D558–D566 *Nucleic Acids Research, 2018, Vol. 46, Database issue* *Published online 13 November 2017*
doi: 10.1093/nar/gkx1063

Data Portal for the Library of Integrated Network-based Cellular Signatures (LINCS) program: integrated access to diverse large-scale cellular perturbation response data

Amar Koleti[1,2], Raymond Terryn[1,2,3], Vasileios Stathias[2,3,4], Caty Chung[1,2], Daniel J. Cooper[2,3], John P. Turner[1,2,3], Dušica Vidović[1,2,3], Michele Forlin[1,2,3], Tanya T. Kelley[2,3], Alessandro D'Urso[1,2], Bryce K. Allen[1,2,3], Denis Torre[2,5], Kathleen M. Jagodnik[2,5], Lily Wang[2,5], Sherry L. Jenkins[2,5], Christopher Mader[1,2], Wen Niu[2,6], Mehdi Fazel[2,6], Naim Mahi[2,6], Marcin Pilarczyk[2,6], Nicholas Clark[2,6], Behrouz Shamsaei[2,6], Jarek Meller[2,6], Juozas Vasiliauskas[2,6], John Reichard[2,6], Mario Medvedovic[2,6], Avi Ma'ayan[2,5], Ajay Pillai[7] and Stephan C. Schürer[1,2,3,*]

[1]Center for Computational Science, University of Miami, FL, USA, [2]BD2K LINCS Data Coordination and Integration Center, Icahn School of Medicine at Mount Sinai, University of Miami, University of Cincinnati, New York NY, Miami FL, Cincinnati OH, USA, [3]Department of Molecular and Cellular Pharmacology, Miller School of Medicine, University of Miami, FL, USA, [4]Department of Human Genetics and Genomics, Miller School of Medicine, University of Miami, FL, USA, [5]Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [6]Division of Biostatistics and Bioinformatics, Department of Environmental Health, University of Cincinnati, Cincinnati, OH, USA and [7]Division of Genome Sciences, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

Received August 15, 2017; Revised October 06, 2017; Editorial Decision October 07, 2017; Accepted October 19, 2017

ABSTRACT

The Library of Integrated Network-based Cellular Signatures (LINCS) program is a national consortium funded by the NIH to generate a diverse and extensive reference library of cell-based perturbation-response signatures, along with novel data analytics tools to improve our understanding of human diseases at the systems level. In contrast to other large-scale data generation efforts, LINCS Data and Signature Generation Centers (DSGCs) employ a wide range of assay technologies cataloging diverse cellular responses. Integration of, and unified access to LINCS data has therefore been particularly challenging. The Big Data to Knowledge (BD2K) LINCS Data Coordination and Integration Center (DCIC) has developed data standards specifications, data processing pipelines, and a suite of end-user software tools to integrate and annotate LINCS-generated data, to make LINCS signatures searchable and usable for different types of users. Here, we describe the LINCS Data Portal (LDP) (http://lincsportal.ccs.miami.edu/), a unified web interface to access datasets generated by the LINCS DSGCs, and its underlying database, LINCS Data Registry (LDR). LINCS data served on the LDP contains extensive metadata and curated annotations. We highlight the features of the LDP user interface that is designed to enable search, browsing, exploration, download and analysis of LINCS data and related curated content.

INTRODUCTION

Since the completion of the Human Genome Project (1), increasingly powerful technologies for large-scale multi-omics profiling and integrative data analytics have transformed the ability to gain insights and model the complex and dynamic networks of molecules and biological processes involved in human disease (2). Increasingly large and diverse datasets have empowered team-based research and big data approaches to model complex biological systems and drug action (3,4). Accordingly, systems biology and big data are also transforming drug discovery (5–7). The

[*]To whom correspondence should be addressed. Tel: +1 305 243 6552; Email: stephan.schurer@gmail.com

Library of Integrated Network-based Cellular Signatures (LINCS) project (http://lincsproject.org/), initiated by the NIH in 2011, aims to catalyze systems-biology approaches to model complex diseases and the development of novel therapeutics via an extensive catalog of perturbation response signatures in a wide array of cell model systems. The current LINCS Phase 2 includes six Data and Signature Generation Centers (DSGCs) and one Data Coordination and Integration Center (DCIC). The LINCS catalog of signatures can be thought of as a data cube, with three main dimensions: (i) the cell model system, including proliferating immortal cell lines, primary cells, and induced pluripotent stem cells (iPSCs); (ii) the perturbation, including small molecules, genetic perturbations, and microenvironment effectors and (iii) the cellular readout, including gene expression, phosphoproteins, epigenetic states, and various cellular phenotypes including morphology, signaling and cell fates, global proteomics, and biochemical small molecule-protein binding.

Another goal of LINCS is to develop information management and analysis software tools to make LINCS data accessible and useful to the research community. In contrast to other large-scale data generation efforts, the LINCS DSGCs employ a wide range of assay technologies of more than 20 high-throughput assays, posing a significant challenge to data processing and integration. To accomplish this goal, rigorous metadata specifications and data exchange standards were developed in the Pilot Phase and are maintained and expanded as new assays, cells, and perturbations are introduced in the Consortium (8). LINCS data standards are based on community best practices (9) to enable the linking and integration of LINCS to other resources.

All LINCS data have been organized via the LINCS Data Registry (LDR) after extensive data standardization and annotations with reference ontologies and identifiers so that all datasets have consistent metadata, enabling their integration and mapping to many external resources. The LINCS Data Portal (LDP) provides a unified interface to access LINCS datasets and metadata contained within the LDR. The LDP provides various options to explore, query, and download LINCS dataset packages and related objects, such as metadata for small molecules and cell lines utilized in the experiments.

In addition to managing the large quantity and diversity of data and extensive metadata records and reference annotations, the implementation of the LDP and design of the underlying registry were guided by the FAIR principles to make digital research objects Findable, Accessible, Interoperable, and Reusable (10) and by the Joint Declaration of Data Citation Principles (JDDCP) (Force11 Data Citation Synthesis Group (2014); https://www.force11.org/datacitation) to cite (attribute) LINCS datasets to their authors. Here we describe for the first time the LDR and the LDP as the two main resources to manage LINCS data and make LINCS resources accessible to the community.

MATERIALS AND METHODS

LINCS content overview

The LINCS Consortium produces data through the use of numerous assays and technologies, including multiple -omics categories (proteomics, transcriptomics, epigenomics), imaging, and the microenvironment microarray assay (MEMA), a novel platform for evaluating the effect of combining microenvironment perturbagens (e.g. growth factors, extracellular matrix proteins) on specific biological endpoints such as proliferation, differentiation, DNA damage, and senescence. High-throughput, large-scale assays include RNA-seq, L1000 (A Next Generation Connectivity Map: L1000 platform and the first 1,000,000 profiles: https://www.biorxiv.org/content/early/2017/05/10/136168), assay for transposase accessible chromatin sequencing (ATAC-seq), fluorescence microscopy, P100, global chromatin profiling (GCP), reverse phase protein array (RPPA), and sequential windowed acquisition of all theoretical fragment ion mass spectra (SWATH-MS). A full list of LINCS assay technologies and assays is provided in Supporting Table S1. In addition to various assays and corresponding data types, the LINCS data matrix expands over numerous cell types and perturbagens. Over 1000 cell types have been used in LINCS experiments, including established cell lines, embryonic stem (ES) cells, induced pluripotent stem cells (iPSCs), differentiated cells, and primary cells. Most are cancer cell lines covering a wide range of cancers such as melanoma, leukemia, lung, colon and breast carcinoma. Additionally, primary cells, ES cells, iPSCs, and differentiated cells are used in numerous disease modeling experiments, such as iPSCs derived from amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) patients and the corresponding *in vitro* differentiated motor neurons. The cells are treated with small molecules (which represent the largest group of perturbagens, with ∼42 000 small molecules tested), protein ligands, micro-environments, clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (CAS9) mediated gene editing, or other perturbagen reagents or environmental factors. The small molecule collection covers a wide range of chemical perturbagens such as FDA-approved drugs, tool compounds (or chemical probes), and screening library compounds including those with clinical utility, known Mechanism of Action (MoA), and compounds previously tested in the NIH Molecular Libraries Program (11).

LINCS data for both experimental reagents and assays are standardized according to the previously established LINCS data standards (8), incorporating annotations from various ontologies, such as Cell Line Ontology (CLO) (12) for cells, Chemical Entities of Biological Interest (ChEBI) (13) for small molecules, and the BioAssay Ontology (BAO) (14,15) for assays. A full list of these ontologies, standards, and associated LINCS data/metadata elements is provided in Supporting Table S2. These data are used to construct the primary DCIC data product, the dataset packages, which contain datasets, their metadata, and any other related digital objects, e.g., property mapping and readme files. These comprehensive, data-analysis-ready packages are available for download as .tar groups from the LDP Landing Pages described below.

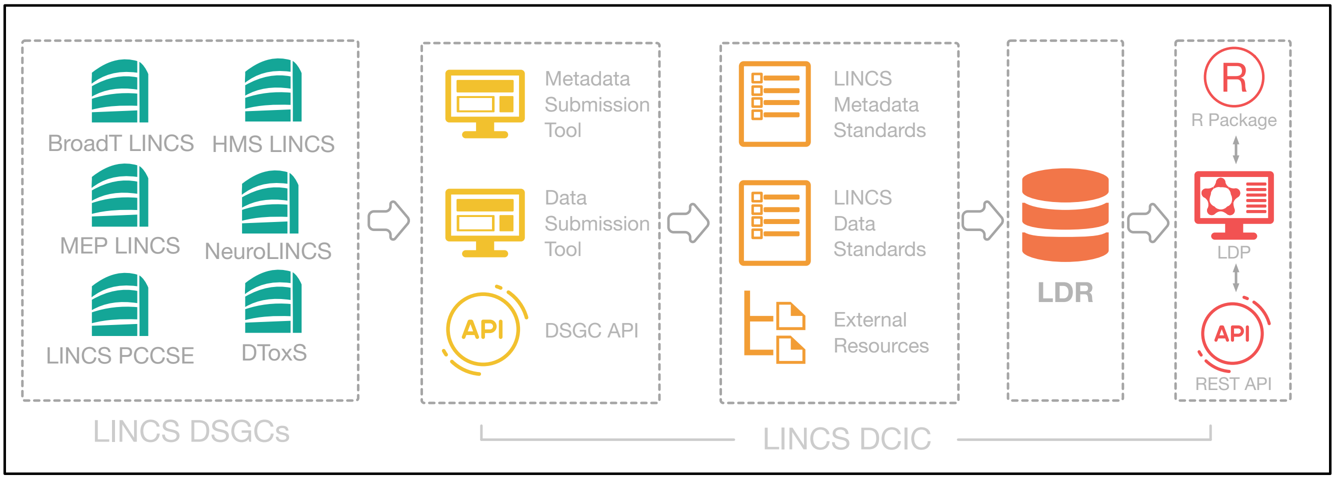


Figure 1. Data flow from LINCS DSGCs into the LDR and LDP. Data are submitted to the DCIC via different tools and then standardized, annotated, and loaded into the LDR. From the LDR, LINCS data are available via different mechanisms. Abbreviations: LINCS, Library of Integrated Network-based Cellular Signatures; DSGC, Data and Signature Generation Centers; DCIC, Data Coordination and Integration Center; HMS, Harvard Medical School; MEP LINCS, Microenvironment Perturbation LINCS Center; PCCSE, Proteomic Characterization Center for Signaling and Epigenetics; DToxS, Drug Toxicity Signature Generation Center; LDR, LINCS Data Registry; LDP, LINCS Data Portal; RESR, Representational State Transfer; API, Application Programming Interface.

External data sources for value-added annotation and validation

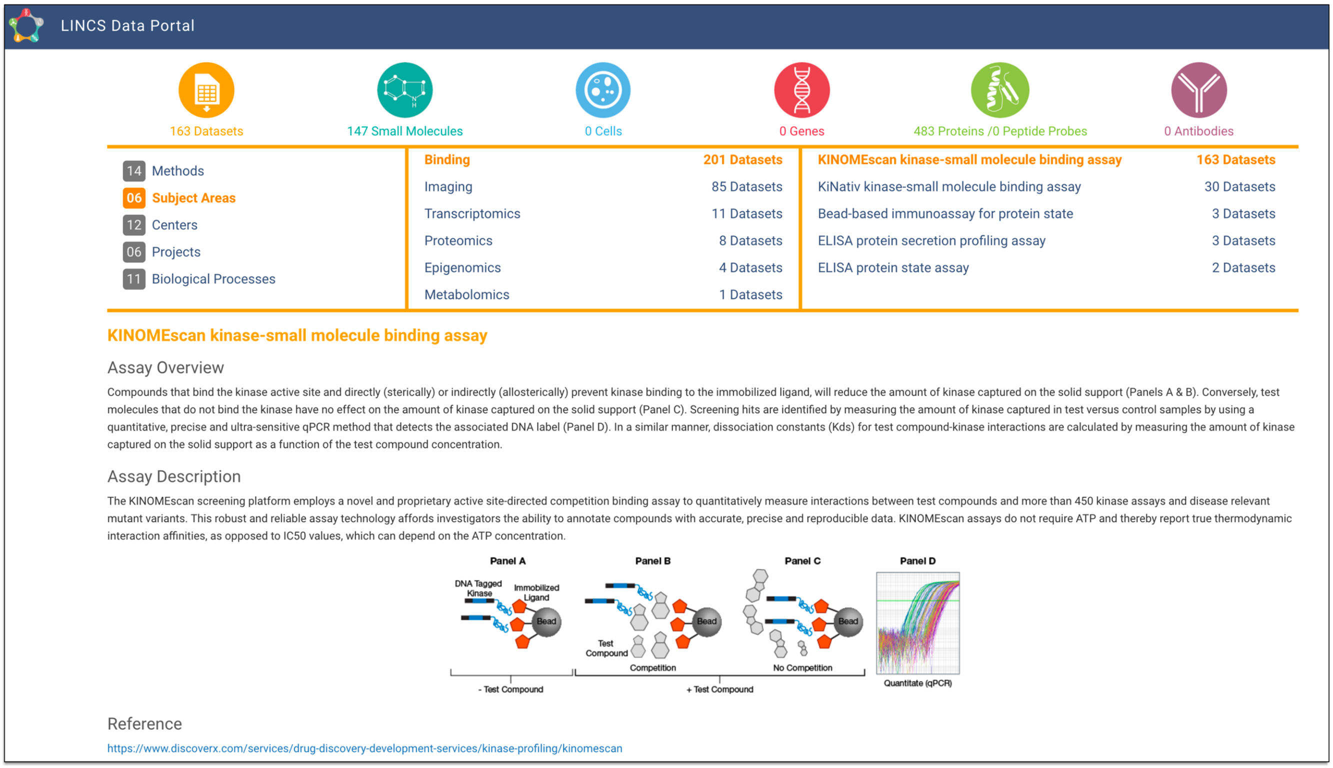
LINCS data standardization, including reference ontologies, enable the mapping, validation, and incorporation of value-added information from various external repositories, including UniProt (16), PubChem Compounds (17), ChEMBL (18), and Cellosaurus (http://web.expasy.org/cellosaurus/). A comprehensive list of these external resources is provided in Supporting Table S3. To automate this integration, extract-transform-load (ETL) pipelines were built for the external data repositories including cleaning, aggregation, and data-type conversions before mapping to the LINCS research objects (e.g. small molecules, cell lines, protein targets, etc.). Examples include pipelines that garner MoA annotations, controlled vocabulary disease terms, aggregated bioactivities (IC_{50}, K_d, etc.), and clinical indications for small molecules and protein targets (see Supporting Table S3). Other pipelines were built to validate consistency in biological annotations such as donor sex, tissue, disease associations, cell markers, culture conditions, and naming for cell lines and other biological entities.

Architecture and data processing

The LDR is the central data repository for the LINCS-DCIC and is the primary data source for the LDP. Data and metadata from DSGCs are transferred and processed by the DCIC via a collection of tools and protocols (e.g. Dataset Submission Tool, Metadata Submission Tool, Application Programing Interfaces (APIs), data downloads, or via a Center Website). The process includes data standardization and annotations from external sources (see MATERIAL & METHODS, External data sources for value-added annotation and validation) via a suite of well-defined automated pipelines (specific to the data types), which have several quality control (QC) inspection and validation points. All data objects and metadata are then registered into the LDR.

The LDR schema is implemented as a relational database combining a standard relational schema with key-value store. The key-value store captures all metadata fields and attributes. This design provides flexibility as the metadata standards evolve, with the ability to ensure data integrity using a relational model for the well-defined connections among entities, datasets, Centers, assays, and projects. The digital objects in the LDR include LINCS datasets, dataset groups, small molecules, cell lines, proteins, nucleic acid reagents, and peptide probes. An Entity Relationship (ER) diagram for the entire LDR is available in Supporting Figure S1.

In order to achieve fluid and intuitive user experience in searching and navigating LINCS data, all data from the LDR are transformed and indexed using Apache Solr, a reliable and scalable search platform. Representational state transfer (REST) APIs have been developed using this Solr index to fetch data for display in the LDP and for public API accessibility (http://lincsportal.ccs.miami.edu/apis/), as illustrated in Figure 1. The LDP is a multi-tier, web-based application intended to function on a wide range of screens and devices. We have used open-source technologies for its three tiers: (i) PostgreSQL and Apache Solr to store data, (ii) Angular Javascript (JS) for presentation and (iii) Java-based servlets deployed on Tomcat as a service layer. For chemical structure search, we use the ChemAxon JChem PostgreSQL Cartridge (JChem Cartridge 2.6, 2017, ChemAxon, (http://www.chemaxon.com). Supporting Figure S2 illustrates a stack diagram of the LDP technologies and data flow.



LINCS Data Portal

163 Datasets | 147 Small Molecules | 0 Cells | 0 Genes | 483 Proteins /0 Peptide Probes | 0 Antibodies

14	Methods
06	**Subject Areas**
12	Centers
06	Projects
11	Biological Processes

Binding	**201 Datasets**
Imaging	85 Datasets
Transcriptomics	11 Datasets
Proteomics	8 Datasets
Epigenomics	4 Datasets
Metabolomics	1 Datasets

KINOMEscan kinase-small molecule binding assay	**163 Datasets**
KiNativ kinase-small molecule binding assay	30 Datasets
Bead-based immunoassay for protein state	3 Datasets
ELISA protein secretion profiling assay	3 Datasets
ELISA protein state assay	2 Datasets

KINOMEscan kinase-small molecule binding assay

Assay Overview

Compounds that bind the kinase active site and directly (sterically) or indirectly (allosterically) prevent kinase binding to the immobilized ligand, will reduce the amount of kinase captured on the solid support (Panels A & B). Conversely, test molecules that do not bind the kinase have no effect on the amount of kinase captured on the solid support (Panel C). Screening hits are identified by measuring the amount of kinase captured in test versus control samples by using a quantitative, precise and ultra-sensitive qPCR method that detects the associated DNA label (Panel D). In a similar manner, dissociation constants (Kds) for test compound-kinase interactions are calculated by measuring the amount of kinase captured on the solid support as a function of the test compound concentration.

Assay Description

The KINOMEscan screening platform employs a novel and proprietary active site-directed competition binding assay to quantitatively measure interactions between test compounds and more than 450 kinase assays and disease relevant mutant variants. This robust and reliable assay technology affords investigators the ability to annotate compounds with accurate, precise and reproducible data. KINOMEscan assays do not require ATP and thereby report true thermodynamic interaction affinities, as opposed to IC50 values, which can depend on the ATP concentration.

Reference

https://www.discoverx.com/services/drug-discovery-development-services/kinase-profiling/kinomescan

Figure 2. The LDP Summary Home Page is the entry point of LDP to interactively explore LINCS content based on several categories (http://lincsportal.ccs.miami.edu/dcic-portal/). Here, a specific selection of the KINOMEscan assay by Subject Area > Binding > KINOMEscan is shown, which contains 163 datasets and 147 small molecules.

RESULTS

Presentation and usability features

The LDP is designed to be broadly applicable and of use to both computational and non-computational scientists. The LDP includes several dedicated modules for exploring the complete collection of LINCS Datasets and the various associated objects, such as small molecules, cells, and other reagents and their metadata and annotations. These LDP modules have a summary page and a catalog browser with search functionality and facets for filtering content. For each category of research object, such as datasets or small molecules, the content is organized into dedicated (landing) pages (see below). The hierarchy of pages to organize and search/explore LINCS content is illustrated in Supporting Figure S3.

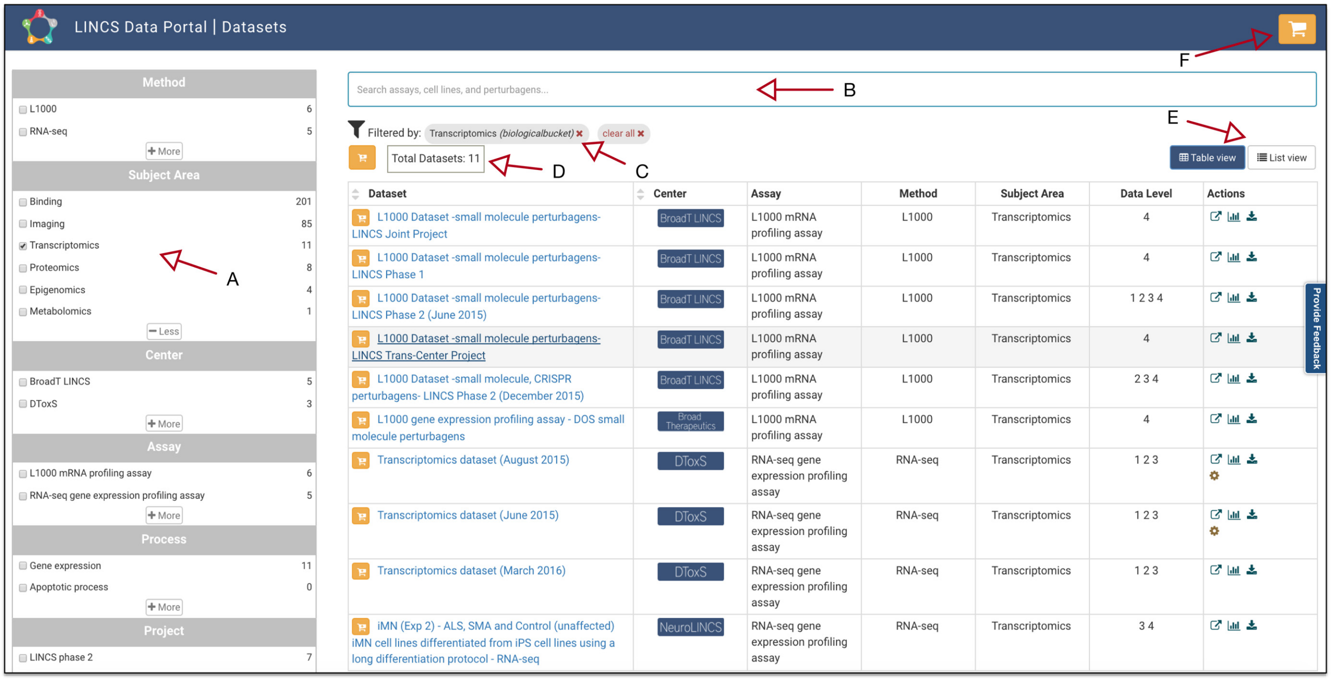
Augmenting the LDP is a REST API (http://lincsportal.ccs.miami.edu/apis/) that supports programmatic access to the search functionality and to all the data contained within the LDR. The API is designed to be self-describing with responses returned in JSON (JavaScript Object Notation) format. The API is of primary interest to computational scientists and developers building novel applications and research pipelines. We anticipate the most common interaction to be via the web interface; hence, here we focus on a description of features implemented in the web interface that enhance usability and exploration of the LINCS content.

Summary home page

The entry point into the LDP is an interactive Summary Home Page (Figure 2). It allows users to get a quick overview of LINCS content based on categories, such as their respective methods (e.g. RNA-seq, ATAC-seq, L1000), biological processes (e.g. gene expression, cell proliferation), and general subject areas (e.g. transcriptomics, proteomics, epigenomics). For example, one can quickly find all binding assays, their corresponding datasets, and the number of tested small molecules (Figure 2). The LDP currently contains more than 350 datasets, almost 42 000 small molecules (including drugs and clinical compounds), and almost 1200 cells. The Summary Home Page links out specific modules including those for datasets, small molecules, or cells, and clicking on each symbol will direct the user to the list of respective objects corresponding to the selections in the Summary page. At the bottom, the home page shows brief descriptions and references for the selected LINCS assays, providing the user with a brief description of their selection.

Search functionality

The LDP provides various options to search, explore, and download the processed LINCS Dataset Packages, small molecules, cells, and other reagents along with their metadata and annotations. Free text search for all content is enhanced by autocomplete suggestions and grouped by various categories. The autocomplete feature is designed to be



LINCS Data Portal | Datasets

Method	
□ L1000	6
□ RNA-seq	5
+ More	

Subject Area	
□ Binding	201
□ Imaging	85
☑ Transcriptomics	11
□ Proteomics	8
□ Epigenomics	4
□ Metabolomics	1
− Less	

Center	
□ BroadT LINCS	5
□ DToxS	3
+ More	

Assay	
□ L1000 mRNA profiling assay	6
□ RNA-seq gene expression profiling assay	5
+ More	

Process	
□ Gene expression	11
□ Apoptotic process	0
+ More	

Project	
□ LINCS phase 2	7

Search assays, cell lines, and perturbagens...

Filtered by: Transcriptomics *(biologicalbucket)* ✖ clear all ✖

Total Datasets: 11

Table view | List view

Dataset	Center	Assay	Method	Subject Area	Data Level	Actions
L1000 Dataset -small molecule perturbagens-LINCS Joint Project	BroadT LINCS	L1000 mRNA profiling assay	L1000	Transcriptomics	4	
L1000 Dataset -small molecule perturbagens-LINCS Phase 1	BroadT LINCS	L1000 mRNA profiling assay	L1000	Transcriptomics	4	
L1000 Dataset -small molecule perturbagens-LINCS Phase 2 (June 2015)	BroadT LINCS	L1000 mRNA profiling assay	L1000	Transcriptomics	1 2 3 4	
L1000 Dataset -small molecule perturbagens-LINCS Trans-Center Project	BroadT LINCS	L1000 mRNA profiling assay	L1000	Transcriptomics	4	
L1000 Dataset -small molecule, CRISPR perturbagens- LINCS Phase 2 (December 2015)	BroadT LINCS	L1000 mRNA profiling assay	L1000	Transcriptomics	2 3 4	
L1000 gene expression profiling assay - DOS small molecule perturbagens	Broad Therapeutics	L1000 mRNA profiling assay	L1000	Transcriptomics	4	
Transcriptomics dataset (August 2015)	DToxS	RNA-seq gene expression profiling assay	RNA-seq	Transcriptomics	1 2 3	
Transcriptomics dataset (June 2015)	DToxS	RNA-seq gene expression profiling assay	RNA-seq	Transcriptomics	1 2 3	
Transcriptomics dataset (March 2016)	DToxS	RNA-seq gene expression profiling assay	RNA-seq	Transcriptomics	1 2 3	
iMN (Exp 2) - ALS, SMA and Control (unaffected) iMN cell lines differentiated from iPS cell lines using a long differentiation protocol - RNA-seq	NeuroLINCS	RNA-seq gene expression profiling assay	RNA-seq	Transcriptomics	3 4	

Figure 3. Overview of the LDP catalog: (**A**) facets for filtering, (**B**) datasets count, (**C**) selected filters, (**D**) search bar for text search, (**E**) toggle between the views, (**F**) shopping cart for dataset bulk download.

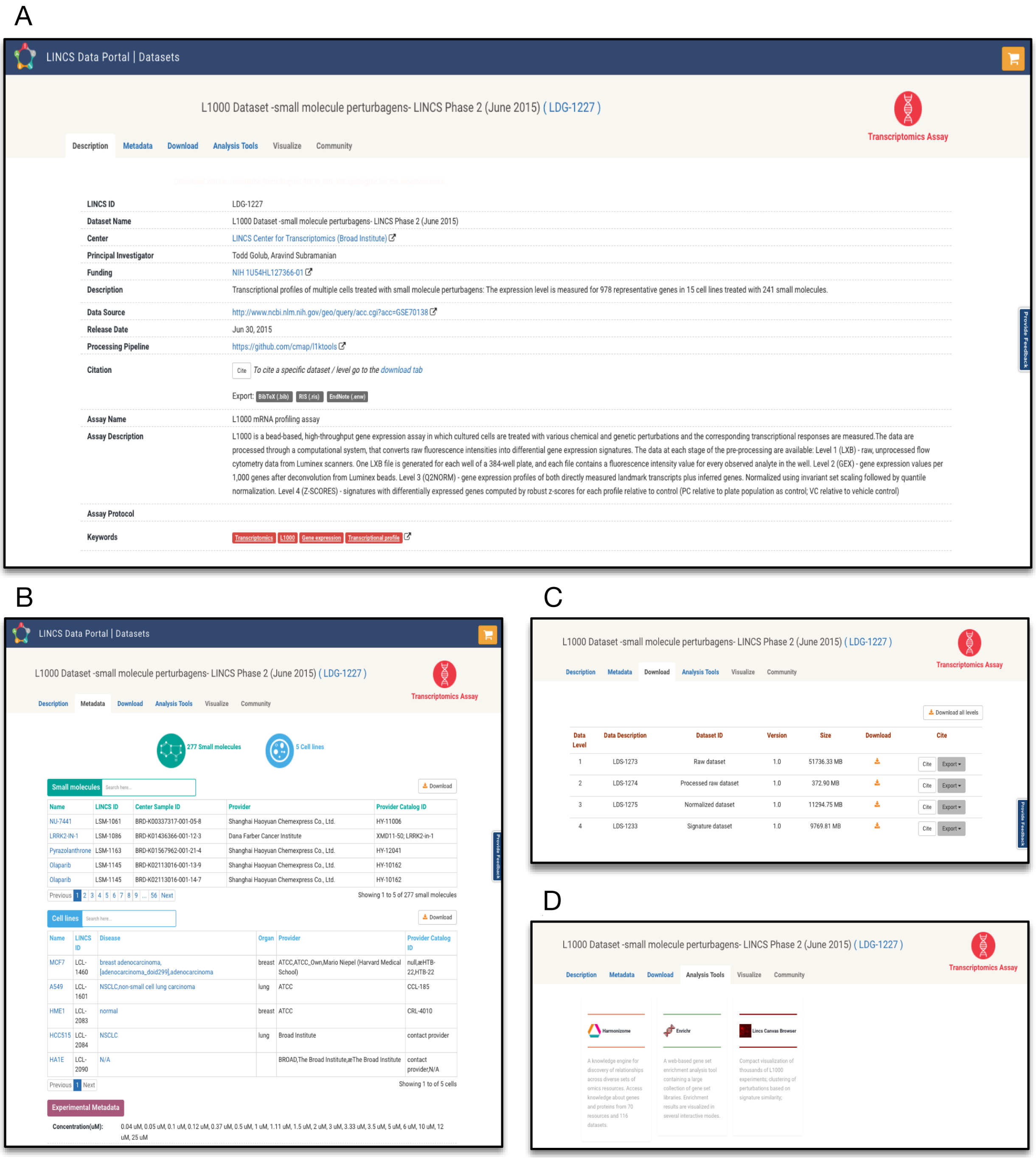
the primary entry point for exploring datasets and reagents. Ontologies, which are used to standardize and annotate LINCS content (see MATERIAL & METHODS, LINCS Content Overview), further expand the search. For example, while typing text, suggestions for drug names, biological targets, mechanisms of action, disease terms, etc., are made. The LDP also provides chemical structure search, enabling users to draw or paste/import .mol files to find small molecules (and associated datasets) by chemical substructure or topological similarity.

Facet filter controls provide simple and intuitive means of filtering search results for datasets and reagents. Facet-based filtering can be used to filter datasets by various categories, such as general study/subject area, assay method, assay name, biological process, center name, etc. For example, by selecting the 'Transcriptomics' area of study, the dataset list is instantly reduced to 11 from the complete list of 350 (Figure 3). The results can be further filtered using other facets or keywords. Both text search and facet filters are enabled by rich metadata annotations and the use of ontologies and controlled vocabularies for identifying the reagents and assays. Selecting a filter will automatically display the matching list of datasets, and multiple filters may be combined using a logical OR within a panel and logical AND in between panels. The count of datasets is dynamically updated and displayed next to each filter. The selected filters and search terms are displayed as tags below the search bar, and can quickly be individually removed or all cleared. Combining filters allows the construction of complex queries. Search results can be viewed in Table and List views, which can be toggled via buttons below the search bar. The tabular view, which is the default, provides a summary of each dataset including the name of the Center that generated the dataset, the assay name, assay method, available data levels, and various other summaries (as action links), such as count of reagents (small molecules, cells), link to the source, visualizations of dataset, and a download. Clicking on the dataset links to the Dataset Landing Page.

Dataset landing pages

Among the central features of LDP are the Dataset Landing Pages. Because LINCS signatures are generated via several stages (data levels) starting from the raw data, the Dataset Landing Pages refer to a dataset group that includes all data levels derived from an experiment. LINCS data levels typically range from level 1 to level 4, from raw instrument-produced data points to derived cellular signatures (Table 1). Each such LINCS dataset group is assigned a landing page by which all relevant information to the corresponding data are presented. The format of the landing pages is uniform across all LINCS dataset groups and currently consists of four sections (tabs): Description, Metadata, Download, and Analysis Tools (Figure 4). The Description tab provides important details describing how and by whom the dataset was generated and processed including a description and protocol of the assay, relevant publications, and standardized keywords. The Metadata tab contains searchable and downloadable information regarding the research objects associated with the dataset, such as small molecules, proteins and cells. Links to relevant external resources are also available in this section.

To enable the integration of diverse LINCS data and to provide a common structure of datasets produced by different Centers using diverse technologies and data processing



L1000 Dataset -small molecule perturbagens- LINCS Phase 2 (June 2015) (LDG-1227)

Download will be unavailable from August 4th to 8th. We apologize for the inconvenience.

LINCS ID	LDG-1227
Dataset Name	L1000 Dataset -small molecule perturbagens- LINCS Phase 2 (June 2015)
Center	LINCS Center for Transcriptomics (Broad Institute)
Principal Investigator	Todd Golub, Aravind Subramanian
Funding	NIH 1U54HL127366-01
Description	Transcriptional profiles of multiple cells treated with small molecule perturbagens: The expression level is measured for 978 representative genes in 15 cell lines treated with 241 small molecules.
Data Source	http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE70138
Release Date	Jun 30, 2015
Processing Pipeline	https://github.com/cmap/l1ktools
Citation	Cite *To cite a specific dataset / level go to the download tab* Export: BibTeX (.bib) RIS (.ris) EndNote (.enw)
Assay Name	L1000 mRNA profiling assay
Assay Description	L1000 is a bead-based, high-throughput gene expression assay in which cultured cells are treated with various chemical and genetic perturbations and the corresponding transcriptional responses are measured.The data are processed through a computational system, that converts raw fluorescence intensities into differential gene expression signatures. The data at each stage of the pre-processing are available: Level 1 (LXB) - raw, unprocessed flow cytometry data from Luminex scanners. One LXB file is generated for each well of a 384-well plate, and each file contains a fluorescence intensity value for every observed analyte in the well. Level 2 (GEX) - gene expression values per 1,000 genes after deconvolution from Luminex beads. Level 3 (Q2NORM) - gene expression profiles of both directly measured landmark transcripts plus inferred genes. Normalized using invariant set scaling followed by quantile normalization. Level 4 (Z-SCORES) - signatures with differentially expressed genes computed by robust z-scores for each profile relative to control (PC relative to plate population as control; VC relative to vehicle control)
Assay Protocol	
Keywords	Transcriptomics L1000 Gene expression Transcriptional profile

277 Small molecules   5 Cell lines

Small molecules Search here... Download

Name	LINCS ID	Center Sample ID	Provider	Provider Catalog ID
NU-7441	LSM-1061	BRD-K00337317-001-05-8	Shanghai Haoyuan Chemexpress Co., Ltd.	HY-11006
LRRK2-IN-1	LSM-1086	BRD-K01436366-001-12-3	Dana Farber Cancer Institute	XMD11-50; LRRK2-in-1
Pyrazolanthrone	LSM-1163	BRD-K01567962-001-21-4	Shanghai Haoyuan Chemexpress Co., Ltd.	HY-12041
Olaparib	LSM-1145	BRD-K02113016-001-13-9	Shanghai Haoyuan Chemexpress Co., Ltd.	HY-10162
Olaparib	LSM-1145	BRD-K02113016-001-14-7	Shanghai Haoyuan Chemexpress Co., Ltd.	HY-10162

Previous 1 2 3 4 5 6 7 8 9 ... 56 Next   Showing 1 to 5 of 277 small molecules

Cell lines Search here... Download

Name	LINCS ID	Disease	Organ	Provider	Provider Catalog ID
MCF7	LCL-1460	breast adenocarcinoma, [adenocarcinoma_doid299],adenocarcinoma	breast	ATCC,ATCC_Own,Mario Niepel (Harvard Medical School)	null,æHTB-22,HTB-22
A549	LCL-1601	NSCLC,non-small cell lung carcinoma	lung	ATCC	CCL-185
HME1	LCL-2083	normal	breast	ATCC	CRL-4010
HCC515	LCL-2084	NSCLC	lung	Broad Institute	contact provider
HA1E	LCL-2090	N/A		BROAD,The Broad Institute,æThe Broad Institute	contact provider,N/A

Previous 1 Next   Showing 1 to of 5 cells

Experimental Metadata

Concentration(uM): 0.04 uM, 0.05 uM, 0.1 uM, 0.12 uM, 0.37 uM, 0.5 uM, 1 uM, 1.11 uM, 1.5 uM, 2 uM, 3 uM, 3.33 uM, 3.5 uM, 5 uM, 6 uM, 10 uM, 12 uM, 25 uM

Download all levels

Data Level	Data Description	Dataset ID	Version	Size	Download	Cite
1	LDS-1273	Raw dataset	1.0	51736.33 MB	⬇	Cite Export ▾
2	LDS-1274	Processed raw dataset	1.0	372.90 MB	⬇	Cite Export ▾
3	LDS-1275	Normalized dataset	1.0	11294.75 MB	⬇	Cite Export ▾
4	LDS-1233	Signature dataset	1.0	9769.81 MB	⬇	Cite Export ▾

Harmonizome: A knowledge engine for discovery of relationships across diverse sets of omics resources. Access knowledge about genes and proteins from 70 resources and 116 datasets.

Enrichr: A web-based gene set enrichment analysis tool containing a large collection of gene set libraries. Enrichment results are visualized in several interactive modes.

Lincs Canvas Browser: Compact visualization of thousands of L1000 experiments; clustering of perturbations based on signature similarity;

Figure 4. LINCS Dataset Landing Page: (**A**) Dataset Description tab, (**B**) Associated Metadata tab, (**C**) Download tab, (**D**) Analysis tools tab. The screenshots correspond to dataset LDS-1233 (http://lincsportal.ccs.miami.edu/datasets/#/view/LDS-1233).

Table 1. LINCS Data level definitions, descriptions and examples

Data Level	Data Type	Description	Examples
1	Raw	Non-normalized, low-level, single-sample data obtained from assay instrumentation	RNA-Seq FASTQ, L1000 LXB
2	Processed	Raw data converted to a basic usable format through data processing, including presence or absence of specific molecular abnormalities	KiNativ binding profile, KINOMEScan relative inhibition
3	Normalized	Normalized, per sample data	L1000 Q2NORM, RNA-Seq raw counts
4	Signature	Quantified association across samples based on two or more characteristics	RNA-Seq Differential expression profile, L1000 GCTX file

pipelines, the data are organized into standardized dataset packages. A dataset, in this context, refers to one specific data level (in contrast, the group includes the corresponding datasets for all levels). Each dataset package contains: (i) a readme file with all the relevant annotations regarding the dataset, (ii) the original data files as produced by the DSGC, (iii) the standardized metadata of all the reagents used in the dataset, with one file per category (e.g. small molecule, cell, protein) and (iv) mapping files that associate the metadata and data files. These files are created by secondary data processing, standardization, annotation, and curation (see MATERIAL & METHODS, Architecture and data processing). Because metadata are all standardized with unique identifiers, different datasets can easily be mapped and integrated. The LINCS data packages are available to download via the Download tab. Citations for the different dataset levels are also made available in the Download tab. Finally, the Analysis Tools tab includes a list of the computational tools that allow the exploration and analysis of the dataset as well as links to pre-generated reports containing the results of analyses that have been performed on the dataset.

To cite LINCS data, we created collections of LINCS digital research objects (DROs) in the Minimal Information Required in the Annotation of Models (MIRIAM) Registry that generate unique, perennial, and location-independent identifiers (http://identifiers.org/) (19). Such collections include data-level specific dataset packages, dataset groups (all data levels), small molecules, and cells. The identifiers.org service, which is built upon the information stored in MIRIAM, provides directly resolvable identifiers in the form of Uniform Resource Locators (URLs). This system provides a globally unique identification scheme to which any external resource can point and a resolving system that gives the owner/creator of the resource collection flexibility to update the resolving URL without changing the global identifiers. These dataset and dataset group identifiers are the central component of the LINCS dataset citation record, which further includes the authors, title, year, repository, resource type, and version. These citation records have been incorporated into the LINCS Data Portal and can be downloaded in several formats, making it easy to cite a specific LINCS dataset or dataset group. All LINCS datasets are indexed in bioCADDIE DataMed (https://datamed.org/) and OmicsDI (http://www.omicsdi.org/), which link back to the dataset landing pages via their global IDs.

Dataset download and shopping cart

LDP supports individual dataset download from the Dataset Landing Page and also bulk download using the shopping cart that allows the addition of selected datasets directly from the catalog page. Bulk download is particularly useful to access related datasets, such as those generated by the same assay. The shopping cart downloads the highest dataset level available, which is what typical end users want, and also contains a Python script that facilitates merging the various files into a single file based on the assays and data format.

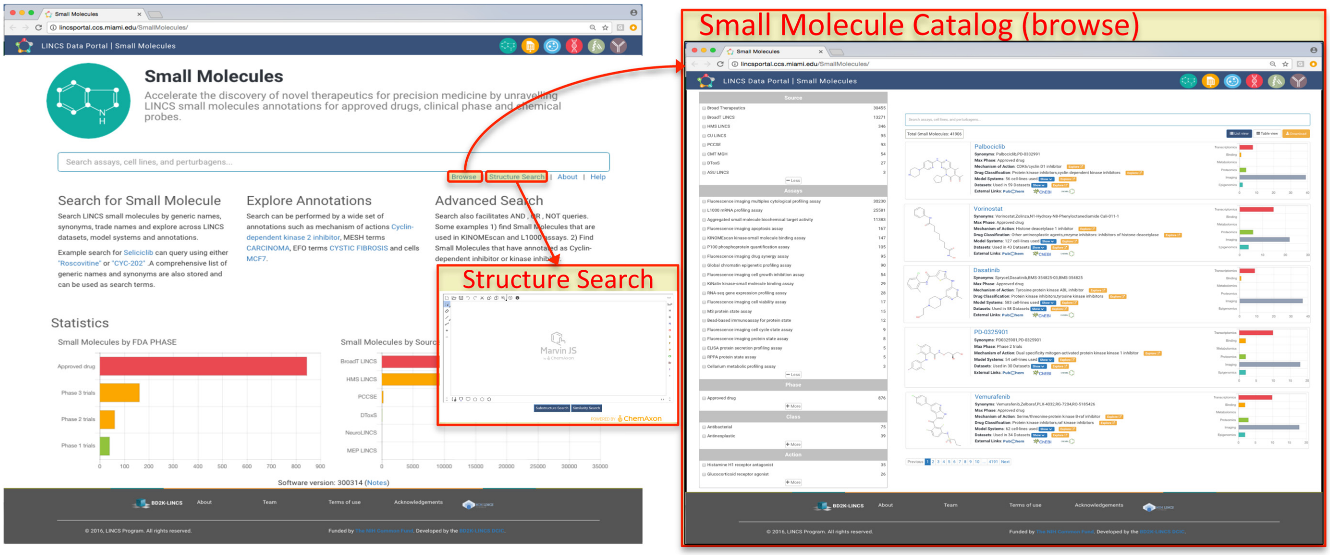
LDP small molecule module

The Small Molecule Landing Page (http://lincsportal.ccs.miami.edu/SmallMolecules/) provides an overview page with statistics displayed by FDA clinical phase and source, a prominent search window, and links to the catalog (browse) and chemical structure search (Figure 5). Before registration into the LDP, LINCS small molecules were standardized following business rules at the DCIC so that different variations of the same compound (such as salt forms, tautomers, and ionization states), but not different chemical structures (e.g. stereoisomers or geometric E/Z isomers), receive the same unique ID to enable data integration. Standardized small molecules are currently cross-referenced to PubChem Compounds (17) (via CID), ChEMBL (18), ChEBI (13), and UniChem (https://www.ebi.ac.uk/unichem/), which provides cross-reference to 37 additional public databases. In addition, small molecules were extensively annotated and curated with characteristics including FDA approval status, clinical trial phases, mechanisms of action, biochemical targets, clinical disease indications, and many computed drug-relevant properties. The small molecule pages are integrated with the datasets so that all datasets in which a drug was tested are immediately available and cross-linked. The database also keeps track of the original specific samples tested at the DSGCs. Small molecules can be searched by (drug) name, MOA, biological target, clinical disease indication, and by free text and chemical structure. The small molecule catalog allows browsing and filtering via various facets, including MOA, clinical phase, and pharmacological class. Similar to datasets, each small molecule has a landing page with a unique URL (which resolves globally via identifiers.org). Each small molecule landing page consists of several sections including Description with basic information (name, synonyms, ID, cross-references, various descriptors), associated LINCS and external Datasets (with an overview by areas of study and cell types), and Curated Data including biological targets and diseases. Via the Description tab, a user can also search for structurally similar compounds.

Other modes of data access

APIs. To accommodate users who seek information about a single dataset, as well as computational biologists who can programmatically operate on the data, the LDP includes advanced search functionality, and serves the data in JSON format through an API (http://lincsportal.ccs.miami.edu/apis/).

R Package. In addition to the REST API, R users can also programmatically access the LDP through the R package LINCSDataPortal (https://github.com/schurerlab/LINCSDataPortal/). This package provides easy access to all the data and metadata that are stored in the LDP. More specifically, LINCS data packages can be retrieved using a variety of search terms for entities of interest (e.g. small molecule, protein, gene, cell line) and downloaded for any of the available data levels. Moreover, all metadata associated with any reagent used in LINCS experiments can also be retrieved.



Small Molecules

Accelerate the discovery of novel therapeutics for precision medicine by unravelling LINCS small molecules annotations for approved drugs, clinical phase and chemical probes.

Search for Small Molecule

Search LINCS small molecules by generic names, synonyms, trade names and explore across LINCS datasets, model systems and annotations.

Example search for Seliciclib can query using either "Roscovitine" or "CYC-202" .A comprehensive list of generic names and synonyms are also stored and can be used as search terms.

Explore Annotations

Search can be performed by a wide set of annotations such as mechanism of actions Cyclin-dependent kinase 2 inhibitor, MESH terms CARCINOMA, EFO terms CYSTIC FIBROSIS and cells MCF7.

Advanced Search

Search also facilitates AND , OR , NOT queries. Some examples 1) find Small Molecules that are used in KINOMEscan and L1000 assays. 2) Find Small Molecules that have annotated as Cyclin-dependent inhibitor or kinase inhibitor.

Statistics

Small Molecules by FDA PHASE: Approved drug; Phase 3 trials; Phase 2 trials; Phase 1 trials (0–900)

Small Molecules by Source: BroadT LINCS; HMS LINCS; PCCSE; DToxS; NeuroLINCS; MEP LINCS (0–35000)

Software version: 300314 (Notes)

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Source	
Broad Therapeutics	30455
BroadT LINCS	13271
HMS LINCS	346
CU LINCS	95
PCCSE	93
CMT MGH	54
DToxS	27
ASU LINCS	3

Assays	
Fluorescence imaging multiplex cytological profiling assay	30230
L1000 mRNA profiling assay	25581
Aggregated small molecule biochemical target activity	11383
Fluorescence imaging apoptosis assay	167
KINOMEscan kinase-small molecule binding assay	147
P100 phosphoprotein quantification assay	105
Fluorescence imaging drug synergy assay	95
Global chromatin epigenetic profiling assay	90
Fluorescence imaging cell growth inhibition assay	54
KiNativ kinase-small molecule binding assay	29
RNA-seq gene expression profiling assay	28
Fluorescence imaging cell viability assay	17
MS protein state assay	15
Bead-based immunoassay for protein state	12
Fluorescence imaging cell cycle state assay	9
Fluorescence imaging protein state assay	8
ELISA protein secretion profiling assay	5
RPPA protein state assay	5
Cellarium metabolic profiling assay	3

Phase	
Approved drug	876

Class	
Antibacterial	75
Antineoplastic	39

Action	
Histamine H1 receptor antagonist	35
Glucocorticoid receptor agonist	26

Total Small Molecules: 41906

Palbociclib
Synonyms: Palbociclib,PD-0332991
Max Phase: Approved drug
Mechanism of Action: CDK6/cyclin D1 inhibitor
Drug Classification: Protein kinase inhibitors,cyclin dependent kinase inhibitors
Model Systems: 56 cell-lines used
Datasets: Used in 59 Datasets
External Links: PubChem ChEBI

Vorinostat
Synonyms: Vorinostat,Zolinza,N1-Hydroxy-N8-Phenyloctanediamide Cali-011-1
Max Phase: Approved drug
Mechanism of Action: Histone deacetylase 1 inhibitor
Drug Classification: Other antineoplastic agents,enzyme inhibitors: inhibitors of histone deacetylase
Model Systems: 127 cell-lines used
Datasets: Used in 43 Datasets
External Links: PubChem ChEBI

Dasatinib
Synonyms: Sprycel,Dasatinib,BMS-354825-03,BMS-354825
Max Phase: Approved drug
Mechanism of Action: Tyrosine-protein kinase ABL inhibitor
Drug Classification: Protein kinase inhibitors,tyrosine kinase inhibitors
Model Systems: 583 cell-lines used
Datasets: Used in 58 Datasets
External Links: PubChem ChEBI

PD-0325901
Synonyms: PD0325901,PD-0325901
Max Phase: Phase 2 trials
Mechanism of Action: Dual specificity mitogen-activated protein kinase kinase 1 inhibitor
Model Systems: 54 cell-lines used
Datasets: Used in 30 Datasets
External Links: PubChem ChEBI

Vemurafenib
Synonyms: Vemurafenib,Zelboraf,PLX-4032,RG-7204,RO-5185426
Max Phase: Approved drug
Mechanism of Action: Serine/threonine-protein kinase B-raf inhibitor
Drug Classification: Protein kinase inhibitors,raf kinase inhibitors
Model Systems: 62 cell-lines used
Datasets: Used in 34 Datasets
External Links: PubChem ChEBI

Figure 5. Left: Small Molecule Landing Page (http://lincsportal.ccs.miami.edu/SmallMolecules/) with statistics displayed by FDA clinical phase and source, a prominent search window, and links to the catalog (browse) and chemical structure search. Right: Small Molecule Catalog with chemical structures, names, and various annotations and links, statistics to the right, filter facets to the left, search window at the top.

DISCUSSION

The LDP organizes LINCS content by datasets and metadata categories via different modules that feature catalog and landing pages (see Supporting Figure S3). The LDP provides extensive search functionality, flexible browsing and filtering, and data download. Citation records for LINCS datasets can easily be created, leveraging unique global identifiers. In building the LDP and the underlying infrastructure and processes, particular emphasis has been placed on data standards including the use of ontologies, extensive curated annotations of LINCS content, globally valid identifiers, and easily accessible APIs. These efforts have been guided by the FAIR principles to make LINCS data Findable, Accessible, Interoperable, and Reusable (10). For example, LINCS data are already indexed in bioCADDIE DataMed (https://datamed.org/) and OmicsDI (http://www.omicsdi.org).

Via its current functionality, the LDP enables a wide range of use cases. For example, if the user wishes to discover all LINCS registered compounds that are indicated to treat glioblastoma (GBM), they can query the Small Molecule Application for the disease by the Medical Subject Heading (MeSH) term or Experimental Factor Ontology (EFO) annotations; this search returns 26 compounds. These compounds can be filtered by protein kinase inhibitors (via the pharmacological class facet), reducing the list to 11 compounds. Search results can be additionally filtered by approved drug (clinical Phase facet), leaving 9 drugs. The corresponding datasets for any of these compounds, including the complete kinase profile (KINOMEscan) or the transcriptional profile in various cells, can be downloaded. To continue this exploration, as epidermal growth factor receptor (EGFR) could be a relevant target in GBM, one can further filter the list by MoA target through the facet or a text search that will suggest EGFR as a target. That leaves one compound, afatinib. The available datasets and annotations are easily accessible through the compound's landing page. Any identified dataset can easily be cited via the Cite button on the Dataset Landing Page, and the citation can be downloaded in several formats. In the described manner, LDP functionality can be utilized in efforts for drug repositioning. As another approved drug studied for GBM, but not a kinase inhibitor, doxorubicin (LSM-4062) can easily be identified using a similar workflow. If a user is interested in related heterocycles with trapped quinones, one can search by chemical structure similarity directly in the doxorubicin page. The 13 compounds that are retrieved at 95% similarity include three additional approved drugs (epirubicin, daunorubicin, idarubicin), which are all also DNA topoisomerase inhibitors. These compounds could be purchased from commercial sources and screened for this activity, if desired. For better understanding, the described workflows are illustrated in Supplementary Figures S4 to S10.

The LDP is the primary access point to all data produced in the LINCS project, including the Pilot Phase and the current Phase 2. As described above, the LDP makes it easy for end users to browse, query, and filter LINCS data based on numerous categories and curated annotations, which were rigorously standardized to enable an integrated view across all LINCS content. The LDP also enables integration with external resources via added links, curated mappings, and external IDs. Content from many resources has been incorporated into the LDP. In addition to the Web-based user interface, LINCS data can easily be accessed via APIs and the R package. Global, perennial identifiers for LINCS datasets, as well as the most important related research objects and their mapping and description by community standard ontologies, are also critical components to ensure the persistence of LINCS data in the future. As the LINCS project progresses, many new released datasets will appear in the LDP, and we will add new features, including user-specific queries, lists, and settings, and further improve the annotations of LINCS content and integration with external data sources. The LDP makes LINCS data widely accessible thus contributing to the success of the LINCS program as a valuable scientific resource.

AVAILABILITY

The LINCS Data Portal (LDP) is freely available without restrictions at http://lincsportal.ccs.miami.edu/dcic-portal/.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR online.

ACKNOWLEDGEMENTS

We thank the LINCS Consortium for feedback regarding LDP end user functionality and for reviewing and approving the representation of the hosted datasets and metadata in the LDP. We acknowledge resources from the Center for Computational Science (University of Miami, FL) for maintaining and administering the production environment and server for the LINCS Data Portal and related infrastructure. We thank ChemAxon Inc. for providing free academic research licenses, which were used in curating and annotating chemical structures, and a license to use the JChem PostgreSQL Cartridge that enables LDP chemical structure search.

FUNDING

National Heart, Lung, and Blood Institute through funds provided by the National Institutes of Health Translational Research [U54HL127624]; Library of Integrated Network-based Cellular Signatures (LINCS) Program (http://www.lincsproject.org/); National Institutes of Health Translational Research Big Data to Knowledge (BD2K) initiative (http://www.bd2k.nih.gov/). Funding for open access charge: NIH [U54HL127624].

Conflict of interest statement. None declared.

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