mining through microRNA targets

The database of human microRNA (miRNA) target predictions, mirDIP (version 5.3.0.1, database version 5.2.3.1) (6), is a resource for miRNA-based regulation information. mirDIP allows the identification of gene regulation through miRNAs while avoiding a prediction bias. Its unidirectional search function can be used to either find miRNAs targeting a given set of genes or to retrieve the set of targeted genes given a set of miRNAs. In both cases, mirDIP now offers the option to visualize and explore the used or found genes using the Drugst.One plugin.

We took 30 IBD-associated genes from Sadegh et al. (29) (Table S4) as mirDIP input to identify all known or predicted miRNA regulators ('miRNA-gene matrix' -> 'Search gene symbols'). Three microRNAs (*hsa-miR-142-3p*, *hsa-miR-3942-5p*, and *hsa-miR-574-3p*) were deemed to be main regulators of IBD genes because they each target three IBD-associated genes. Interestingly, *hsa-miR-142-3p* levels have been found to be elevated in the saliva of ulcerative colitis (UC) patients (69). For these microRNAs, we identified the targets using mirDIP unidirectional search and loaded the list of all targeted genes into the Drugst.One plugin to identify relevant drugs and disorders (Figure S5).

Using the first neighbor drug and first neighbor drug-disease association annotation in Drugst.One a number of drugs can be found, that have indications for UC but are not targeting any of the 30 IBD-associated genes but other genes that are regulated by at least one of the three miRNAs. The drugs are sulfadiazine, azathioprine, methylprednisolone, cortisone acetate, budesonide, prednisone/prednisolone, sulfasalazine, loperamide, and hydrocortisone. These drugs target seven genes, namely *NR3C1*, *CALM1*, *RAC1*, *SLC7A11*, *HTR2A*, *SCN3A*, and *GRIN2A*.

Comorbidity between UC, or any other IBD disorder, and diseases associated with those seven genes would give an indication for a shared underlying mechanism that can be dysregulated by the investigated microRNAs. Comorbidities could not be found, even though evidence for their participation in UC, Crohn's disease, or general IBD exists (*NR3C1* (70), *RAC1* (71), *SLC7A11* (72), *HTR2A* (73)). Some indications are given by carvedilol, a hypertensive drug. It has (pre-)clinical implications for IBD and targets both *HTR2A* and *SLC7A11* (74, 75).

This leaves room for further investigation of the mechanistic role of identified genes, especially *SLC7A11* and *HTR2A*, in IBD.

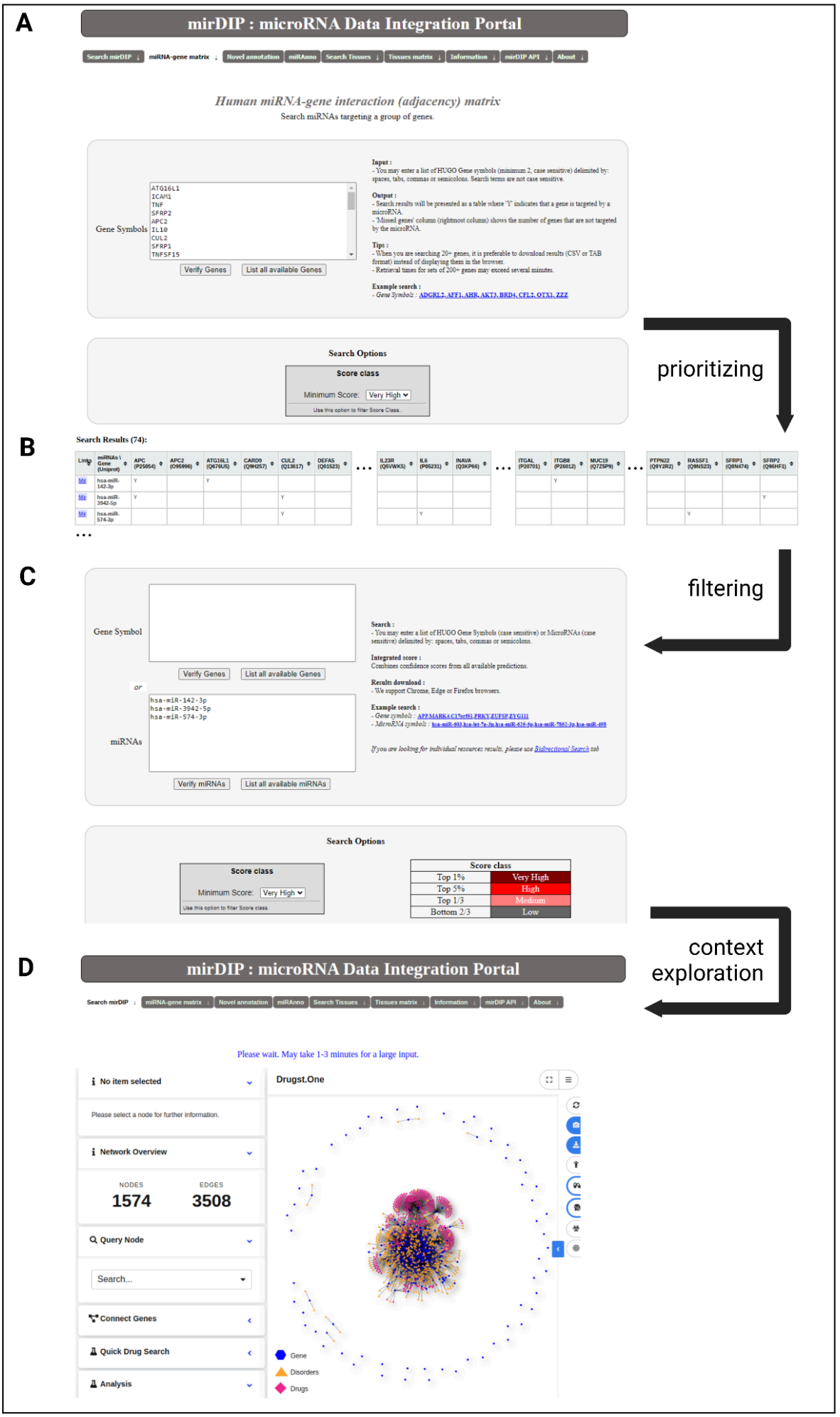
A
mirDIP : microRNA Data Integration Portal
Search mirDIP
miRNA-gene matrix
Novel annotation
miRAnno
Search Tissues
Tissues matrix
Information
mirDIP API
About
Human miRNA-gene interaction (adjacency) matrix
Search miRNAs targeting a group of genes.
Gene Symbols
ATG16L1
ICAM1
TNF
SFRP2
APC2
IL10
CUL2
SFRP1
TNFSF15
Verify Genes
List all available Genes
Input :
- You may enter a list of HUGO Gene symbols (minimum 2, case sensitive) delimited by: spaces, tabs, commas or semicolons. Search terms are not case sensitive.
Output :
- Search results will be presented as a table where 'Y' indicates that a gene is targeted by a microRNA.
- 'Missed genes' column (rightmost column) shows the number of genes that are not targeted by the microRNA.
Tips :
- When you are searching 20+ genes, it is preferable to download results (CSV or TAB format) instead of displaying them in the browser.
- Retrieval times for sets of 200+ genes may exceed several minutes.
Example search :
- Gene Symbols : ADGRL2, AFF1, AHR, AKT3, BRD4, CFL2, OTX1, ZZZ
Search Options
Score class
Minimum Score: Very High
Use this option to filter Score Class..
prioritizing
B
Search Results (74):
Links
miRNAs \ Gene (Uniprot)
APC (P25054)
APC2 (O95996)
ATG16L1 (Q676U5)
CARD9 (Q9H257)
CUL2 (Q13617)
DEFA5 (Q01523)
IL23R (Q5VWK5)
IL6 (P05231)
INAVA (Q3KP66)
ITGAL (P20701)
ITGB8 (P26012)
MUC19 (Q7Z5P9)
PTPN22 (Q9Y2R2)
RASSF1 (Q9NS23)
SFRP1 (Q8N474)
SFRP2 (Q96HF1)
Mir
hsa-miR-142-3p
hsa-miR-3942-5p
hsa-miR-574-3p
C
filtering
Gene Symbol
Verify Genes
List all available Genes
or
miRNAs
hsa-miR-142-3p
hsa-miR-3942-5p
hsa-miR-574-3p
Verify miRNAs
List all available miRNAs
Search :
- You may enter a list of HUGO Gene Symbols (case sensitive) or MicroRNAs (case sensitive) delimited by: spaces, tabs, commas or semicolons.
Integrated score :
Combines confidence scores from all available predictions.
Results download :
- We support Chrome, Edge or Firefox browsers.
Example search :
- Gene symbols : APP,MARK4,C17orf81,PRKY,ZUFSP,ZYG11I
- MicroRNA symbols : hsa-miR-603,hsa-let-7a-3p,hsa-miR-625-5p,hsa-miR-7862-3p,hsa-miR-495
If you are looking for individual resources results, please use Bidirectional Search tab
Search Options
Score class
Minimum Score: Very High
Use this option to filter Score class.
Score class
Top 1%
Very High
Top 5%
High
Top 1/3
Medium
Bottom 2/3
Low
context exploration
D
mirDIP : microRNA Data Integration Portal
Search mirDIP
miRNA-gene matrix
Novel annotation
miRAnno
Search Tissues
Tissues matrix
Information
mirDIP API
About
Please wait. May take 1-3 minutes for a large input.
No item selected
Please select a node for further information.
Network Overview
NODES
1574
EDGES
3508
Query Node
Search...
Connect Genes
Quick Drug Search
Analysis
Drugst.One
Gene
Disorders
Drugs

Figure S5: Workflow using mirDIP portal with Drugst.One plugin to identify microRNA targets for the 30 IBD genes (Table S4), and related drug targets. mirDIP was queried to identify regulating miRNAs, using all databases (**A**). 74 microRNAs were identified, of which only three regulate three IBD-associated genes each (**B**). Using the three microRNAs as a query to mirDIP (**C**) identifies 534 target genes. This set of genes is used to interrogate Drugst.One (**D**).

5. Use Case: Plugin integration with ROBUST-Web

ROBUST-Web (https://robust-web.net) presents a modified version of ROBUST (76) in an online web interface. It provides a network-based disease module identification algorithm based on prize-collecting Steiner trees that mitigates study bias using edge costs derived from study-attention or bait-usage information. Given a set of seed genes and a PPI network, ROBUST-Web constructs disease modules and passes nodes and edges to the Drugst.One plugin that takes care of result presentation and visualization in an interactive network view. Drugst.One also serves as a network explorer for the analysis of modules by offering an estimation of functional coherence with DIGEST (77), GO enrichment with g:Profiler, or a lookup in NDEx IQuery for identifying pathways with the same participants. Additionally, it adds disease annotations and drug repurposing functions to make the results of ROBUST-Web more actionable and derive hypotheses for follow-up research.

6. Other Collaborations

The Drugst.One initiative has collaborations with other projects to further extend its capabilities.

Table S7. Additional already initiated collaborations that are upcoming improvements to the Drugst.One platform. These are collaborations that concern the Drugst.One platform directly through the integration of standardized frameworks within the network medicine community.

Tool	URL	Tool Description	Collaboration
BioCypher (78)	https://biocypher.org	Drugst.One uses BioCypher to facilitate the extensibility of the database and offer additional datasets, e.g. Omnipath	Integration in Drugst.One data warehouse
NDEx IQuery (8)	https://www.ndexbio.org/iquery/	Web tool for pathway and network-based gene set analysis. Allows Drugst.One users to search for curated pathways based on selected genes	Integration in Drugst.One plugin
NDEx (79, 80)	https://www.ndexbio.org/	Web platform for storing, sharing, and publishing user-created biological networks.	Integration of “Export to NDEx” function into Drugst.One plugin

References

1. Lazareva,O., Canzar,S., Yuan,K., Baumbach,J., Blumenthal,D.B., Tieri,P., Kacprowski,T. and List,M. (2020) BiCoN: Network-constrained biclustering of patients and omics data. *Bioinformatics*, 10.1093/bioinformatics/btaa1076.

2. Levi,H., Rahmanian,N., Elkon,R. and Shamir,R. (2022) The DOMINO web-server for active module identification analysis. *Bioinformatics*, **38**, 2364–2366.

3. Sadegh,S., Skelton,J., Anastasi,E., Maier,A., Adamowicz,K., Möller,A., Kriege,N.M., Kronberg,J., Haller,T., Kacprowski,T., *et al.* (2023) Lacking mechanistic disease definitions and corresponding association data hamper progress in network medicine and beyond. *Nat. Commun.*, **14**, 1662.

4. List,M., Schmidt,S., Christiansen,H., Rehmsmeier,M., Tan,Q., Mollenhauer,J. and Baumbach,J. (2016) Comprehensive analysis of high-throughput screens with HiTSeekR. *Nucleic Acids Res.*, **44**, 6639–6648.

5. Interactive-Enrichment-Analysis: A set of Shiny apps to provide interactive enrichment analysis and exploration of results Github.

6. Hauschild,A.-C., Pastrello,C., Ekaputeri,G.K.A., Bethune-Waddell,D., Abovsky,M., Ahmed,Z., Kotlyar,M., Lu,R. and Jurisica,I. (2023) MirDIP 5.2: tissue context annotation and novel microRNA curation. *Nucleic Acids Res.*, **51**, D217–D225.

7. Brown,K.R., Otasek,D., Ali,M., McGuffin,M.J., Xie,W., Devani,B., van Toch,I.L. and Jurisica,I. (2009) NAViGaTOR: Network Analysis, Visualization and Graphing Toronto. *Bioinformatics*, **25**, 3327–3329.

8. Pillich,R.T., Chen,J., Churas,C., Fong,D., Ideker,T., Liu,S.N., Gyori,B.M., Karis,K., Ono,K., Pico,A., *et al.* (2022) NDEx IQuery: a multi-method network gene set analysis leveraging the Network Data Exchange. *bioRxiv*, 10.1101/2022.10.24.513552.

9. Hoffmann,M., Poschenrieder,J.M., Incudini,M., Baier,S., Fitz,A., Maier,A., Hartung,M., Hoffmann,C., Trummer,N., Adamowicz,K., *et al.* (2023) Network medicine-based epistasis detection in complex diseases: ready for quantum computing. *bioRxiv*, 10.1101/2023.11.07.23298205.

10. Helmy,M., Mee,M., Ranjan,A., Hao,T., Vidal,M., Calderwood,M.A., Luck,K. and Bader,G.D. (2022) OpenPIP: An Open-source Platform for Hosting, Visualizing and Analyzing Protein Interaction Data. *J. Mol. Biol.*, **434**, 167603.

11. Pastrello,C., Kotlyar,M., Abovsky,M., Lu,R. and Jurisica,I. (2024) PathDIP 5: improving coverage and making enrichment analysis more biologically meaningful. *Nucleic Acids Res.*, **52**, D663–D671.

12. Hanspers,K., Riutta,A., Summer-Kutmon,M. and Pico,A.R. (2020) Pathway information extracted from 25 years of pathway figures. *Genome Biol.*, **21**, 273.

13. Adamowicz,K., Arend,L., Maier,A., Schmidt,J.R., Kuster,B., Tsoy,O., Zolotareva,O., Baumbach,J. and Laske,T. (2023) Proteomic meta-study harmonization, mechanotyping and drug repurposing candidate prediction with ProHarMeD. *npj Systems Biology and Applications*, **9**, 1–10.

14. Sarkar,S., Lucchetta,M., Maier,A., Abdrabbou,M.M., Baumbach,J., List,M., Schaefer,M.H. and Blumenthal,D.B. (2023) Online bias-aware disease module mining with

ROBUST-Web. *Bioinformatics*, 10.1093/bioinformatics/btad345.

15. Oubounyt,M., Adlung,L., Patroni,F., Wenke,N.K., Maier,A., Hartung,M., Baumbach,J. and Elkjaer,M.L. (2023) Inference of differential key regulatory networks and mechanistic drug repurposing candidates from scRNA-seq data with SCANet. *Bioinformatics*, **39**, btad644.

16. Wang,R.-S. and Loscalzo,J. (2018) Network-Based Disease Module Discovery by a Novel Seed Connector Algorithm with Pathobiological Implications. *J. Mol. Biol.*, **430**, 2939–2950.

17. Pico,A.R., Kelder,T., van Iersel,M.P., Hanspers,K., Conklin,B.R. and Evelo,C. (2008) WikiPathways: pathway editing for the people. *PLoS Biol.*, **6**, e184.

18. Alonso-López,D., Campos-Laborie,F.J., Gutiérrez,M.A., Lambourne,L., Calderwood,M.A., Vidal,M. and De Las Rivas,J. (2019) APID database: redefining protein–protein interaction experimental evidences and binary interactomes. *Database* , **2019**, baz005.

19. Stark,C., Breitkreutz,B.-J., Reguly,T., Boucher,L., Breitkreutz,A. and Tyers,M. (2006) BioGRID: a general repository for interaction datasets. *Nucleic Acids Res.*, **34**, D535–9.

20. Mendez,D., Gaulton,A., Bento,A.P., Chambers,J., De Veij,M., Félix,E., Magariños,M.P., Mosquera,J.F., Mutowo,P., Nowotka,M., *et al.* (2019) ChEMBL: towards direct deposition of bioassay data. *Nucleic Acids Res.*, **47**, D930–D940.

21. Davis,A.P., Grondin,C.J., Johnson,R.J., Sciaky,D., Wiegers,J., Wiegers,T.C. and Mattingly,C.J. (2021) Comparative Toxicogenomics Database (CTD): update 2021. *Nucleic Acids Res.*, **49**, D1138–D1143.

22. Freshour,S.L., Kiwala,S., Cotto,K.C., Coffman,A.C., McMichael,J.F., Song,J.J., Griffith,M., Griffith,O.L. and Wagner,A.H. (2020) Integration of the Drug–Gene Interaction Database (DGIdb 4.0) with open crowdsource efforts. *Nucleic Acids Res.*, **49**, D1144–D1151.

23. Pinero,J., Queralt-Rosinach,N., Bravo,A., Deu-Pons,J., Bauer-Mehren,A., Baron,M., Sanz,F. and Furlong,L.I. (2015) DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes. *Database*, **2015**, bav028–bav028.

24. Wishart,D.S., Feunang,Y.D., Guo,A.C., Lo,E.J., Marcu,A., Grant,J.R., Sajed,T., Johnson,D., Li,C., Sayeeda,Z., *et al.* (2018) DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.*, **46**, D1074–D1082.

25. Avram,S., Bologa,C.G., Holmes,J., Bocci,G., Wilson,T.B., Nguyen,D.-T., Curpan,R., Halip,L., Bora,A., Yang,J.J., *et al.* (2021) DrugCentral 2021 supports drug discovery and repositioning. *Nucleic Acids Res.*, **49**, D1160–D1169.

26. Carithers,L.J., Ardlie,K., Barcus,M., Branton,P.A., Britton,A., Buia,S.A., Compton,C.C., DeLuca,D.S., Peter-Demchok,J., Gelfand,E.T., *et al.* (2015) A novel approach to high-quality postmortem tissue procurement: The GTEx project. *Biopreserv. Biobank.*, **13**, 311–319.

27. Kotlyar,M., Pastrello,C., Ahmed,Z., Chee,J., Varyova,Z. and Jurisica,I. (2022) IID 2021: towards context-specific protein interaction analyses by increased coverage, enhanced annotation and enrichment analysis. *Nucleic Acids Res.*, **50**, D640–D647.

28. Orchard,S., Ammari,M., Aranda,B., Breuza,L., Briganti,L., Broackes-Carter,F., Campbell,N.H., Chavali,G., Chen,C., del-Toro,N., *et al.* (2014) The MIntAct project--IntAct as a common curation platform for 11 molecular interaction databases. *Nucleic Acids Res.*, **42**, D358–63.

29. Sadegh,S., Skelton,J., Anastasi,E., Bernett,J., Blumenthal,D.B., Galindez,G., Salgado-Albarrán,M., Lazareva,O., Flanagan,K., Cockell,S., *et al.* (2021) Network medicine for disease module identification and drug repurposing with the NeDRex platform. *Nat. Commun.*, **12**, 6848.

30. Amberger,J.S., Bocchini,C.A., Scott,A.F. and Hamosh,A. (2019) OMIM.org: leveraging knowledge across phenotype-gene relationships. *Nucleic Acids Res.*, **47**, D1038–D1043.

31. Snel,B., Lehmann,G., Bork,P. and Huynen,M.A. (2000) STRING: a web-server to retrieve and display the repeatedly occurring neighbourhood of a gene. *Nucleic Acids Res.*, **28**, 3442–3444.

32. Junker,B.H., Koschützki,D. and Schreiber,F. (2006) Exploration of biological network centralities with CentiBiN. *BMC Bioinformatics*, **7**, 219.

33. Girvan,M. and Newman,M.E.J. (2002) Community structure in social and biological networks. *Proc. Natl. Acad. Sci. U. S. A.*, **99**, 7821–7826.

34. Rochat,Y. Closeness centrality extended to unconnected graphs: The harmonic centrality index.

35. Koschützki,D. and Schreiber,F. (2008) Centrality analysis methods for biological networks and their application to gene regulatory networks. *Gene Regul. Syst. Bio.*, **2**, 193–201.

36. Jalili,M., Salehzadeh-Yazdi,A., Gupta,S., Wolkenhauer,O., Yaghmaie,M., Resendis-Antonio,O. and Alimoghaddam,K. (2016) Evolution of Centrality Measurements for the Detection of Essential Proteins in Biological Networks. *Front. Physiol.*, **7**, 375.

37. Zhang,H., Fiszman,M., Shin,D., Miller,C.M., Rosemblat,G. and Rindflesch,T.C. (2011) Degree centrality for semantic abstraction summarization of therapeutic studies. *J. Biomed. Inform.*, **44**, 830–838.

38. Tang,X., Wang,J., Zhong,J. and Pan,Y. (2014) Predicting Essential Proteins Based on Weighted Degree Centrality. *IEEE/ACM Trans. Comput. Biol. Bioinform.*, **11**, 407–418.

39. List,M., Alcaraz,N., Dissing-Hansen,M., Ditzel,H.J., Mollenhauer,J. and Baumbach,J. (2016) KeyPathwayMinerWeb: online multi-omics network enrichment. *Nucleic Acids Res.*, **44**, W98–W104.

40. Sadegh,S., Matschinske,J., Blumenthal,D.B., Galindez,G., Kacprowski,T., List,M., Nasirigerdeh,R., Oubounyt,M., Pichlmair,A., Rose,T.D., *et al.* (2020) Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing. *Nat. Commun.*, **11**, 3518.

41. Ahmed,R., Angelini,P., Sahneh,F.D., Efrat,A., Glickenstein,D., Gronemann,M., Heinsohn,N., Kobourov,S.G., Spence,R., Watkins,J., *et al.* (2019) Multi-level Steiner Trees. *ACM J. Exp. Algorithmics*, **24**, 1–22.

42. Guney,E., Menche,J., Vidal,M. and Barábasi,A.-L. (2016) Network-based in silico drug efficacy screening. *Nat. Commun.*, **7**, 10331.

43. Gyöngyi,Z., Garcia-Molina,H. and Pedersen,J. (2004) - Combating Web Spam with TrustRank. In Nascimento,M.A., Özsu,M.T., Kossmann,D., Miller,R.J., Blakeley,J.A., Schiefer,B. (eds), *Proceedings 2004 VLDB Conference*. Morgan Kaufmann, St Louis, pp. 576–587.

44. Page,L., Brin,S., Motwani,R. and Winograd,T. (1999) The PageRank Citation Ranking: Bringing Order to the Web.

45. Gyongyi,Z., Garcia-Molina,H. and Pedersen,J. Error - Stanford InfoLab Publication Server.

46. Agrawal,M., Kim,E.S. and Colombel,J.-F. (2020) JAK Inhibitors Safety in Ulcerative Colitis: Practical Implications. *J. Crohns. Colitis*, **14**, S755–S760.

47. Bjerrum,J.T., Nielsen,O.H., Riis,L.B., Pittet,V., Mueller,C., Rogler,G. and Olsen,J. (2014) Transcriptional analysis of left-sided colitis, pancolitis, and ulcerative colitis-associated dysplasia. *Inflamm. Bowel Dis.*, **20**, 2340–2352.

48. Broom,O.J., Widjaya,B., Troelsen,J., Olsen,J. and Nielsen,O.H. (2009) Mitogen activated protein kinases: a role in inflammatory bowel disease? *Clin. Exp. Immunol.*, **158**, 272–280.

49. Coskun,M., Olsen,J., Seidelin,J.B. and Nielsen,O.H. (2011) MAP kinases in inflammatory bowel disease. *Clin. Chim. Acta*, **412**, 513–520.

50. Sayoc-Becerra,A., Krishnan,M., Fan,S., Jimenez,J., Hernandez,R., Gibson,K., Preciado,R., Butt,G. and McCole,D.F. (2020) The JAK-Inhibitor Tofacitinib Rescues Human Intestinal Epithelial Cells and Colonoids from Cytokine-Induced Barrier Dysfunction. *Inflamm. Bowel Dis.*, **26**, 407–422.

51. Armuzzi,A., Hart,A., Cappelleri,J.C., Mammar,N., Hur,P., Hoskin,B., Hennessy,F., Milligan,G. and Dignass,A. (2023) Characteristics, clinical outcomes and patient-reported outcomes of patients with ulcerative colitis receiving tofacitinib: a real-world survey in the United States and five European countries. *BMC Gastroenterol.*, **23**, 17.

52. Del Sordo,R., Lupinacci,G., Tanzi,G., Bassotti,G. and Villanacci,V. (2022) Imatinib and Dasatinib-induced Ulcerative Colitis: Case Report. *Inflamm. Bowel Dis.*, **28**, e1–e2.

53. Yamauchi,K., Inaba,T., Colvin,H.S., Sakakihara,I., Yamamoto,K., Izumikawa,K., Takahashi,S., Tanaka,S., Ishikawa,S., Wato,M., *et al.* (2022) Dasatinib-induced colitis: clinical, endoscopic and histological findings. *Scand. J. Gastroenterol.*, **57**, 449–456.

54. Lopez-Millan,B., Diaz de la Guardia,R., Roca-Ho,H., García-Herrero,C.M., Lavoie,J.R., Rosu-Myles,M., Gonzalez-Rey,E., O'Valle,F., Criado,G., Delgado,M., *et al.* (2017) Therapeutic effect of the immunomodulatory drug lenalidomide, but not pomalidomide, in experimental models of rheumatoid arthritis and inflammatory bowel disease. *Exp. Mol. Med.*, **49**, e290.

55. Srinivasan,R. and Akobeng,A.K. (2009) Thalidomide and thalidomide analogues for induction of remission in Crohn's disease. *Cochrane Database Syst. Rev.*

56. Millrine,D. and Kishimoto,T. (2017) A Brighter Side to Thalidomide: Its Potential Use in

Immunological Disorders. *Trends Mol. Med.*, **23**, 348–361.

57. Issac,A.G., Szafron,D., Wei,D., McQuade,J.L. and Wang,Y. (2022) Severe Inflammatory Colitis Related to Encorafenib and Binimetinib following Immune Checkpoint Inhibitor Therapy. *Case Rep. Gastroenterol.*, **16**, 388–393.

58. Gareb,B., Otten,A.T., Frijlink,H.W., Dijkstra,G. and Kosterink,J.G.W. (2020) Review: Local Tumor Necrosis Factor-α Inhibition in Inflammatory Bowel Disease. *Pharmaceutics*, **12**.

59. Cui,G., Fan,Q., Li,Z., Goll,R. and Florholmen,J. (2021) Evaluation of anti-TNF therapeutic response in patients with inflammatory bowel disease: Current and novel biomarkers. *EBioMedicine*, **66**, 103329.

60. Goenka,M.K., Kochhar,R., Tandia,B. and Mehta,S.K. (1996) Chloroquine for mild to moderately active ulcerative colitis: comparison with sulfasalazine. *Am. J. Gastroenterol.*, **91**, 917–921.

61. Bak,Y.-K., Lampe,J.W. and Sung,M.-K. (2014) Effects of dietary supplementation of glucosamine sulfate on intestinal inflammation in a mouse model of experimental colitis. *J. Gastroenterol. Hepatol.*, **29**, 957–963.

62. Shailubhai,K., Palejwala,V., Arjunan,K.P., Saykhedkar,S., Nefsky,B., Foss,J.A., Comiskey,S., Jacob,G.S. and Plevy,S.E. (2015) Plecanatide and dolcanatide, novel guanylate cyclase-C agonists, ameliorate gastrointestinal inflammation in experimental models of murine colitis. *World J. Gastrointest. Pharmacol. Ther.*, **6**, 213–222.

63. Izeboud,C.A., Monshouwer,M., van Miert,A.S. and Witkamp,R.F. (1999) The beta-adrenoceptor agonist clenbuterol is a potent inhibitor of the LPS-induced production of TNF-alpha and IL-6 in vitro and in vivo. *Inflamm. Res.*, **48**, 497–502.

64. Fiebich,B.L., Collado,J.A., Stratz,C., Valina,C., Hochholzer,W., Muñoz,E. and Bellido,L.M. (2012) Pseudoephedrine inhibits T-cell activation by targeting NF-κB, NFAT and AP-1 signaling pathways. *Immunopharmacol. Immunotoxicol.*, **34**, 98–106.

65. Liao,J., Keiser,J.A., Scales,W.E., Kunkel,S.L. and Kluger,M.J. (1995) Role of epinephrine in TNF and IL-6 production from isolated perfused rat liver. *Am. J. Physiol.*, **268**, R896–901.

66. Griffin,É.W., Yssel,J.D., O'Neill,E., Ryan,K.J., Boyle,N., Harper,P., Harkin,A. and Connor,T. (2018) The β2-adrenoceptor agonist clenbuterol reduces the neuroinflammatory response, neutrophil infiltration and apoptosis following intra-striatal IL-1β administration to rats. *Immunopharmacol. Immunotoxicol.*, **40**, 99–106.

67. Wu,Z., Kong,X., Zhang,T., Ye,J., Fang,Z. and Yang,X. (2014) Pseudoephedrine/ephedrine shows potent anti-inflammatory activity against TNF-α-mediated acute liver failure induced by lipopolysaccharide/D-galactosamine. *Eur. J. Pharmacol.*, **724**, 112–121.

68. Ihara,S., Hirata,Y. and Koike,K. (2017) TGF-β in inflammatory bowel disease: a key regulator of immune cells, epithelium, and the intestinal microbiota. *J. Gastroenterol.*, **52**, 777–787.

69. Yarani,R., Shojaeian,A., Palasca,O., Doncheva,N.T., Jensen,L.J., Gorodkin,J. and Pociot,F. (2022) Differentially Expressed miRNAs in Ulcerative Colitis and Crohn's Disease. *Front. Immunol.*, **13**, 865777.

70. Skrzypczak-Zielinska,M., Gabryel,M., Marszalek,D., Dobrowolska,A. and Slomski,R. (2021) NGS study of glucocorticoid response genes in inflammatory bowel disease patients. *Arch. Med. Sci.*, **17**, 417–433.

71. Seinen,M.L., van Nieuw Amerongen,G.P., de Boer,N.K.H. and van Bodegraven,A.A. (2016) Rac Attack: Modulation of the Small GTPase Rac in Inflammatory Bowel Disease and Thiopurine Therapy. *Mol. Diagn. Ther.*, **20**, 551–557.

72. Xu,S., He,Y., Lin,L., Chen,P., Chen,M. and Zhang,S. (2021) The emerging role of ferroptosis in intestinal disease. *Cell Death Dis.*, **12**, 289.

73. Alvarado,D.M. and Ciorba,M.A. (2020) Serotonin Receptors Regulate Inflammatory Response in Experimental Colitis. *J. Nutr.*, **150**, 1678–1679.

74. Ramadan,N., Sami,S., Elmenshawy,S. and Salem,A.E. (2021) Possible protective effects of propranolol and carvedilol and their interaction with mesalazine on experimentally induced ulcerative colitis in male albino rats under supervision of. 10.13140/RG.2.2.22062.38724.

75. Murnane,K.S., Guner,O.F., Bowen,J.P., Rambacher,K.M., Moniri,N.H., Murphy,T.J., Daphney,C.M., Oppong-Damoah,A. and Rice,K.C. (2019) The adrenergic receptor antagonist carvedilol interacts with serotonin 2A receptors both in vitro and in vivo. *Pharmacol. Biochem. Behav.*, **181**, 37–45.

76. Bernett,J., Krupke,D., Sadegh,S., Baumbach,J., Fekete,S.P., Kacprowski,T., List,M. and Blumenthal,D.B. (2022) Robust disease module mining via enumeration of diverse prize-collecting Steiner trees. *Bioinformatics*, 10.1093/bioinformatics/btab876.

77. Adamowicz,K., Maier,A., Baumbach,J. and Blumenthal,D.B. (2022) Online in silico validation of disease and gene sets, clusterings or subnetworks with DIGEST. *Brief. Bioinform.*, **23**.

78. Lobentanzer,S., Aloy,P., Baumbach,J., Bohar,B., Carey,V.J., Charoentong,P., Danhauser,K., Doğan,T., Dreo,J., Dunham,I., *et al.* (2023) Democratizing knowledge representation with BioCypher. *Nat. Biotechnol.*, 10.1038/s41587-023-01848-y.

79. Pratt,D., Chen,J., Pillich,R., Rynkov,V., Gary,A., Demchak,B. and Ideker,T. (2017) NDEx 2.0: A Clearinghouse for Research on Cancer Pathways. *Cancer Res.*, **77**, e58–e61.

80. Pillich,R.T., Chen,J., Churas,C., Liu,S., Ono,K., Otasek,D. and Pratt,D. (2021) NDEx: Accessing Network Models and Streamlining Network Biology Workflows. *Curr Protoc*, **1**, e258.