

HHS Public Access

Curr Protoc Bioinformatics. Author manuscript; available in PMC 2021 January 21.

Published in final edited form as:

Author manuscript

Curr Protoc Bioinformatics. 2020 March ; 69(1): e92. doi:10.1002/cpbi.92.

How to Illuminate the Druggable Genome using Pharos

Timothy Sheils¹, Stephen L. Mathias², Vishal B. Siramshetty¹, Giovanni Bocci², Cristian G. Bologa², Jeremy J. Yang², Anna Waller³, Noel Southall¹, Dac-Trung Nguyen¹, Tudor I. Oprea^{2,4,5,6,*}

¹National Center for Advancing Translational Sciences, Rockville, MD, USA

²Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM, USA

³Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM, USA

⁴UNM Comprehensive Cancer Center, Albuquerque, NM, USA

⁵Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

⁶Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Abstract

Pharos is an integrated web-based informatics platform for analysis of data aggregated by the Illuminating the Druggable Genome (IDG) Knowledge Management Center, an NIH Common Fund initiative. The current version of Pharos (as of October 2019) spans 20,244 proteins in the human proteome, 19,880 disease and phenotype associations and 226,829 ChEMBL compounds. This resource not only collates and analyzes data from over 60 high quality resources to generate these types, it uses text indexing to find less apparent connections between targets and has recently begun to collaborate with institutions that generate data and resources. Proteins are ranked according to a knowledge-based classification system, which can help researchers to identify lesser studied "dark" targets that could be potentially further illuminated. This is an important process for both drug discovery and target validation, as more knowledge can accelerate target identification, and previously understudied proteins can serve as novel targets in drug discovery. Two basic protocols are discussed that illustrate the various levels of detail available for targets, and several methods of finding targets of interest. An Alternate Protocol is used to illustrate the difference of available knowledge between lesser and well-studied targets.

Keywords

Bioinformatics; dark genome; disease; drug discovery; drug targets; phenotype; proteins; target validation

^{*}Corresponding author, toprea@salud.unm.edu.

Introduction

Since its introduction in early 2017, Pharos (Nguyen et al., 2017) has expanded in the quantity and type of datasets aggregated, while continually adding visualizations and widgets designed to aid in the discovery and illumination of target knowledge. Pharos can be used to browse and search the human proteome and analyze lists of proteins, allowing for lateral filtering and comparisons via multiple target parameters. This information can be used to drive research into further illuminating putative drug target proteins that would otherwise remain understudied.

A frequent metaphor used in drug discovery is to "not only search under the lamp post" (Oprea, Jan, et al., 2018), meaning that more data, information and knowledge may be accessible outside of the realm of common knowledge. Pharos shows how much common knowledge is available and can help bring the search away from well-studied targets, and further from the well-studied lamppost.

All targets in Pharos are categorized according to their "Target development level" (TDL), a knowledge-based classification for human proteins (Oprea, Bologa, et al., 2018) that can be used to explore the dark genome (Oprea, 2019). In brief, **Tclin** are proteins via which approved drugs act (i.e., mode-of-action drug targets); **Tchem** are proteins known to bind small molecules with high potency; **Tbio** are proteins with well-studied biology, having a fractional publication count (Pletscher-Frankild, Palleja, Tsafou, Binder, & Jensen, 2015) above 5; and **Tdark** are understudied proteins that do not meet criteria for the above 3 categories, respectively. See Background Information for additional details.

Basic Protocol 1 describes a basic target search, as well as an explanation of several key elements of a target details page, ending with filtering targets related to the original search. *Alternate Protocol 1* follows the same steps as *Basic Protocol 1*, but is focused on a lesser studied target, and discusses some of the differences in detail pages between target knowledge levels. *Basic Protocol 2* shows how the entire human proteome can be filtered to zoom in on 5 GPCR (G-protein coupled receptor) proteins annotated by GWAS (Genomewide association studies) as related to breast cancer, that are expressed in female tissues. This second query illustrates the concept of *serendipitous browsing*, whereby Pharos can be explored through areas of interest rather than specific targets, an exploration that can lead to interesting results.

Basic Protocol 1 - search for a target and view details

The Pharos web interface is available at https://pharos.nih.gov. The main landing page is focused on the Pharos database search, with subdomains that navigate to pages to browse and filter targets, ligands and diseases.

Necessary Resources

Hardware

Computer with Internet connection

Software •

Up-to-date Web browser such as Chrome (recommended), Firefox, or Safari.

Search for a target

The search function of Pharos uses an autocomplete service to make suggestions as the user types. Several fields are available to provide suggestions: UniProt Gene Symbol, UniProt Name, Target Name, Disease, or OMIM term (Apweiler et al., 2004; Hamosh et al., 2002).

1. Navigate to https://pharos.nih.gov. Click on the search bar and enter "CDK13" as a query term. Selecting a value from the dropdown will populate the search field with that text, but it is sufficient to enter "CDK13" and press enter or click the magnifying glass icon on the right of the search bar (Fig 1).

View a Search Results Page

The query results page lists all proteins associated with the searched term, as well as metadata available. This may return a larger list than may be anticipated due to the addition of targets found via text mining algorithms. This results list is further filterable by the use of lists of checkboxes on the left side of the screen, or by sections of the donut chart visible near the top. If applicable, a list of associated ligands, as well as a list of associated diseases, are shown below the pageable targets list. Diseases are searched by name, not by target relationships.

2. Scroll down the page to view a list of 19 matched targets, ligands and diseases.

Note: In this example ("CDK13"), no disease results are returned.

Analyze a Tchem target (CDK13)

This query was for a fairly well studied target in order to illustrate some of the core details available. The higher a target is ranked according to TDL, the more information is available on the protein details page.

3. A specific target search should return a table with CDK13 as the first entry. Click on the target name or gene to navigate to the details page. Figure 5 shows the initial target details page, with a target identifier header, gene description (if available), and a breadcrumb of links that subdivide the Drug Target Ontology (Lin et al., 2017) and illustrate the various ontology level that the target belongs to.

View the Protein Knowledge Summary

4. Scroll down the page to view the Protein Summary panel. This panel (Fig. 6) contains several different target identifiers, with links (where available) to the original resource. Also available is an illumination graph and corresponding knowledge table, which collectively illustrate the amount of aggregated knowledge available for a target, and highlights areas with the most knowledge.

5. Click on the illumination graph to open up a larger view of the radar chart (Fig. 7), and hover over different apexes to view the relative (0 to 1) value of each parameter, as well as the data sources used to generate this value.

View the Development Level Summary

6. Scroll down or click on the "IDG Development Level Summary" section on the left side. TDL designations are summarized in the IDG Development Level Summary panel, which is individually displayed for each protein. In this case, the "Tchem" TDL indicates that small molecules are known to modulate this protein (Fig. 8). TDLs range from Tdark, for understudied proteins, to Tclin, which denotes that approved drugs exist for this target (Oprea, Bologa, et al., 2018).

View IDG Generated Resources

 Scroll down or click on the "IDG Generated Resources" section on the left side. A pageable list of reagents and datasets generated by IDG consortium members is shown.

Note: Click on the header to navigate to a dataset metadata collection page, the bottom link of the panel redirects to a vendor page for the physical resource, if available.

View Active Ligands

8.

Scroll down the page or click on the "Active Ligands" section on the left side. Here is a pageable list of all active ligands associated with a target. For targets with approved drugs, this section will be preceded by a similar Approved Drugs section. Chemical structures are shown, as well as brief target information and the activity level discovered for the target-ligand relationship.

Note: Click on the ligand card to open up a new page with more detailed ligand information, as well as other targets this ligand is active on.

View Disease Associations

9. Scroll down or click on the "Disease Associations" section on the left side. Users can explore a pageable list of diseases associated with this target. Click on a disease name to display the data source used to generate this association, as well as the available supporting evidence and confidence values.

View Publication Information

10. Scroll down or click on the "Publication Information" section on the left side. This panel is composed of 3 tabs. The first tab shows several line charts that display publication trends from various services and measurement matrices. Hover over a point to get a more specific value for the year (Fig. 12). **11.** Click on the second tab of the Publication information section to view a list of text mined references in which the search target is mentioned, and lastly, click on the third tab to view a list of GeneRIF annotations.

Find related targets

- **12.** Scroll to the bottom of the page or click the "Related Targets" section of the left side. The final section of the detail page provides links to view a list of targets that share a common property.
- **13.** Click on the "cyclin-dependent protein serine-threonine kinase activity" link in the "GO Function" column as shown in Figure 13. The results are shown in Figure 14: a list of 30 targets that share the same GO Function. A common use of these lists is to find similar targets that may be less studied but may be similar enough to aid in drug discovery.
- 14. Click on the header of the "Knowledge Availability" column right above the first small illumination chart (Fig. 15). The table is now sorted in ascending order of knowledge availability. This tends to start with darker targets, which may offer unique research opportunities.

Note: Knowledge Availability is not closely linked to target development level, meaning some "dark" targets may have a higher knowledge availability score that a target with an approved drug.

15. Alternatively, click on the "Tdark" value in the "Refine by Category" panel, under the "Development Level" subheading (Fig 16). This filters the 30 targets listed down to a single dark target.

16.

Alternate Protocol 1 - search for dark target and view details

Although all targets listed in Pharos are discoverable using the above steps, the details view may be sparser if the query is a dark target. The only Tdark protein related to CDK13 (CDKL4) is used here to highlight a few differences in available sections and knowledge between dark and better studies targets. Compared to CDK13, a well-studied target, there are no approved drugs or active ligands associated with this target, therefore, those panels are absent.

Necessary Resources: See Basic Protocol 1

1. Following the example outlined in *Basic Protocol 1*, click the CDKL4 target from the Related Targets menu on the left. Alternatively, follow *Basic Protocol 1*, and use "CDKL4" as the search query. Figure 17 shows the Illumination graph and knowledge as in the previous example. However, this illumination chart displays several deficiencies in knowledge, which could be directions to focus research on.

- Scroll down or click on the "IDG Development Level Summary" section on the left side, which provides an overview of the TDL progression for CDKL4 (Fig. 18).
- **3.** Scroll down or click on the "Publication Details" section on the left side, Compared to *Basic Protocol 1* and CDK13, CDKL4 has minimal publication information available.

Basic Protocol 2 - Filter a target list to get refined results

While the most straightforward way to find information about a target is to use the search function, Pharos also provides an interface to browse and search all targets in the human genome. Similar to an e-commerce site, this allows for serendipitous browsing, where the user may be able to discover lesser known targets of significance to a topic of interest. This example will focus on GPCRs in cancer, which are rarely targeted in cancer treatments (Insel et al., 2018; Wu et al., 2019).

Necessary Resources

Hardware

• Computer with Internet connection

Software

• Up-to-date Web browser such as Chrome (recommended), Firefox, or Safari.

Browse and filter all targets

- 1. Navigate to https://pharos.nih.gov. Click on the Targets link on the main navigation bar (Fig. 20). A main page to browse and filter targets will be shown (Fig. 21).
- Pharos displays several common filters, but users are not limited to these. Click on the "See All Categories" button to view an expanded range of filters. Figure 21 shows the main target browse page, and Figure 22 shows the expanded filter category panel.
- 3. Enter "GWAS" as a search term in order to refine the categories.
- 4. Select "Breast Cancer" from the list of possible GWAS traits (Fig 23).
- Click the "All Categories" button under the "Refine Categories" header to minimize the category list. The initial list of 20244 targets has been reduced to 492 targets (Fig. 24).
- 6. This list can be further refined to filter out GPCRs, the target family of interest. Scroll down the filter panel on the side. Select the "GPCR" value from the "Target Family" panel. The list is reduced from 492 targets to just 6 (Fig. 25).
- 7. While a list with 6 targets is manageable, it may be further refined. This step will use a different filter interface. Select the Tissue button underneath the donut chart above the target list, then click the wedge that corresponds to "Female Tissues"

(Fig. 26). The list has been reduced by 1, with 5 GPCR targets annotated by GWAS to be related to breast cancer, that are also expressed in female tissues (Fig. 27) remaining.

Guideline for Understanding Results

Basic Protocol 1 and Alternate Protocol 1

The anticipated results from *Basic Protocol 1* and *Alternate Protocol 1* are an in-depth view of aggregated protein information and knowledge. This aggregated set, which is by no means exhaustive, can still act as a barometer to illustrate the amount and frequency of data, information and knowledge generated by the scientific community about a protein, and aid in the process of target selection and validation. Researchers can use this information to guide the early drug discovery process and focus on novel targets or re-evaluate previously more studied targets in an integrative manner. Program staff can help guide research into areas of need as well and avoid studies of targets that have fairly saturated the research landscape.

Basic Protocol 2

Basic Protocol 2 generates a list of related targets based on text mined, aggregated relationships. Subsequent literature searches may be helpful to validate or repudiate a relationship between targets, or between a target and a disease or ligand. For example, a quick literature search of the targets listed in *Basic Protocol 2* revealed that one of the Tbio targets (GPR161) is 'an important regulator and a potential drug target for triple-negative breast cancer' (Feigin, Xue, Hammell, & Muthuswamy, 2014). Thus, Pharos may provide useful starting points for scientists interested in novel targets to study.

While filtering targets, there are a multitude of ways to subdivide the target lists. Pharos makes attempts to minimize the ability to filter by unrelated values, e.g., Tdark targets by ligand activity, by removing filters in which no values will be returned. Should 0 results be returned, facets can be removed to broaden the search.

Commentary

Background Information

The process of information aggregation and display for in-depth biomedical data is not unique to Pharos. Open Targets (Koscielny et al., 2017), GeneCards (Rebhan, Chalifa-Caspi, Prilusky, & Lancet, 1997), OMIM and GO all perform similar functions, though each has a different emphasis. What sets Pharos apart is the ranking of targets by TDL, and the ease of identification of dark targets. Another unique characteristic is the ability to browse and filter the entire curated human proteome. While paging through 20,244 proteins may not initially be fruitful, the ability to filter and refine the entire proteome to a more actionable list has major potential with respect to comparative analyses, leading to novel suggestions that may help illuminate novel drug targets, thus aiding the drug discovery process. None of the above-listed resources offer a knowledge-based classification for proteins, or the ability to

Illuminating the Druggable Genome History—The druggable genome was described as 'the subset of the \sim 30,000 genes in the human genome that express proteins potentially able to bind drug-like molecules' (Hopkins & Groom, 2002). However, since the mapping of the human genome, research has not moved past the study of the same genes known before the mapping was completed (Edwards et al., 2011). The NIH, therefore, started the Illuminating the Druggable Genome (IDG) program (Rodgers et al., 2018) in order to improve our understanding of the properties and functions of proteins that are currently not well studied within commonly drug-targeted protein families (Oprea, Bologa, et al., 2018). The IDG collated data from over 60 sources (Nguyen et al., 2017), which is released as the Target Central Resource Database (TCRD). Pharos is a web-based platform to browse and analyze the data contained within the TCRD.

Target Development Level Ranking Details—The TCRD ranks targets based on several scores, and these rankings are also used in Pharos. There are 4 distinct target development levels used in Pharos: Tdark, Tbio, Tchem, and Tclin (Oprea, Bologa, et al., 2018). Tdark targets have minimal knowledge about them. Tbio targets are targets that have been referenced in literature, have GeneRIF annotations, antibodies and molecular or biological function data and phenotypes. Tchem targets have all of the preceding values, as well as active ligands. Tclin targets are targets with approved drugs available.

Ligand Activity Cutoffs—To be displayed as an active ligand in Pharos, a ligand:

- must have a pChEMBL value (i.e. a -Log M value)
- must be from a binding assay
- must have a MOL structure type
- must have a target type of SINGLE PROTEIN
- must have standard_flag = 1 and exact standard_relation (i.e. no > 10uM type values)
- must be associated with a publication
- must pass family-specific thresholds:
 - Kinases: 30nM a.
 - b. GPCRs: 100nM
 - Nuclear Receptors: 100nM c.
 - d. Ion Channels: 10µM
 - Others: 1µM e.

Critical Parameters and Troubleshooting

- There are very few parameters that are settable by users. The length of the results table can be modified to minimize paging.
- Search results can take some time in assessing. For example, a user entering a specific target would not expect to see a long list of results, but more target connections are returned due to the use of text mining.
- As Pharos is a web-based site, with a REST API, there may be times where web traffic is especially heavy and may decrease performance of Pharos. There are several methods to contact the Pharos team listed on the site, should a user experience frequent problem.
- Pharos is also a database consisting of external data. While every effort has been made to ensure high quality, datasets are imported from external sources, analyzed, and returned, and it is possible that errors may be introduced anywhere within this workflow. Again, should inconsistencies be discovered, the Pharos team is available through several methods of communication.

References

- Apweiler R, Bairoch A, Wu CH, Barker WC, Boeckmann B, Ferro S, ... Yeh LS (2004). UniProt: the Universal Protein knowledgebase. Nucleic Acids Res, 32(Database issue), D115–119. doi:10.1093/nar/gkh131 [PubMed: 14681372]
- Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, ... Sherlock G (2000). Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet, 25(1), 25– 29. doi:10.1038/75556 [PubMed: 10802651]
- Cannon DC, Yang JJ, Mathias SL, Ursu O, Mani S, Waller A, ... Oprea TI (2017). TIN-X: target importance and novelty explorer. Bioinformatics, 33(16), 2601–2603. doi:10.1093/bioinformatics/ btx200 [PubMed: 28398460]
- Edwards AM, Isserlin R, Bader GD, Frye SV, Willson TM, & Yu FH (2011). Too many roads not taken. Nature, 470(7333), 163–165. doi:10.1038/470163a [PubMed: 21307913]
- Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The Reactome pathway Knowledgebase. Nucleic Acids Res, 44(D1), D481–487. doi:10.1093/nar/ gkv1351 [PubMed: 26656494]
- Feigin ME, Xue B, Hammell MC, & Muthuswamy SK (2014). G-protein-coupled receptor GPR161 is overexpressed in breast cancer and is a promoter of cell proliferation and invasion. Proc Natl Acad Sci U S A, 111(11), 4191–4196. doi:10.1073/pnas.1320239111 [PubMed: 24599592]
- Hamosh A, Scott AF, Amberger J, Bocchini C, Valle D, & McKusick VA (2002). Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res, 30(1), 52–55. doi:10.1093/nar/30.1.52 [PubMed: 11752252]
- Hopkins AL, & Groom CR (2002). The druggable genome. Nat Rev Drug Discov, 1(9), 727–730. doi:10.1038/nrd892 [PubMed: 12209152]
- Huttlin EL, Bruckner RJ, Paulo JA, Cannon JR, Ting L, Baltier K, ... Harper JW (2017). Architecture of the human interactome defines protein communities and disease networks. Nature, 545(7655), 505–509. doi:10.1038/nature22366 [PubMed: 28514442]
- Insel PA, Sriram K, Wiley SZ, Wilderman A, Katakia T, McCann T, ... Murray F (2018). GPCRomics: GPCR Expression in Cancer Cells and Tumors Identifies New, Potential Biomarkers and Therapeutic Targets. Front Pharmacol, 9, 431. doi:10.3389/fphar.2018.00431 [PubMed: 29872392]
- Jimeno-Yepes AJ, Sticco JC, Mork JG, & Aronson AR (2013). GeneRIF indexing: sentence selection based on machine learning. BMC Bioinformatics, 14, 171. doi:10.1186/1471-2105-14-171 [PubMed: 23725347]

- Koscielny G, An P, Carvalho-Silva D, Cham JA, Fumis L, Gasparyan R, ... Dunham I (2017). Open Targets: a platform for therapeutic target identification and validation. Nucleic Acids Res, 45(D1), D985–d994. doi:10.1093/nar/gkw1055 [PubMed: 27899665]
- Lin Y, Mehta S, Kucuk-McGinty H, Turner JP, Vidovic D, Forlin M, ... Schurer SC (2017). Drug target ontology to classify and integrate drug discovery data. J Biomed Semantics, 8(1), 50. doi:10.1186/s13326-017-0161-x [PubMed: 29122012]
- Nguyen DT, Mathias S, Bologa C, Brunak S, Fernandez N, Gaulton A, ... Guha R (2017). Pharos: Collating protein information to shed light on the druggable genome. Nucleic Acids Res, 45(D1), D995–d1002. doi:10.1093/nar/gkw1072 [PubMed: 27903890]
- Oprea TI (2019). Exploring the dark genome: implications for precision medicine. Mammalian Genome, 30(7–8), 192–200. doi: 10.1007/s00335-019-09809-0 [PubMed: 31270560]
- Oprea TI, Bologa CG, Brunak S, Campbell A, Gan GN, Gaulton A, ... Zahoranszky-Kohalmi G (2018). Unexplored therapeutic opportunities in the human genome. Nat Rev Drug Discov, 17(5), 317–332. doi:10.1038/nrd.2018.14 [PubMed: 29472638]
- Oprea TI, Jan L, Johnson GL, Roth BL, Ma'ayan A, Schurer S, ... McManus MT (2018). Far away from the lamppost. PLoS Biol, 16(12), e3000067. doi:10.1371/journal.pbio.3000067 [PubMed: 30532236]
- Pletscher-Frankild S, Palleja A, Tsafou K, Binder JX, & Jensen LJ (2015). DISEASES: text mining and data integration of disease-gene associations. Methods, 74, 83–89. doi:10.1016/ j.ymeth.2014.11.020 [PubMed: 25484339]
- Rebhan M, Chalifa-Caspi V, Prilusky J, & Lancet D (1997). GeneCards: integrating information about genes, proteins and diseases. Trends Genet, 13(4), 163. doi:10.1016/s0168-9525(97)01103-7 [PubMed: 9097728]
- Rodgers G, Austin C, Anderson J, Pawlyk A, Colvis C, Margolis R, & Baker J (2018). Glimmers in illuminating the druggable genome. Nat Rev Drug Discov, 17(5), 301–302. doi:10.1038/ nrd.2017.252 [PubMed: 29348682]
- Rouillard AD, Gundersen GW, Fernandez NF, Wang Z, Monteiro CD, McDermott MG, & Ma'ayan A (2016). The harmonizome: a collection of processed datasets gathered to serve and mine knowledge about genes and proteins. Database (Oxford), 2016. doi:10.1093/database/baw100
- Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, ... Mering CV (2019). STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res, 47(D1), D607–d613. doi:10.1093/nar/gky1131 [PubMed: 30476243]
- Wu V, Yeerna H, Nohata N, Chiou J, Harismendy O, Raimondi F, ... Gutkind JS (2019). Illuminating the Onco-GPCRome: Novel G protein-coupled receptor-driven oncocrine networks and targets for cancer immunotherapy. J Biol Chem, 294(29), 11062–11086. doi:10.1074/jbc.REV119.005601 [PubMed: 31171722]

Sheils et al.



Figure 1: Main search page for Pharos, with autocomplete functionality visible.

Sheils et al.

PH	AROS Targets Diseas	ses Ligands	API About	FAQ						sea	arch	٩	Sign In
B Refine See Al Dev	e by Category ICategories → relopment Level Tbio Tchem Tclin Tdark	Clear All S	Hide Filters \Xi	С		evelopment Level Colle	Click on a slic	be to filter the li m Disease	st Tīssue	Target Family			
Coll	lection	^	Selected Filte	rs:									Clear All 🔕
	Kinase: IDG Consortium (Complete/Control)	2	query cdk13 ⊗	×)								
	Kinase: IDG Consortium (Targets)	1	Targets (1	9)									
IMP	PC Term	^	A						Items per	page: 10 👻	Page: 1 of 2	< <	: > >I
	preweaning lethality, complete penetrance	3	Target Name		Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein Interactions		Knowledge Availability
	preweaning lethality, incomplete penetrance	1	Cyclin-dependent ki	nase 13	CDK13	Tchem	Kinase	-1.31	20.47	142	25		
	abnormal eye morphology	1											
	hypoactivity embryonic lethality prior to	1	Cyclin-K		ССИК	Tbio	Non-IDG	-1.35	18.45	119	2		
п	increased startle reflex	1											Ale

Figure 2:

Primary Search results/browse page layout. Main results are in a pageable table (**A**). The left-hand column (**B**) contains multiple fields to filter on, similar to an e-commerce site. The donut chart on the top half of the screen (**C**) also shows a proportional breakdown of the filterable properties and is also interactive.

Targets (19)								
					Items per	page: 10 -	Page: 1 of 2	< < > >1
Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein Interactions	Knowledge Availability
Cyclin-dependent kinase 13	CDK13	Tchem	Kinase	-1.31	20.47	142	25	

Figure 3:

Brief metadata is available for each target, which includes several identifiers such as: Target development level, TDL (Oprea, Bologa, et al., 2018), target family, computed target novelty (TIN-X) score (Cannon et al., 2017), fractional publication count (Pletscher-Frankild, Palleja, Tsafou, Binder, & Jensen, 2015), available antibodies (from antibodypedia.com), listed protein-protein interactions (Fabregat et al., 2016; Huttlin et al., 2017; Szklarczyk et al., 2019) and knowledge availability (based on Harmonizome (Rouillard et al., 2016)).

PH	AROS Targets Di	seases Ligands	s API About FAQ						S	earch	۹	Sign In
	Kidney cancer	8	Cyclin-dependent kinase 11B	CDK11B	Tchem	Kinase	-1.15	16.56	0			*
	lung adenocarcinoma	0	Coiled-coil domain-containing protein 66	CCDC66	Tdark	Non-IDG	-0.6	4.07	79			-
Tiss	sue	^										
	Liver and Pancreas	18										SIL
	Digestive Tract	18	Protein inturned	INTU	Tbio	Non-IDG	-1.76	53.86	56	17		
	Urinary Tract	18										
	Endocrine System	18	Cyclin-dependent kinase 6	CDK6	Tclin	Kinase	-2.71	390.15	730	12		EK)
	Blood and immune system	18										
	Female tissues	18						Items per	page: 10 👻	Page: 1 of 2	< <	> >I
	Male tissues	18	Ligands (4)									
	Nervous System	18	5 ()					Itoma por	paga: 20 =	Page: 1 of 1		/ X XI
	Respiratory system	17						iterns per	page. 20 +	Fage. 1011		
	Skin and soft tissues	17										
			CHEMBL296468	CDK12	inhibitor 2	CHEME	3L445813	CH	IEMBL5747	'38		
Targ	get Family	^	-B	н,	a.L		CL			-M-1		
	Kinase	13	J. K		Y S	HNCT				NH NH		
	Non-IDG	9	in star	ing a	्र	HN	=8 0	Ex.	\Diamond			
	Enzyme	4	н,с,Ссн,	Ŷ	\bigcirc			F* Y	CH, CH,			
	Epigenetic	1										
				n								
	NCATS		IDG			PHA	ROS			CONTAG	CTUS	

Figure 4:

Relevant diseases and ligands are displayed in separate pageable lists.

Sheils et al.

Page 15

PHAROS Targets Dis	eases Ligands API About FAQ			search Q	Sign
Tchem CDK1	Cyclin-dependent kinase 13				
A ×	Cyclin-dependent kinase which displays CTD kinase a largest RNA polymerase II subunit RPB1, thereby actir In case of infection by HIV-1 virus, interacts with HIV-1 protein Nef. The protein encoded by this gene is a me in cell cycle control. The exact function of this protein	ctivity and is required for RNA splicing. Has CT og as a key regulator of transcription elongation Tat protein acetylated at 'Lys-50' and 'Lys-51' mber of the cyclin-dependent serine/threonine has not yet been determined, but it may play a	TD kinase activity by hyperphosphorylating the C-te n. Required for RNA splicing, probably by phosphor , thereby increasing HIV-T mRNA splicing and prom protein kinase family. Members of this family are we role in mRNA processing and may be involved in re-	rminal heptapeptide repeat domain (C ylating SRSF1/SF2. Required during h toting the production of the doubly sp ill known for their essential roles as m gulation of hematopoiesis. Alternative	TD) of the mematopoiesis liced HIV-1 aster switche
Protein Summary	largets / Kinase / Protein Kinase	7 Cmgc Group 7 Cdk Family	/ Crk/ Subfamily / Cyclin-depende	nt Kinase 13	
G Development Level Summary	Protein Summary Uniprot Accession IDs	Illumination Graph	Knowle	dge Table	0
tive Ligands	Q14004 ¹² Q53G78 ¹² Q6DKQ9 ¹² Q75MH4 ¹² Q75MH5 ¹² Q96JN4 ¹² Q9H4A0 ¹² Q9H4A1 ¹²		Mos	t Knowledge About	Knowled Value (0 1 scale
sease Associations by Source	Q9UDR4 ^{IZ}		- 0.8 dru	g perturbation	0.99
B Viewer	Gene Name		0.6 mol	ecular function	0.98
get Expression Data	CDK13		0.2 tran	scription factor perturbation	0.97
tein to Protein Interactions	ENST00000181839 ENSP00000181839 ENSG0000065883 ENST00000340829 ENSP00000340557		co	expressed gene scription factor binding site profile	0.87
olication Information	Symbol CHED CDC2L CDC2L5 hCDK13 CHDFIDD				
quence Details					
lated Targets					
	IDG Development Level Summary				a
	Tdark	Tbio	Tchem	Tclin	
	These are targets about which virtually T nothing is known. They do not have known s drug or small molecule activities - AND - s satisfy two or more of the following criteria:	hese targets do not have known drug or mall molecule activities - AND - atisfy the preceding conditions - AND -	Target has at least one ChEMBL compound with an activity cutoff of < 30 nM - AND - satisfies the preceding conditions	Target has at least one approve - AND - satisfies the preceding conditio Or Active Drug: 0	d drug ns

Figure 5:

Target details view. The density of sections is dependent on the data available. The left side column (A) acts as section navigation and allows the user to quickly jump to areas of interest.

Protein Summary Uniprot Accession IDs	Illumination Graph	Knowledge Table	0
Q14004ଅ Q53G78ଅ Q6DKQ9ଅ Q75MH4ଅ Q75MH5ଅ Q96JN4ଅ Q9H4A0ଅ Q9H4A1ଅ		Most Knowledge About	Knowledge Value (0 to 1 scale)
Q9UDR4 ^亿	0.8	drug perturbation	0.99
Gene Name	0.6	molecular function	0.98
CDK13 ¹²	0.2	transcription factor perturbation	0.97
Ensembl ID ENST00000181839 ENSP00000181839		co-expressed gene	0.87
ENSG0000065883 ENST00000340829 ENSP00000340557		transcription factor binding site profile	0.85
Symbol			
CHED CDC2L CDC2L5 hCDK13 CHDFIDD			

Figure 6:

Target Summary overview with protein and gene identifiers, illumination graph and knowledge table.

Sheils et al.



Figure 7: Expanded view of the illumination graph.

DG Development Level Summary				0
Tdark	Тыо	Tchem	Tclin	
These are targets about which virtually nothing is known. They do not have known drug or small molecule activities - AND - satisfy two or more of the following criteria: Image: Solution of the solution	These targets do not have known drug or small molecule activities - AND - satisfy the preceding conditions - AND - satisfy one or more of the following criteria: Gene Ontology Molecular Functions: 31	Target has at least one ChEMBL compound with an activity cutoff of < 30 nM - AND - satisfies the preceding conditions CACTIVE Ligands: 4	Target has at least one approved drug - AND - satisfies the preceding conditions Active Drug: 0	
Antibodies: 142 (req: > 50)	OMIM Phenotype: 0			

Figure 8:

Development Level Summary shows previous development milestones reached, as well as progress towards incomplete milestones. CDK13 is a Tchem target, which means that multiple active ligands have been discovered, but no approved drugs as of yet. It has also been fairly well published about, both in text-mined PubMed literature reviews, and GeneRIF annotations (Jimeno-Yepes, Sticco, Mork, & Aronson, 2013). Its molecular function (from GO Gene Ontology (Ashburner et al., 2000)) is also fairly well known.

lter By:	·	Items per page: 10	▼ Page: 1 of 1	< < >
THZ531 (Small Molecule)				
H,C-NCH3 CI-EL				
" Eri				
Order THZ531 from: MedChemExpress				

Figure 9: Resources available from research funded by the IDG program



Figure 10: Active Ligands section.

Disease Associations by Source (16)

1 - 10 of 16 |< < > >|

0

- > Intellectual disability (1 sources)
- > Kidney cancer (1 sources)
- > Carcinoma (1 sources)
- > Congenital hereditary endothelial dystrophy of cornea (1 sources)
- > astrocytic glioma (1 sources)
- > ependymoma (1 sources)
- > Gaucher disease type 1 (1 sources)
- > group 3 medulloblastoma (1 sources)
- > juvenile dermatomyositis (1 sources)
- > malignant mesothelioma (1 sources)

Figure 11:

Collapsed disease associations view

Publication Information 0 **Publication Statistics** Text Mined References (47) GeneRif Annotations (9) PubMed Score 20.47 PubMed score by year Reset Zoom 3.0 2.5 2.0 Score 1.0 0.5 0.0 .98 . of 200 200 2001 2010 Yea

Figure 12:

Shown is one of several available line charts that show the frequency of publication for a target.

Find similar targets by:							0
Panther Protein Class		GO Function		GO Component		GO Process	
transferase	Ø	transcription regulatory region DNA binding	ß	cytosol	ß	positive regulation of transcription from RNA polymerase II promoter	
kinase		protein kinase binding	Ø	nucleoplasm	Ø	positive regulation of cell proliferation	Ø
protein kinase	Z	ATP binding	Ľ	Golgi apparatus		multicellular organism development	Ø
non-receptor tyrosine protein kinase	Z	RNA binding	Ľ	extracellular region	Ø	transcription elongation from RNA polymerase II promoter	Ľ
		transcription factor binding	Ľ	extracellular space	Z	viral process	Ø
		protein kinase activity		chromosome		neutrophil degranulation	ß
		cyclin binding	Ľ	nuclear speck	Z	regulation of mitotic nuclear division	Ø
		cyclin-dependent protein serine- threonine kinase activity	Z	ficolin-1-rich granule lumen		alternative mRNA splicing, via spliceosome	Z
		RNA polymerase II carboxy- terminal domain kinase activity	ß	cyclin-CDK positive transcription elongation factor complex	Z	hemopoiesis	Z
				nuclear cyclin-dependent protein kinase holoenzyme complex		negative regulation of stem cell differentiation	Z

Figure 13:

Common target properties are shown, and a link to a list of common targets.

Selected Filters:								Clear All 🛞
GO Function X								
cyclin-dependent protein serine- threonine kinase activity								
Targets (30)								
					Items	per page: 10 👻	Page: 1 of 3	I< < > >I
Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein Interactions	Knowledge Availability
Cyclin-dependent kinase 12	CDK12	Tchem	Kinase	-1.38	29.42	157		*
Cyclin-dependent kinase 20	CDK20	Tbio	Kinase	-1.82	67.7	248		*
Cyclin-dependent kinase 11B	CDK11B	Tchem	Kinase	-1.15	16.56	0		×
MAPK/MAK/MRK overlapping kinase	мок	Tbio	Kinase	-1.78	60.31	312	3	*

Figure 14:

List of cyclin-dependent protein serine-threonine kinase activity targets as annotated by their GO Function.

Selected Filters: GO Function X cyclin-dependent protein serine- threonine kinase activity								Clear All 😒
Targets (30)					Items	: per page: 10 💌	Page: 1 of 3	 I< < > >1
Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein Interactions	A Knowledge Availability ↑
Cyclin-dependent kinase-like 4	CDKL4	Tdark	Kinase	0	0.5	155	7	*
Cyclin-dependent kinase 15	CDK15	Tchem	Kinase	0.63	0.78	158	84	*
MAPK/MAK/MRK overlapping kinase	мок	Tbio	Kinase	-1.78	60.31	312	3	*
Cyclin-dependent kinase 3	CDK3	Tchem	Kinase	-1.44	25.27	65	17	*

Figure 15:

Shows the same list of 30 targets from Figure 14, this time sorted by knowledge availability (A).

Sheils et al.

PHAROS Targets Di	seases Ligands API About	FAQ				sea	arch	٩	Sign In
			Tchem 20						
		Click	on a slice to filter the list						
	De	evelopment Level Collection	IMPC Term Disease	Tissue Target F	amily				
Selected Filters:								(Clear All 🔞
GO Function	X IDG Development Level	×							
cyclin-dependent protein serine- threonine kinase activity	S Tdark S								
Targets (1)									
					Item	s per page: 10 💌	Page: 1 of 1	<	< > >
Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein Interactions		Knowledge Availability
Cyclin-dependent kinase-like 4	CDKL4	Tdark	Kinase	0	0.5	155	7		*
					Iten	is per page: 10 👻	Page: 1 of 1	<	< > >1

Figure 16:

The same list as Figure 14, this time filtered by "Tdark", leaving 1 target. When more targets are available, it is possible to combine filter values to refine large lists.

Protein Summary			?
Uniprot Accession IDs	Illumination Graph	Knowledge Table	
Q5MAI5 ^[2] Q2NME9 ^[2]		Most Knowledge About	Knowledge Value (0 to 1 scale)
Gene Name	0.8	molecular function	0.93
Ensembl ID	or	cell type or tissue	0.59
ENST00000378803 ENSP00000368080 ENSG00000255111 ENST00000395035		protein domain	0.58
ENSP00000378476		PubMedID	0.49
		tissue	0.48



IDG Development Level Summary			0
Tdark	Тыо	Tchem	Tclin
These are targets about which virtually nothing is known. They do not have known drug or small molecule activities - AND - satisfy two or more of the following criteria:	These targets do not have known drug or small molecule activities - AND - satisfy the preceding conditions - AND - satisfy one or more of the following criteria: Sene Ontology Molecular Functions: 5	Target has at least one ChEMBL compound with an activity cutoff of < 30 nM - AND - satisfies the preceding conditions C Active Ligand: 0	Target has at least one approved drug - AND - satisfies the preceding conditions C Active Drug: 0
Antibodies: 155 (req: > 50)	OMIM Phenotype: 0		

Figure 18:

IDG Development Level Summary of CDKL4, a dark target.

Publication Informat	ion		
Publication Statistics	Text Mined References (4)	GeneRif Annotations (1)	
PubMed Score 0.50)	BubMed scare by year	
Reset Zoom		Publikeu scole by year	
1		2015: 0.5	
e o o o o o o o o o o o o o o o o o o o		•	
		Year	





Figure 20:

Navigation bar header as seen on the Pharos home page. Subsequent pages within Pharos will lack the background image.

Sheils et al.

PH.	AROS Targets Diseas	ses Ligands X	s API About FAQ Hide Filters -						se	arch	۹	Sign In
efine See All Devo	e by Category Categories →	Clear All ⊗				тыо 1144	45					
	Tbio	6588										
	Tchem	1598				Click on a clic	a ta filtar tha li	ot				
	Tclin	613		(Development Level	Collection IMPC Te	rm Disease	Tissue	Target Family			
Colle	ection	^	Targets (2024	4)								
	GPCR: IDG Consortium (Targets)	126						ltems per p	oage: 10 👻	Page: 1 of 2025	<	< > >I
	Kinase: IDG Consortium (Targets)	125	Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein		Knowledge Availability
	Ion Channel: IDG Consortium (Targets)	99	Endethelia economica							Intelactions		SM
	Kinase: IDG Consortium (Complete/Control)	37	enzyme 1	ECE1	Tchem	Enzyme	-2.56	355.04	278			
	GPCR: IDG Consortium (Complete/Control)	25	Trafficking protein particle complex subunit 2-like protein	TRAPPC2L	Tdark	Non-IDG	-0.18	0.74	35			*
IMP	C Term	^			_							Aby
	preweaning lethality, complete penetrance	979	Beta-secretase 2	BACE2	Tchem	Enzyme	-2.1	113.98	418			×
	preweaning lethality, incomplete penetrance	499	Uncharacterized protein	ZSWIM9	Tdark	Non-IDG		0	12			

Figure 21: Main target browse page

PH	AROS Targets Disea	ses Ligands API	About FAQ			search		Q Sign In
Refin All Car searc	e by Category tegories X th facets					Clear All 🕹		
Ant	ibody Count	^	Data Source	^	Entrez Gene	^		
	100:200	5418	TCRDv5.4.0	20244	0	199		
	50:100	4786	UniProt	20244	3106	35		
	>200	4017	HCA RNA	18868	3105	21		
	0:10	2585	□ GTEx	18679	3107	14		
	30:40	891	Consensus	18503	3123	13		
	20:30	865	HPA RNA	18499	100616102	5	1 of 2025	$ \langle \ \langle \ \rangle \rightarrow \rangle $
	40:50	852	UniProt Tissue	17989	64006	5	otein otein	Knowledge Availability
	10:20	830	D OMA	17914	619465	5	actions	
			Inparanoid	17398	100862685	5		
			JensenLab Experiment HPA-RNA	16979	449619	5		
Dev	velopment Level	^	IDG Target	^	Target Family	^		×
	Tbio	11445	TCRD:20133	1	Non-IDG	12091		Nhy
	Tdark	6588	TCRD:2440	1	Enzyme	4145		
	Tchem	1598	TCRD:1362	1	Transcription Factor	1400		
	Tclin	613	TCRD:8467	1	Kinase	634		

Figure 22: Expanded filter category panel.

н	AROS Targets Diseases	Ligands API
	by Category	
at	egories X	
ch f	acets	
Ē		
N	AS Trait	^
	Obesity-related traits	569
	Schizophrenia	533
	Breast cancer	492
	Body mass index	379
	Height	369
	Coronary artery disease	367
	Blood protein levels	351
	Post bronchodilator FEV1-FVC ratio	308
ן	Mean corpuscular volume	283
	Platelet count	275

Figure 23: Refined category filter list.

Selected Filters:								Clear All 😒
GWAS Trait Breast cancer ⊗	×							
Targets (492)								
					Items	per page: 10 👻	Page: 1 of 50	< < > >
Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein Interactions	Knowledge Availability
Poly [ADP-ribose] polymerase 4	PARP4	Tchem	Enzyme	-1.46	25.96	123		Ser .
RNA-binding protein Raly	RALY	Tbio	Non-IDG	-1.12	14.35	176		*
SCAN domain-containing protein 3	ZBED9	Tdark	Non-IDG	-0.99	9.59	50		*
Adenylate cyclase type 8	ADCY8	Tbio	Enzyme	-2.05	112.36	147		×
Annexin A13	ANXA13	Tbio	Non-IDG	-1.19	15.57	162		×
E3 ubiquitin-protein ligase AMFR	AMFR	Tbio	Enzyme	-2.47	292.79	203		×

Figure 24:

Target list reduced from 20244 to 492 targets.

	0									
lissue		Selected Filters:								Clear All
Digestive Tract	6	GWAS Trait X	IDG Target F	amily X						
Endocrine System	6	Breast cancer	GPCR 😣							
Nervous System	6									
Blood and immune system	5	Targets (6)								
Female tissues	5						ltem	s per page: 10 👻	Page: 1 of 1	
Liver and Pancreas	5							o per page.	- Protein	15 5 7
Male tissues	5	Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Interactions	Knowledge Availability
Respiratory system	5									F
Skin and soft tissues	5	Metabotropic glutamate receptor 3	GRM3	Tchem	GPCR	-2.31	186.87	274		×
Urinary Tract	5									
		Metabotropic glutamate	GBM7	Tchem	GPCB	-2.25	190.84	304		
		receptor 7		Toricin						1
farget Family	^									
Non-IDG	260	Leucine-rich repeat-containing G-protein coupled receptor 6	LGR6	Tbio	GPCR	-1.42	26.49	156	4	
Enzyme	105									
Transcription Factor	54									
Kinase	22	Melanin-concentrating hormone receptor 2	MCHR2	Tchem	GPCR	-1.95	81.84	127	1	
Transporter	17									
Epigenetic	15	Gastric inhibitory polypeptide	CIPP	Tabarra	CRCR	1.90	79.60	247		
GPCR	6	receptor	GIPK	Ichem	GPUR	-1.82	18.69	347	I.	
Ion Channel	5									
Nuclear Receptor	4	G-protein coupled receptor 161	GPR161	Tbio	GPCR	-2.26	179.81	175	13	

Figure 25:

Select "GPCR" from target family to further reduce the list.

PH	AROS Targets Diseas	ses Ligano	ds API About FAQ						sear	rch	Q Sign In
_	ovanan Gango	5	Hide Filters \Xi			_					
ב	primitive neuroectodermal tumor	3									
]	Kidney cancer	2									
ב	Schizophrenia	2				Female	tissues				
	adult high grade glioma	2				5	5				
	astrocytic glioma	2									
Гiss	ue	^					lice to filter the	liet			
	Digestive Tract	6				Unick off a 3					
	Endocrine System	6		Ľ	Development Level Coll	ection IMPC	Ierm Diseas	ie Tissue	Target Family		
	Nervous System	6	Selected Filters:								Clear All 😵
	Blood and immune system	5	GWAS Trait	X IDG Target	Family X IDO	à Tissue	×				
<u>~</u>	Female tissues	5	Breast cancer ⊗	GPCR 😒	F	emale tissues 🛛 🕲					
	Liver and Pancreas	5	Targets (5)								
	Male tissues	5	Targets (5)								
	Respiratory system	5						Items	s per page: 10 💌	Page: 1 of 1	$ \langle \rangle \rangle$
	Skin and soft tissues	5	Target Name	Gene	Development Level	Target Family	Log Novelty	Pubmed Score	Antibody Count	Protein Protein	Knowledge Availability
	Urinary Tract	5					5.			Interactions	
			Metabotropic glutamate receptor 3	GRM3	Tchem	GPCR	-2.31	186.87	274		×
Targ	et Family	^									
	Non-IDG	248	Metabotropic glutamate	GRM7	Tchem	GPCR	-2.25	190.84	304		S
	Enzyme	100	receptor /								A.
	Transcription Factor	53									

Figure 26:

The donut chart above the target list can also be used to filter results.

mily X IDG Fe Development Level	a Tissue male tissues (2) Target Family GPCR	Log Novelty -2.31	Items Pubmed Score	a per page: <u>10</u> Antibody Count	Page: 1 of 1 Protein Protein Interactions	I > >I Knowledge Availability
Development Level	Target Family GPCR	Log Novelty -2.31	Items Pubmed Score	a per page: 10 💌 Antibody Count	Page: 1 of 1 Protein Protein Interactions	IKnowledge Availability
Development Level	Target Family GPCR	Log Novelty -2.31	Pubmed Score	a per page: 10 💌 Antibody Count	Page: 1 of 1 Protein Protein Interactions	Knowledge
Development Level	Target Family GPCR	Log Novelty -2.31	Pubmed Score	a per page: 10 V	Page: 1 of 1 Protein Protein Interactions	Knowledge
Development Level	Target Family GPCR	Log Novelty	Pubmed Score	Antibody Count	Protein Protein Interactions	Knowledge Availability
Tchem	GPCR	-2.31	100.07			
			186.87	274		×
Tchem	GPCR	-2.25	190.84	304		×
Tbio	GPCR	-1.42	26.49	156	4	×
Tchem	GPCR	-1.82	78.69	347	1	*
This	GPCR	-2.26	179.81	175	13	×
	Tchem	Tchem GPCR Tbio GPCR	TchemGPCR-1.82TbioGPCR-2.26	Tchem GPCR -1.82 78.69 Tbio GPCR -2.26 179.81	Tchem GPCR -1.82 78.69 347 Tbio GPCR -2.26 179.81 175	Tchem GPCR -1.82 78.69 347 1 Tbio GPCR -2.26 179.81 175 13

Figure 27:

Final list of 5 GPCR targets with "breast cancer" as a GWAS trait that are expressed in female tissues.