

Open Targets Platform: mining gene-disease evidence for improved drug target selection

Washington DC, SLAS2017
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Open Targets Consortium, Core Bioinformatics



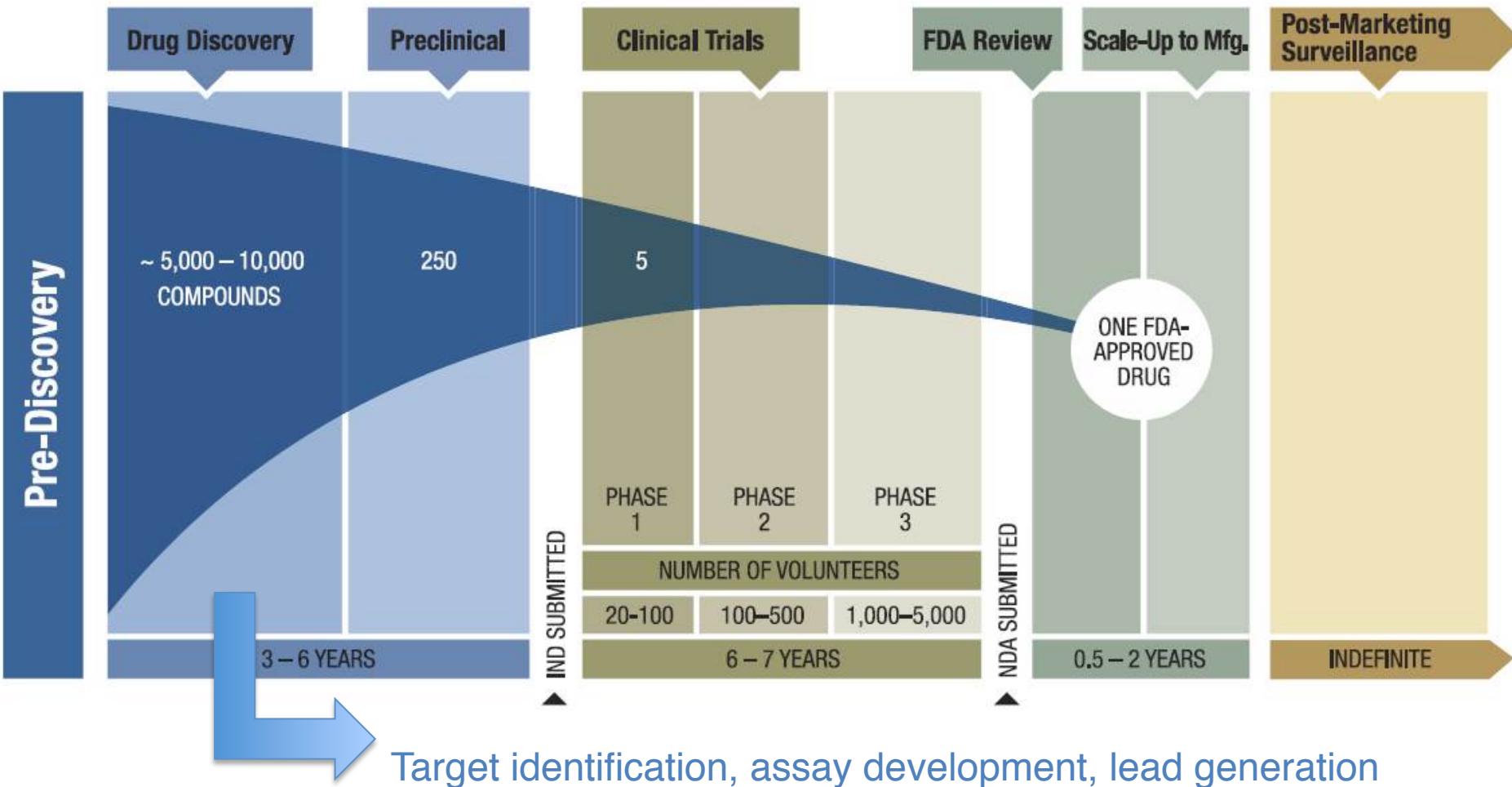
What I will cover in this talk

- Open Targets Consortium
- Experimental projects and the Platform
- What makes Open Targets unique
- What is next in 2017

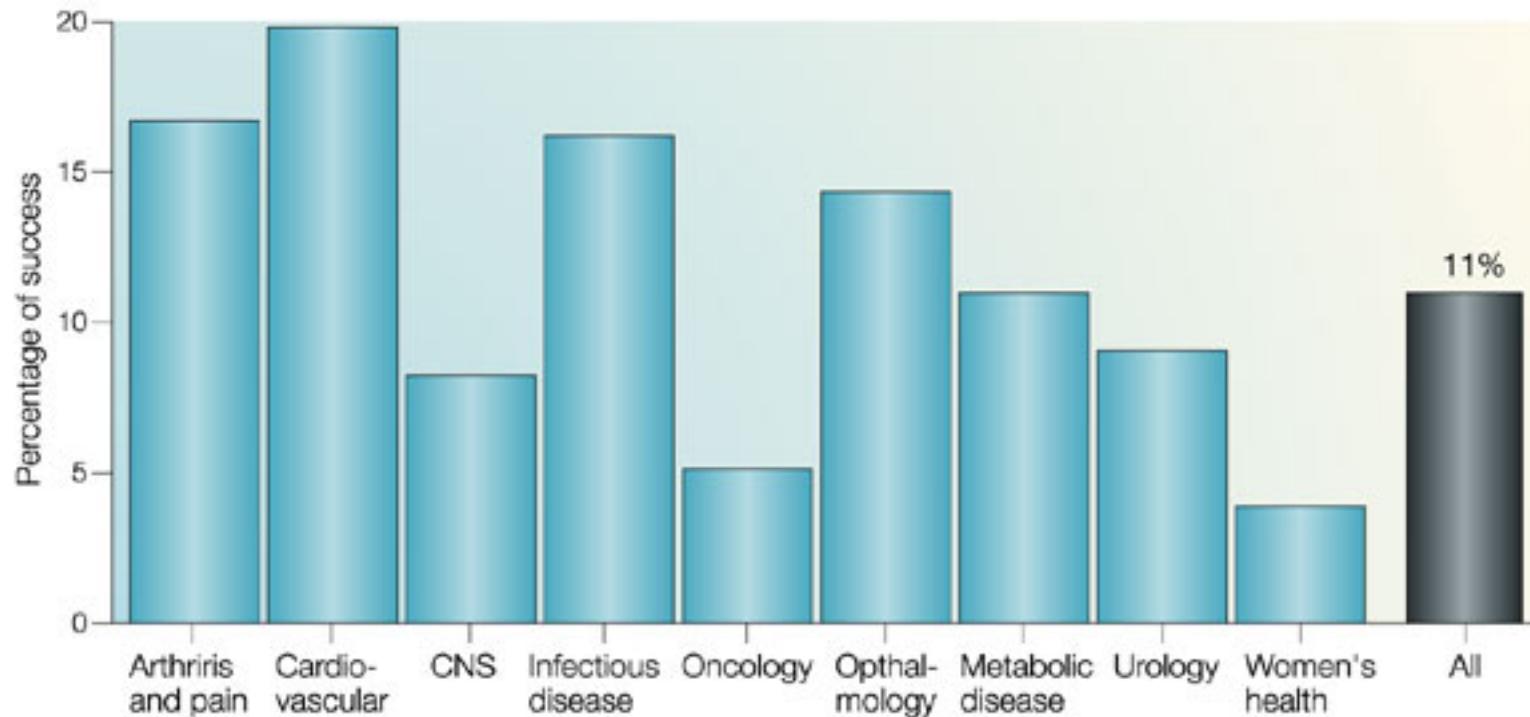
Acknowledgments



Drug discovery path: timeline



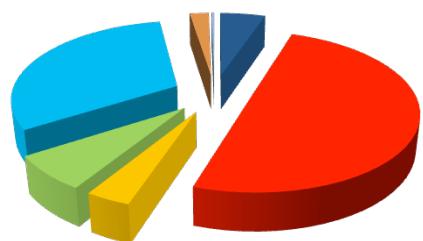
Drug discovery: what are the challenges



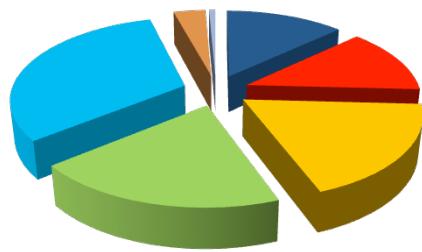
Lengthy, costly, low success rate, **high attrition rate**

What are the causes for the attrition?

Pre-clinical



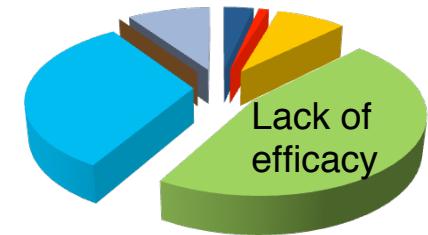
Phase I



Phase II



Phase III



- Pharmacokinetics/bioavailability
- Clinical safety
- Commercial
- Regulatory

- Non-clinical toxicology
- Efficacy
- Technical



*Professor Sir
Mike Stratton
Director, Sanger Institute*

Can we improve
target identification?



*Patrick Vallance, President
Pharmaceuticals R&D
GlaxoSmithKline*



*Professor Dame
Janet Thornton
former Director, EMBL-EBI*

Yes, we can!
And we should.

But one institution
can not do it alone.



Open Targets Consortium*



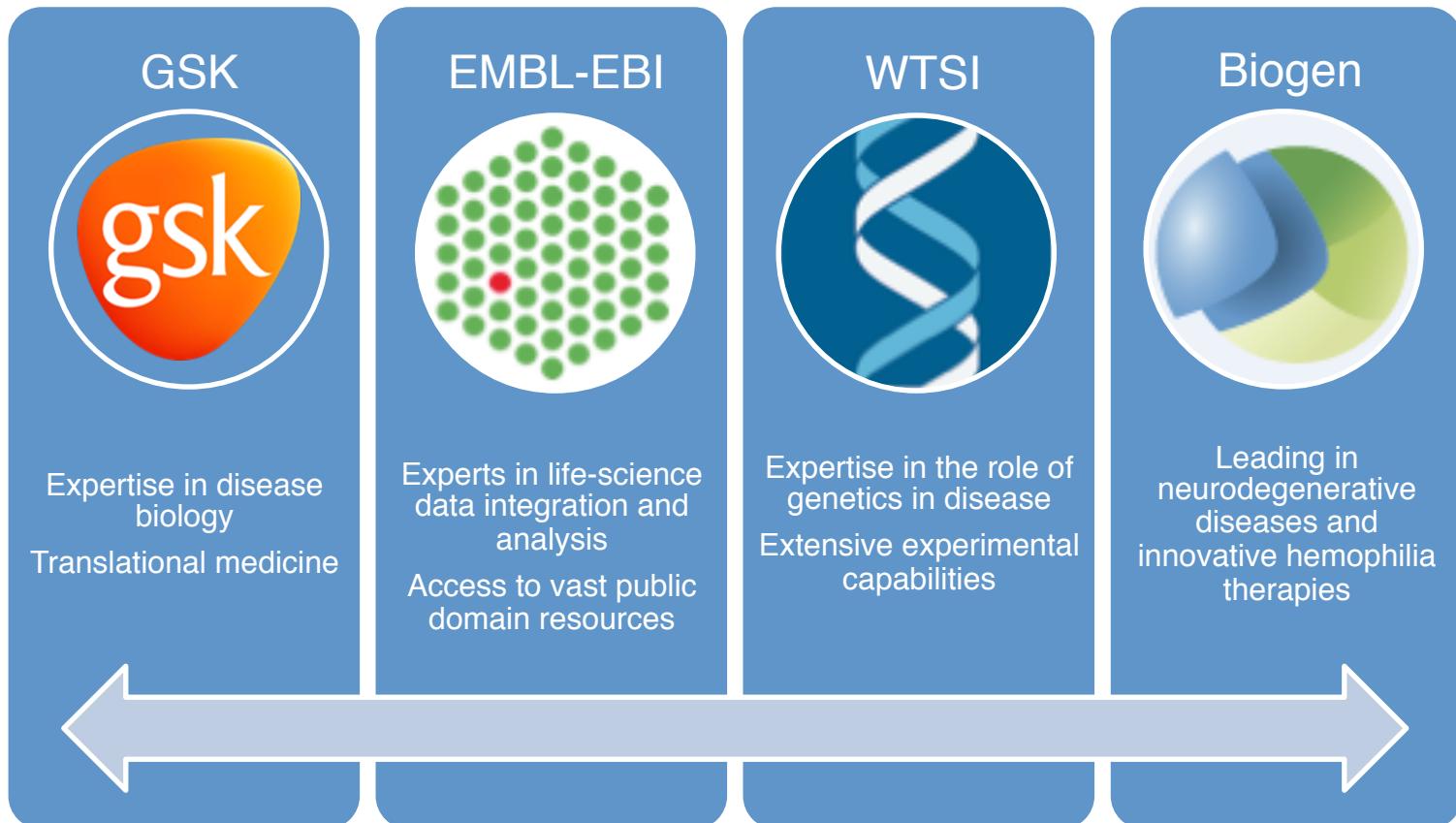
* Launched in March 2014
Three founding partners



EMBL-EBI



Biogen joined Open Targets in 2016



Open Targets

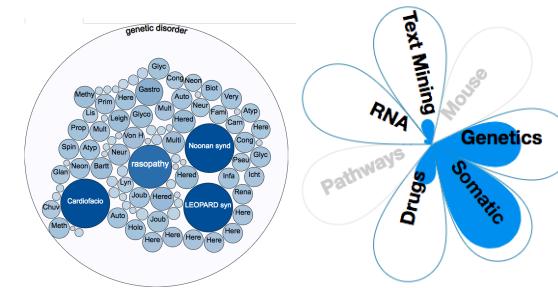
The two major areas of work* within Open Targets

Experimental projects



Generate new evidence
CRISPR
Organoids
Single cell RNASeq
Cell line fusion analyses
Metabolite GWAS

Core bioinformatics pipelines

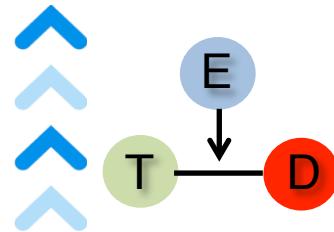


Database for data integration
Web portal
REST API
Python client (fully supported)
R client (community)
Data dumps

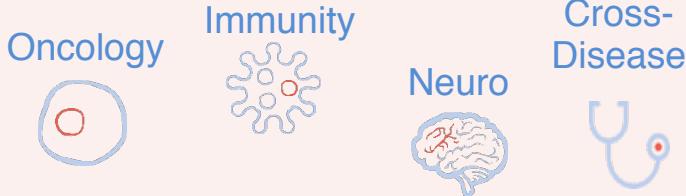
* Concurrent
www.opentargets.org/projects

Integration of existing and new data

Public Databases and Pipelines



Open Targets experimental data: NEW
Physiologically relevant and at scale



Graphical user interface

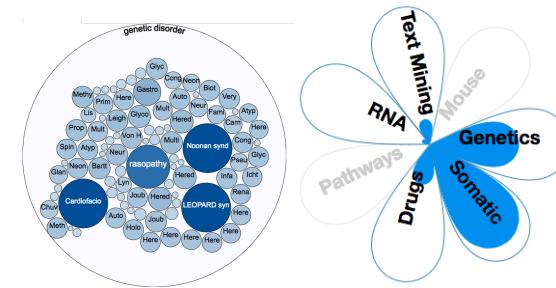
The two major areas of work* within Open Targets

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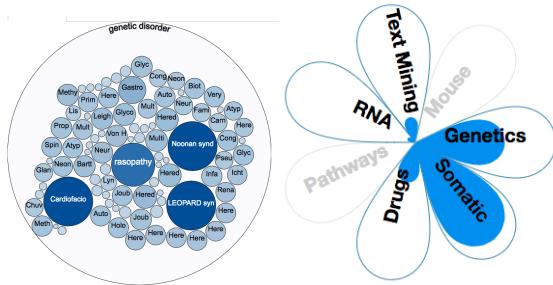


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Open Targets Platform*

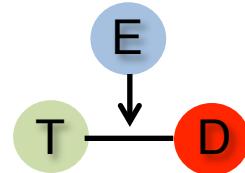
- Developed by the Core Bioinformatics team at EMBL-EBI
- Allow scientists to identify target–disease associations
- Frequent updates: new data, new web features
- Improvements driven by our user communities

<https://www.targetvalidation.org/>



* First release: December 2015

Publicly available data



- Similar data sources are grouped into data types

Data sources	Data types
GWAS catalog, UniProt, EVA, G2P	Genetic associations
Cancer Gene Census, EVA, IntOgen	Somatic mutations
Expression Atlas	RNA expression
ChEMBL	Drugs
Reactome	Affected pathways
Europe PMC	Text mining
PhenoDigm	Animal models
Your favourite data?	Let us know!

<http://tinyurl.com/platform-your-say>

Confidence score for the T-D associations

Oliver Stegle's team EMBL-EBI



where \textcircled{H} is a harmonic series defined by $S_{1,I} = S_1 + \frac{S_2}{2^2} + \frac{S_3}{3^2} + \frac{S_4}{4^2} \dots + \frac{S_I}{I^2}$

It allow for replication, deflates the effect of large amounts of data <http://bit.ly/OpenTargets>

We support decision-making

A) Which targets are associated with a disease?

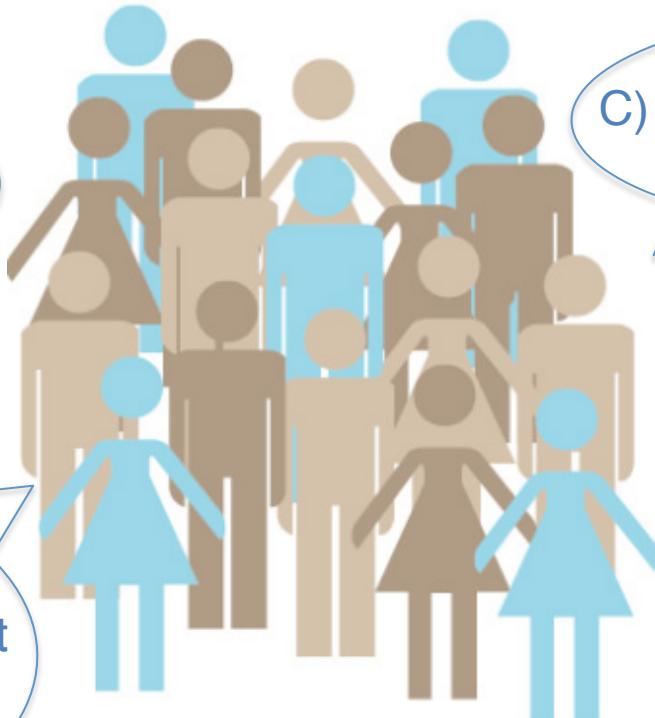
B) What evidence supports this target-disease association?

F) What else can I find out about my drug target?

E) If this target is associated with other diseases, can I get the association for diseases from different therapeutic areas?

C) Are there FDA drugs for this association?

D) For a given target, are there other diseases associated with it?



A) Which targets are associated with a disease?



https://www.targetvalidation.org

Survey About Help API Downloads Blog

Open Targets Platform

Find new targets for drug discovery

Search for a target or disease

Try: BRAF PTEN Asthma Inflammatory bowel disease

Feedback Follow us

The Open Targets Platform homepage. It features a search bar at the top with the placeholder "Search for a target or disease". Below the search bar, there is a "Try:" section with links to BRAF, PTEN, Asthma, and Inflammatory bowel disease. On the right side of the header, there are links for "Feedback" and "Follow us". The main title "Open Targets Platform" is displayed with a logo consisting of three overlapping shapes.

renal cell

renal cell carcinoma
4543 targets associated

Disease

A heterogeneous group of sporadic or hereditary carcinoma derived from cells of the KIDNEYS. There are several subtypes including the clear cells, the papillary, the chromophobe, the collecting duct, the spindle cells (sarcomatoid), or mixed cell-type carcinoma.. A carcinoma arising from the renal p...

Targets

PNN pinin, desmosome associated protein

GLIS2 GLIS family zinc finger 2

PRCC papillary renal cell carcinoma (translocation-associated)

Diseases

renal carcinoma

kidney disease > kidney neoplasm > renal carcinoma

papillary renal cell carcinoma

renal carcinoma > renal cell carcinoma > papillary renal cell carcinoma

A detailed search result for "renal cell carcinoma" on the Open Targets Platform. The result shows 4543 targets associated with the disease. The "Disease" section provides a brief description of renal cell carcinoma, mentioning its subtypes and origin. The "Targets" section lists several genes/proteins associated with the disease, such as PNN, GLIS2, and PRCC. The "Diseases" section shows the hierarchical classification of renal carcinoma under kidney disease, kidney neoplasm, and renal carcinoma. A large red arrow points from the female icon on the left towards this search result.

<https://www.targetvalidation.org/>

15 targets associated with renal cell carcinoma

 View disease profile

Filter the results

Filter by

Data types

Clear all Select all

- Genetic associations (15)
 - GWAS catalog (8)
 - UniProt literature (5)
 - European Variation Archive ... (4)
 - UniProt (3)
- Somatic mutations (526)
- Drugs (94)
- Affected pathways (0)
- RNA expression (3k)
- Text mining (2k)
- Animal models (1)

Pathway types

- Clear
- Developmental Biology
 - Signal Transduction (3)
 - Disease (2)
 - Immune System (2)
 - Cellular responses to stress (2)
 - Chromatin organization (2)
 - Metabolism (1)
 - Cell Cycle (1)
 - Metabolism of proteins (1)
 - Circadian Clock (1)
 - Vesicle-mediated transport (1)
 - Gene Expression (1)

Target class

- Unclassified protein
- Enzyme (1)
- Epigenetic regulator (1)

Your target list

Choose File No file chosen

Target class (Receptor, Kinase)

Upload your own list

Showing 1 to 15 of 15 targets

Search:

Total number of targets associated with renal cell carcinoma based on Genetic association only

Target symbol	Association score	Genetic associations	Somatic mutations	Drugs	Affected pathways	RNA expression	Text mining	Animal models	Target name
MET									MET proto-oncogene, receptor ...
VHL									von Hippel-Lindau tumor suppr...
PBRM1									polybromo 1
HNF1A									HNF1 homeobox A
SETD2									SET domain containing 2
FLCN									folliculin
EPAS1									endothelial PAS domain protein 1
MYC									v-myc avian myelocytomatosis ...
HNF1B									HNF1 homeobox B
MYEOV									myeloma overexpressed
ZEB2									zinc finger E-box binding home...
SCARB1									scavenger receptor class B me...
BHLHE41									basic helix-loop-helix family me...
PDZD2									PDZ domain containing 2
CEP85L									centrosomal protein 85 like

Previous 1 Next

[http://www.targetvalidation.org/
disease/EFO_0000681/associations?
fcts=datatype:genetic_association](http://www.targetvalidation.org/disease/EFO_0000681/associations?fcts=datatype:genetic_association)



Open Targets Platform Survey About ▾ Help ▾ API ▾ Downloads

4543 targets associated with renal cell carcinoma

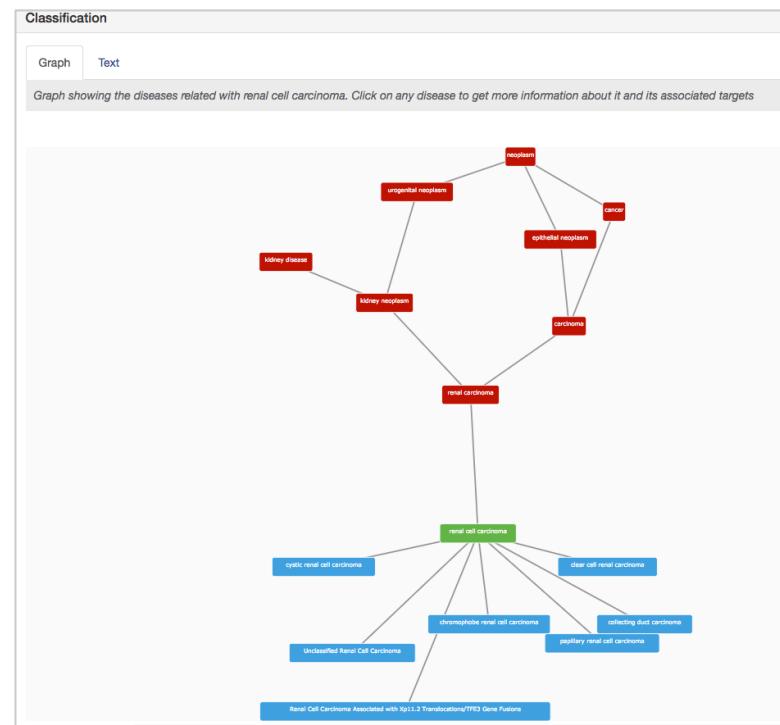
[View disease profile](#)

Phenotypes, Drugs, Disease Classification

“I’m really impressed with Open Targets. All this info in one place and for free?”



Drugs						
Source: CHEMBL						
Found 35 unique drugs: AFLIBERCEPT ALDESLEUKIN APITOLISIB AXITINIB AZD-2014 Anlotinib BEVACIZUMAB CABOZANTINIB EVEROLIMUS Farnitinib GIRENTUXIMAB INTERFERON ALFA-2A IXABEPILONE LINIFANIB MK-2206 NINTEDANIB NIVOLUMAB SEMAXANIB SORAFENIB SUNITINIB Savolitinib TANDUTINIB TEMSIROLIMUS TIVANTINIB TIVOZANIB VANDETANIB VOLOCXI						
Showing 1 to 10 of 1,000 entries						
Search:						
Drug Information						
Disease	Drug	Phase	Status	Type	Mechanism of action	Activity
renal cell carcinoma	EVEROLIMUS	Phase IV	Recruiting	Small molecule	FK506-binding protein 1A inhibitor DailyMed ↗	antagonist
renal cell carcinoma	EVEROLIMUS	Phase IV	Completed	Small molecule	FK506-binding protein 1A inhibitor DailyMed ↗	antagonist
renal cell carcinoma	EVEROLIMUS	Phase IV	Recruiting	Small molecule	FK506-binding protein 1A inhibitor DailyMed ↗	antagonist
clear cell renal carcinoma	AXITINIB	Phase IV	Recruiting	Small molecule	Vascular endothelial growth factor receptor inhibitor DailyMed ↗	antagonist



Alternative ways to access our data

Looking for our entire datasets?

<https://www.targetvalidation.org/downloads/data>

- All 2.5 M target-disease associations: 215 MB
- All 4.9 M evidence: 4.35 GB

Looking for extracts of our datasets?

REST API endpoints



public : Publicly supported stable API.

Open/Hide | List operations | Expand operations

GET /public/evidence

POST /public/evidence

GET /public/evidence/filter

POST /public/evidence/filter

GET /public/association

GET /public/association/filter

POST /public/association/filter

GET /public/search

GET /public/auth/request_token

GET /public/auth/validate_token

GET /public/utils/ping

GET /public/utils/version

GET /public/utils/stats

- Query association and evidence by gene identifiers and diseases
- Filter by type of evidence

- Paste the URL in a location bar in a browser
- Use the terminal window (e.g. with CURL)
- Use one of our clients (i.e. R and Python)

<https://www.targetvalidation.org/documentation/api>

Python and R clients for the REST API

opentargets
latest

Search docs

Tutorial
High Level API
Low Level API
Code Documentation
Changelog

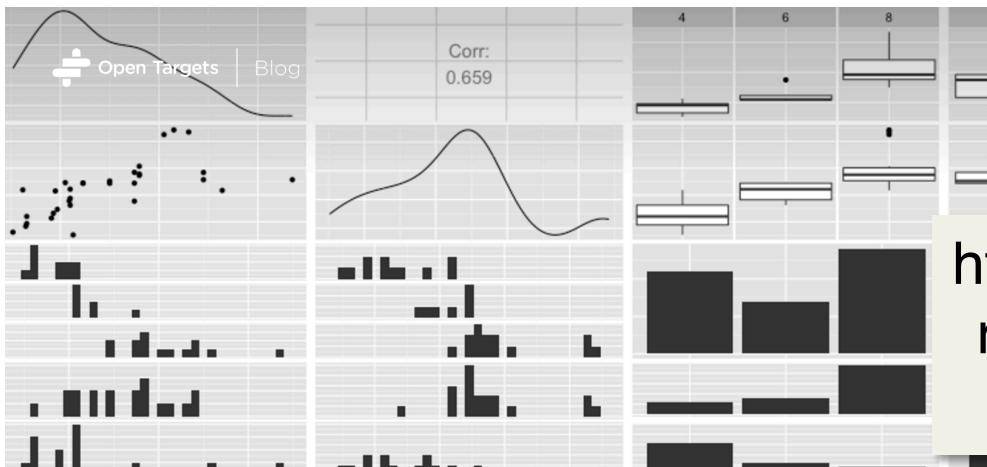
Docs » opentargets - Python client for targetvalidation.org

Edit on GitHub

opentargets - Python client for targetvalidation.org

opentargets is the official python client for the [Open Targets REST API](#) at [targetvalidation.org](#)

<http://opentargets.readthedocs.io>



[https://blog.opentargets.org/
rest-api-exploration-using-
an-r-client/](https://blog.opentargets.org/rest-api-exploration-using-an-r-client/)

How to access Open Targets
with R

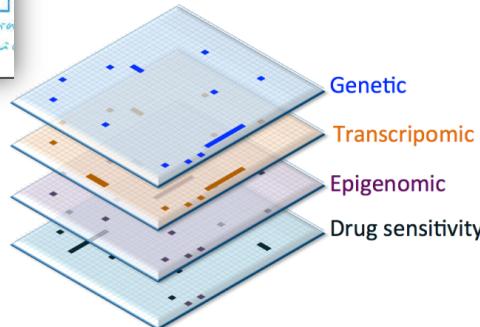
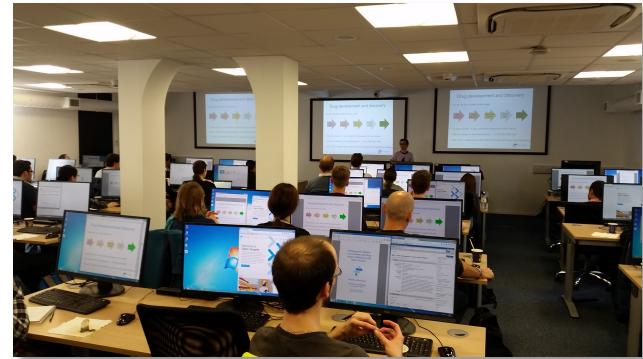
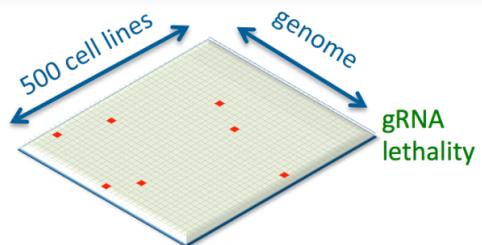
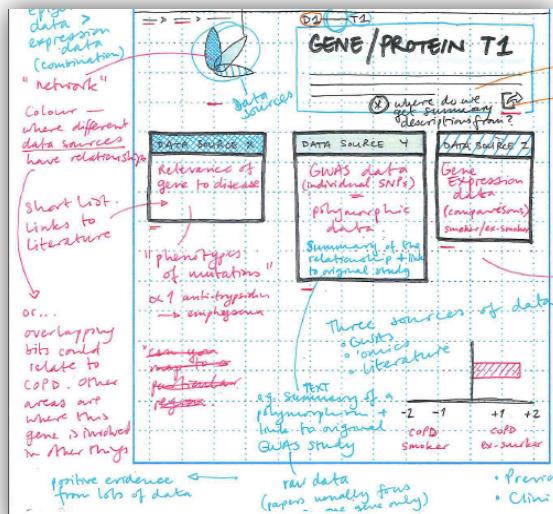
What makes Open Targets unique?

Addressing all areas of human disease

Putting our users first

Working genome wide

Bringing the partners together



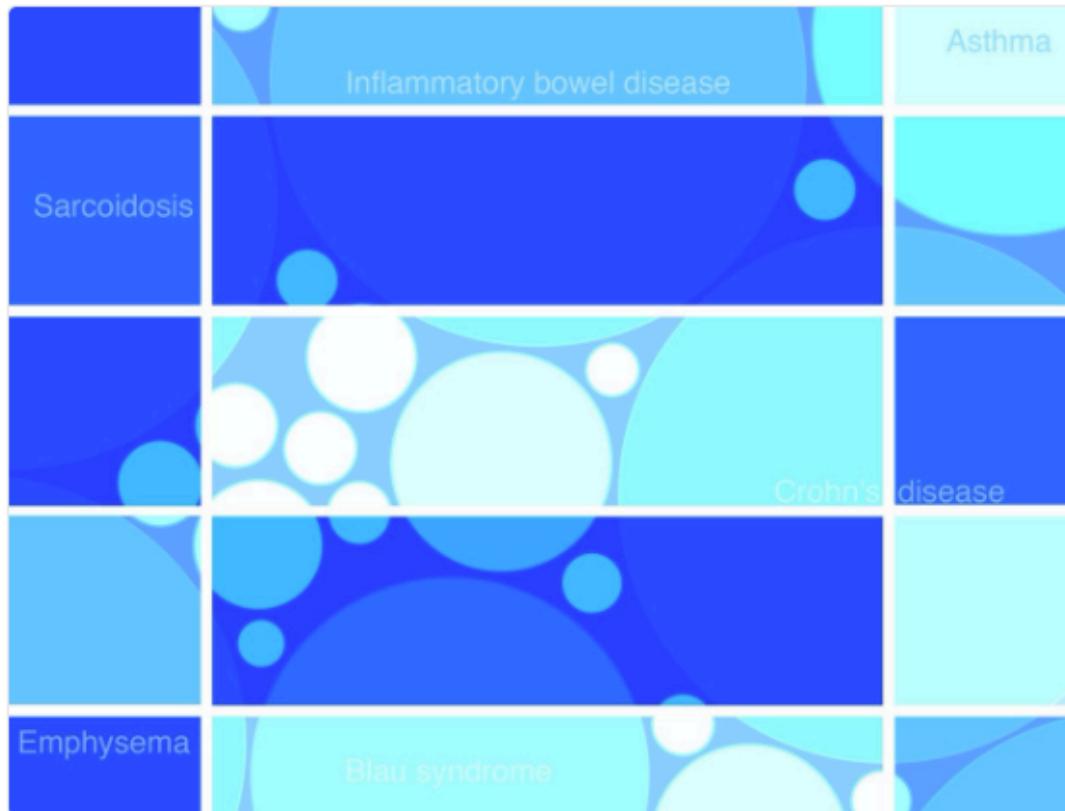
What is next in our 2017 roadmap?



...And the 2017 Breakthrough Articles Award goes to...

#OpenTargets, as well as @MonarchInit & @denovodb! @NAR_Open buff.ly/2iGMXlc

<http://www.narbreakthrough.com/>



RETWEETS
10

LIKES
8



Get in touch



@targetvalidate



support@targetvalidation.org



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blog.opentargets.org/



<http://tinyurl.com/opentargets-in>



Want to give input into the future development of our Platform?

Please take a moment to complete our survey

Take survey

<http://tinyurl.com/platform-your-say>