

Mining gene-disease associations for drug identification and discovery with Open Targets

CRUK Manchester Institute

Denise Carvalho-Silva

Wellcome Genome Campus

Open Targets

Core Bioinformatics and Computational Pipelines



Open Targets



Materials

<https://github.com/deniseOme/training>



slides



exercises



answers

Today 09:30-15:15

- Introduction to the Open Targets Consortium,
- Using the Open Targets Platform

12:30-13:15 lunch

- “Advanced” use of the Open Targets Platform
- Wrap up and feedback survey

Course objectives



What is the Open Targets Consortium?

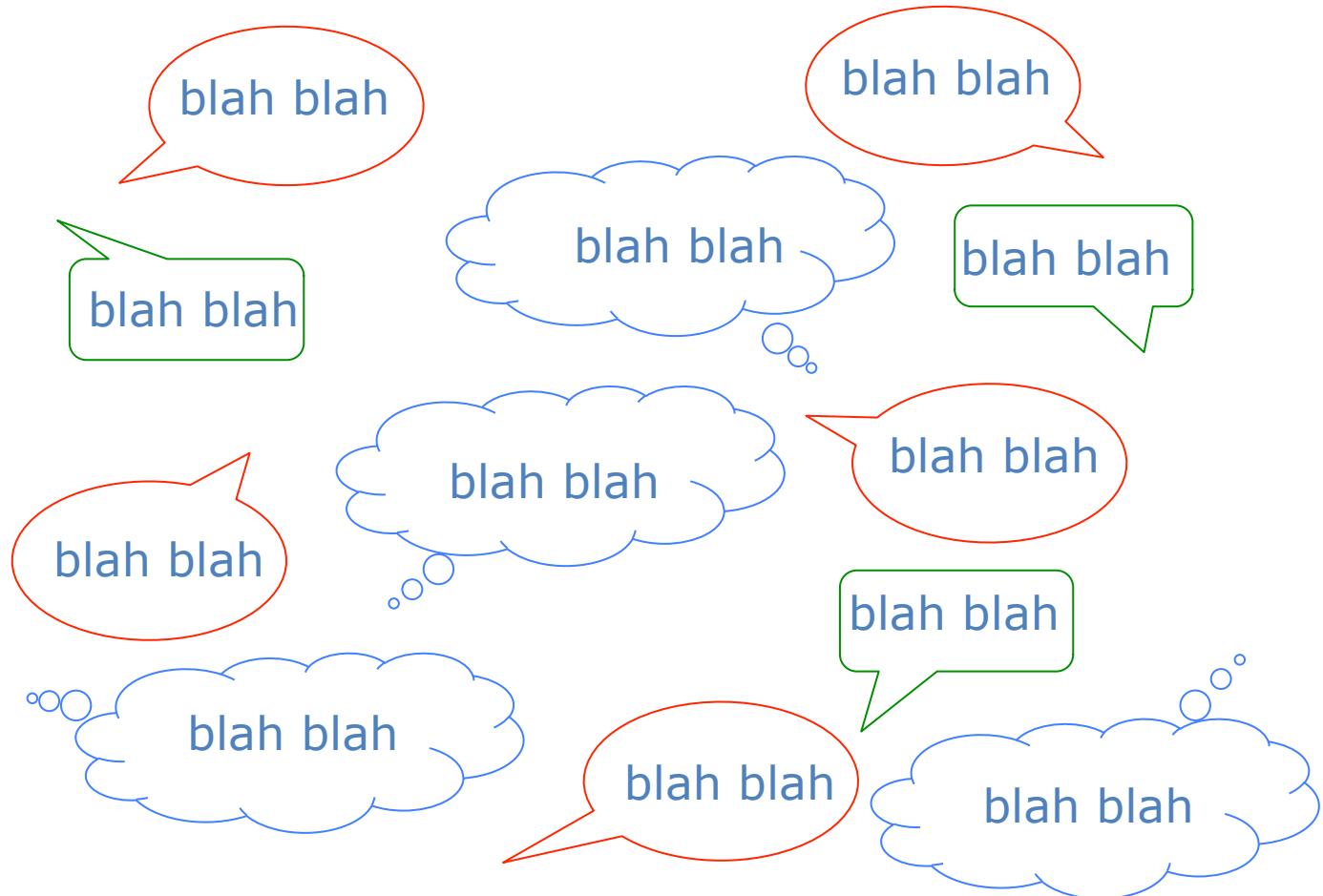
What is the Open Targets Platform?

How to navigate the platform?

How to connect us



Open Targets



Open Targets

Do we need programmes for drug development and discovery?

YES

NO

Quora Ask or Search Quora Ask Question

Infectious Diseases Medical Conditions and Diseases +1

How many diseases today have **no** cure? Which ones?



Karen Tiede, Hula hoop for your health.

641 Views · Most Viewed Writer in Infectious Diseases with 90+ answers

How many? **Most of them, probably.** We have treatments, and support, and care, and some of the time, you live through the disease, but it's not exactly that we "cured" it. You simply didn't have to die of it.

To add to Meghana's list,* diabetes (both kinds), heart disease, arthritis, pretty much all of the auto-immune disorders, most of the mental illnesses, many of the genetic disorders (cystic fibrosis, for example).

The list of diseases that can actually be cured, rather than prevented or treated, is pretty short.

Written Aug 9, 2014 · View Upvotes · Answer requested by 1 person

Upvote | 4

Downvote Comment

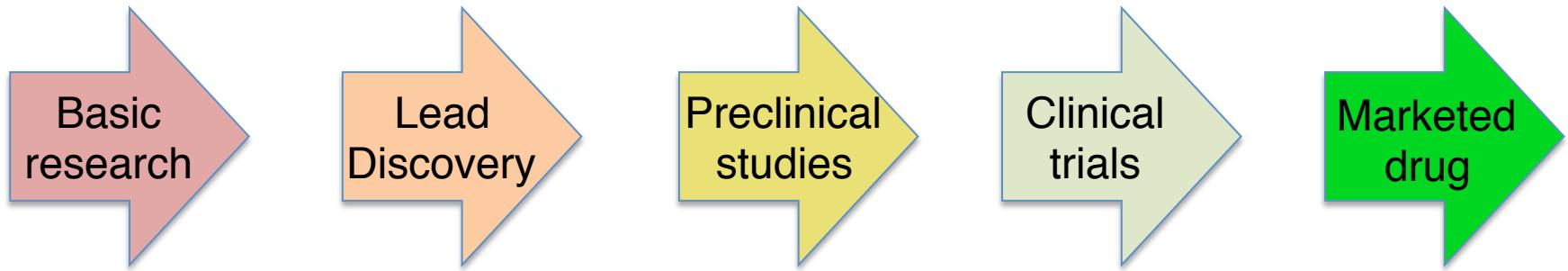


* **Meghana Rastogi**, Research Scholar

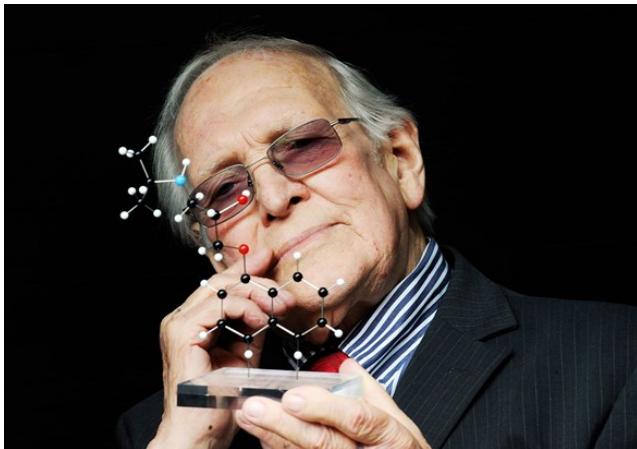
Ebola, HIV, Cancer, Dystonia are one of those disease which don't have any cure.

Drug development and discovery

- Driven by this unmet clinical need



- 10 year journey → new drug from discovery to the market
- Cost for research and development: ~ 2,000,000,000 GBP
- 10% only → approved by the FDA (U.S Food and Drug Administration)



Sir James Black, winner of the 1988 Nobel Prize in Physiology and Medicine for his work in drug development e.g. propranolol (beta blocker) and cimetidine (histamine H₂ receptor antagonist).

“The most fruitful basis for the discovery of a **new** drug is to start with an **old drug**”.

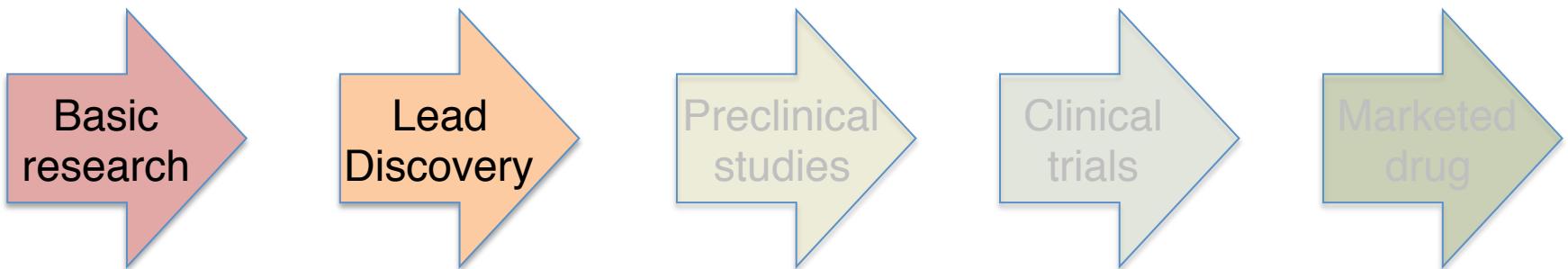
Drug repurposing

Drugs do fail in the clinic

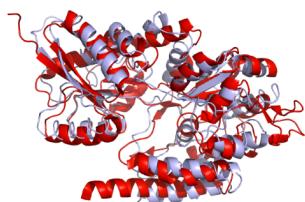
They don't work

They are not safe

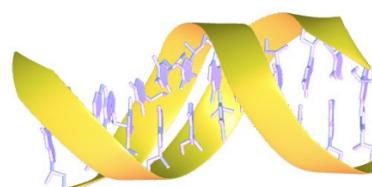
Important role of target identification and validation



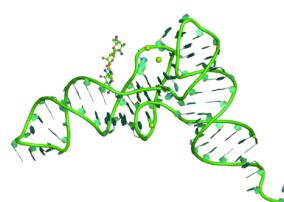
But what is a target?



protein



DNA



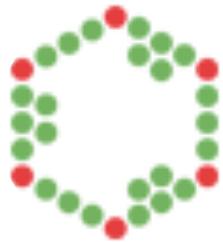
RNA



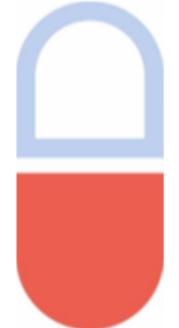
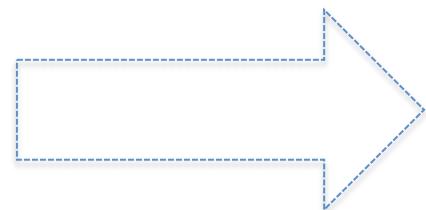
Open Targets

Public databases for drug discovery

- European Bioinformatics Institute (part of EMBL)



- Supporting all stages of drug discovery
- ‘Fitting together like a jigsaw puzzle’ to build hypotheses



?



Open Targets

Huge hurdle: data is everywhere



Wouldn't it be great to have a **one stop shop** with all these data **integrated**?



Yes, a database with **comprehensive, trustworthy** data that we all could access it for **free**?



That'd be fab! It'd be much quicker to carry out our experiments in the lab validating drugs and identifying new ones.



Open Targets



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



*Patrick Vallance, President
Pharmaceuticals R&D
GlaxoSmithKline*



*Professor Sir
Mike Stratton
Director, Sanger Institute*



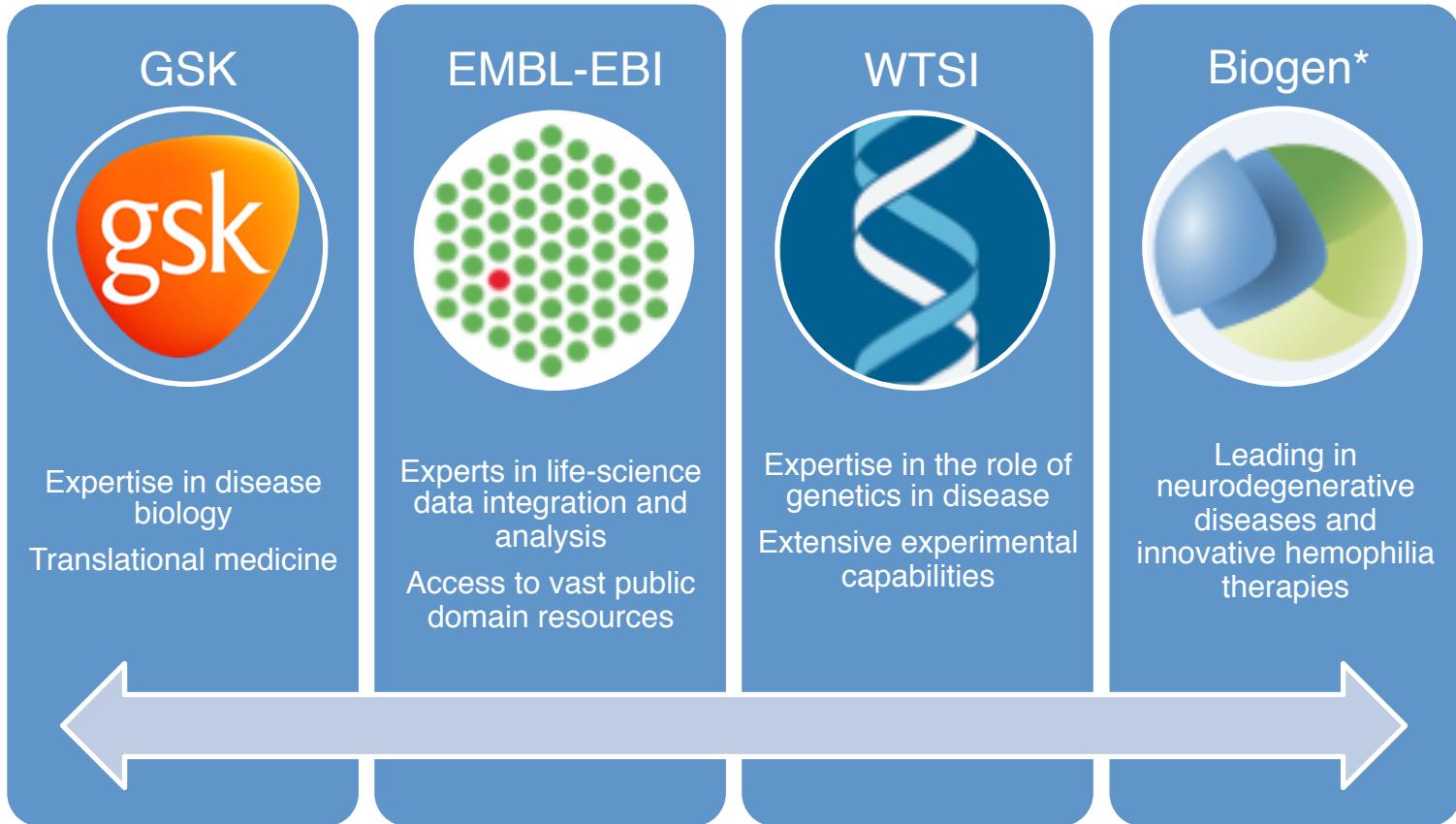
- Target validation can (should) be improved
- One institution could not necessarily or easily do it alone
- Strong desire to collaborate based on highly complimentary skills set
- Existing strong relationships, real commitment to the mission

The consortium

- Launched in March 2014
- Formerly known as CTTV
- Rebranded to Open Targets in April 2016
- Public-private initiative, precompetitive, rapid publication
- Aim: **transform** drug discovery
- How? Through the **identification** and **prioritisation** of targets

<http://www.ebi.ac.uk/about/news/press-releases/open-targets-new-name-new-data>

Who is Open Targets?



*Biogen joined the consortium in February 2016

The two major areas of work within Open Targets*

Core bioinformatics pipelines



Database for data integration

Web portal

REST API

Python and R clients

Data dumps

Experimental projects



Generate new data

CRISPR

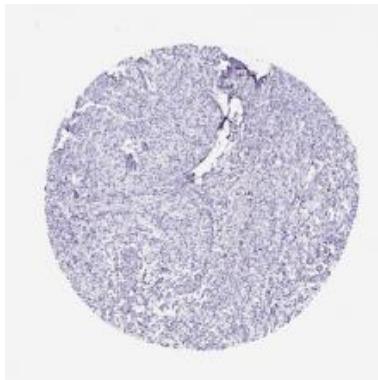
Organoids

Single cell RNASeq

Cell line fusion analyses

*www.opentargets.org/projects

Experimental projects



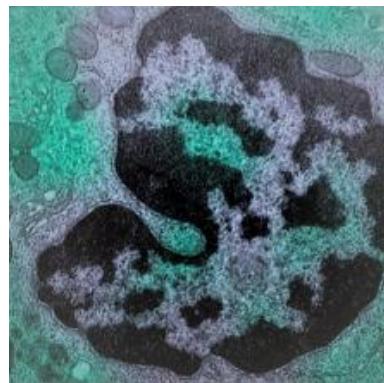
Oncology



Respiratory



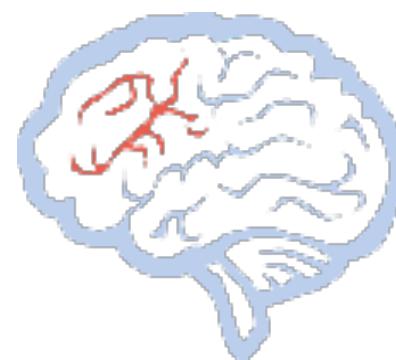
IBD



Inflammation
and immunity



Cell line
epigenomes



Neurodegenerative
diseases

Scientific project portfolio

Oncology



Immunology



Neurodegeneration



Cross-Disease



Human cellular experiments

- 1000 Cell-line Fusion Analysis
- CRISPR synthetic lethality screen
- NK cell receptors

- IBD Organoids,
- MacroScreen
- Dendritic Cell Screen
- Asthma Single-cell

- Ox. stress & tau CRISPR
- Familial Alzheimer's single-cell RNAseq



Genetics as a tool

- NGS Melanoma
- Cancer Signaling Pathways

- IBD & MS GWAS fine-mapping
- Bronchiectasis

- Parkinson's & Alzheimer's GWAS resolution

- Influential Variants
- Metabolite GWAS



Enabling resource

- Immune cell functional maps
- IBD BioResource

- Neuron functional maps

- CELLector
- Cell line Epigenomics



Robust Data Integration
www.targetvalidation.org

Browsing the Open Targets website

Can you explore Open Targets consortium website to find out:

- More about the consortium, including its core principles
- Types of cancer under experimental investigation
- The key challenge of the Core Bioinformatics team
- How to get to the Target Validation Platform

Core bioinformatics pipelines

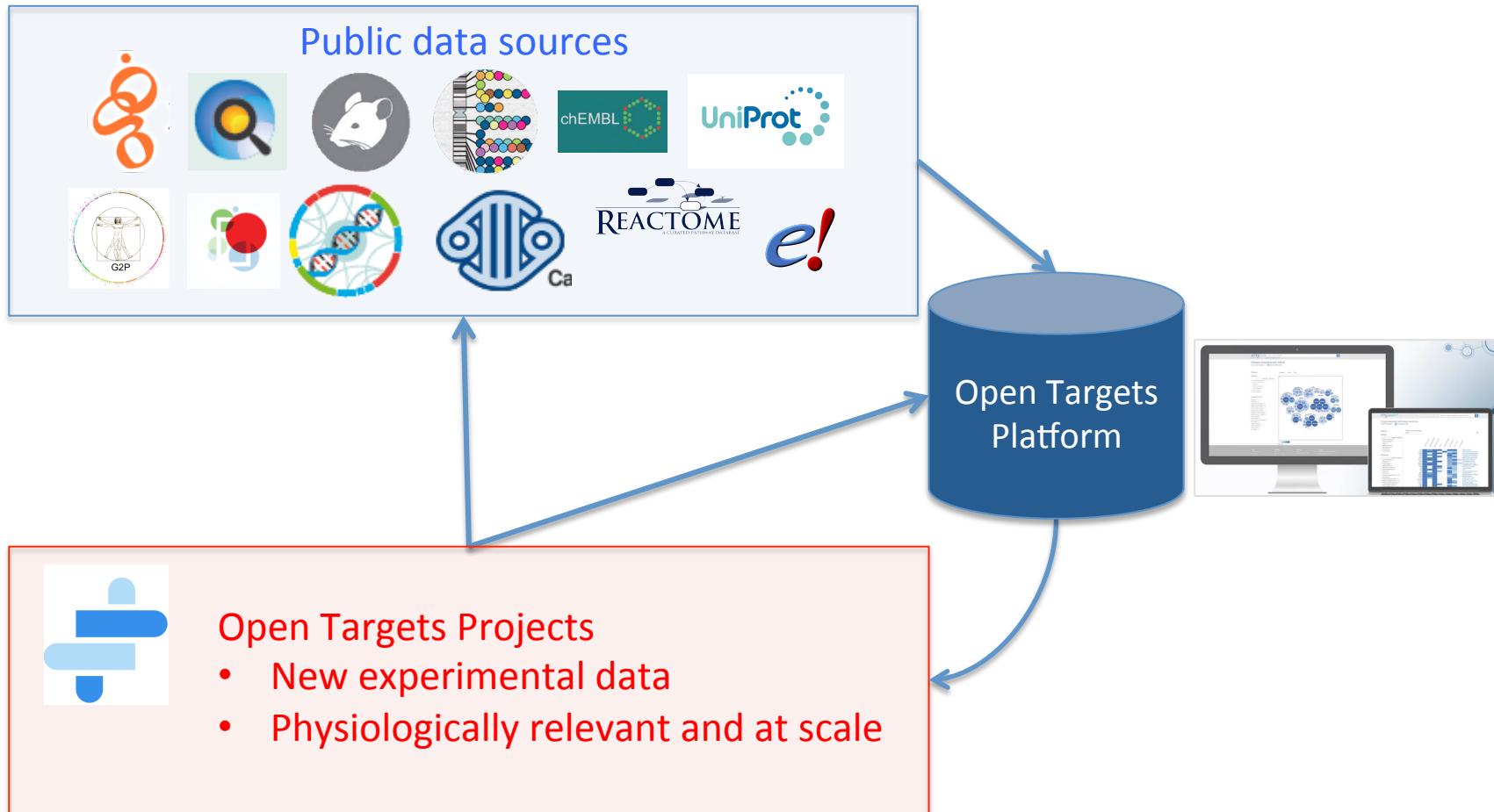
- Open Targets Platform: first release (Dec 2015)

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



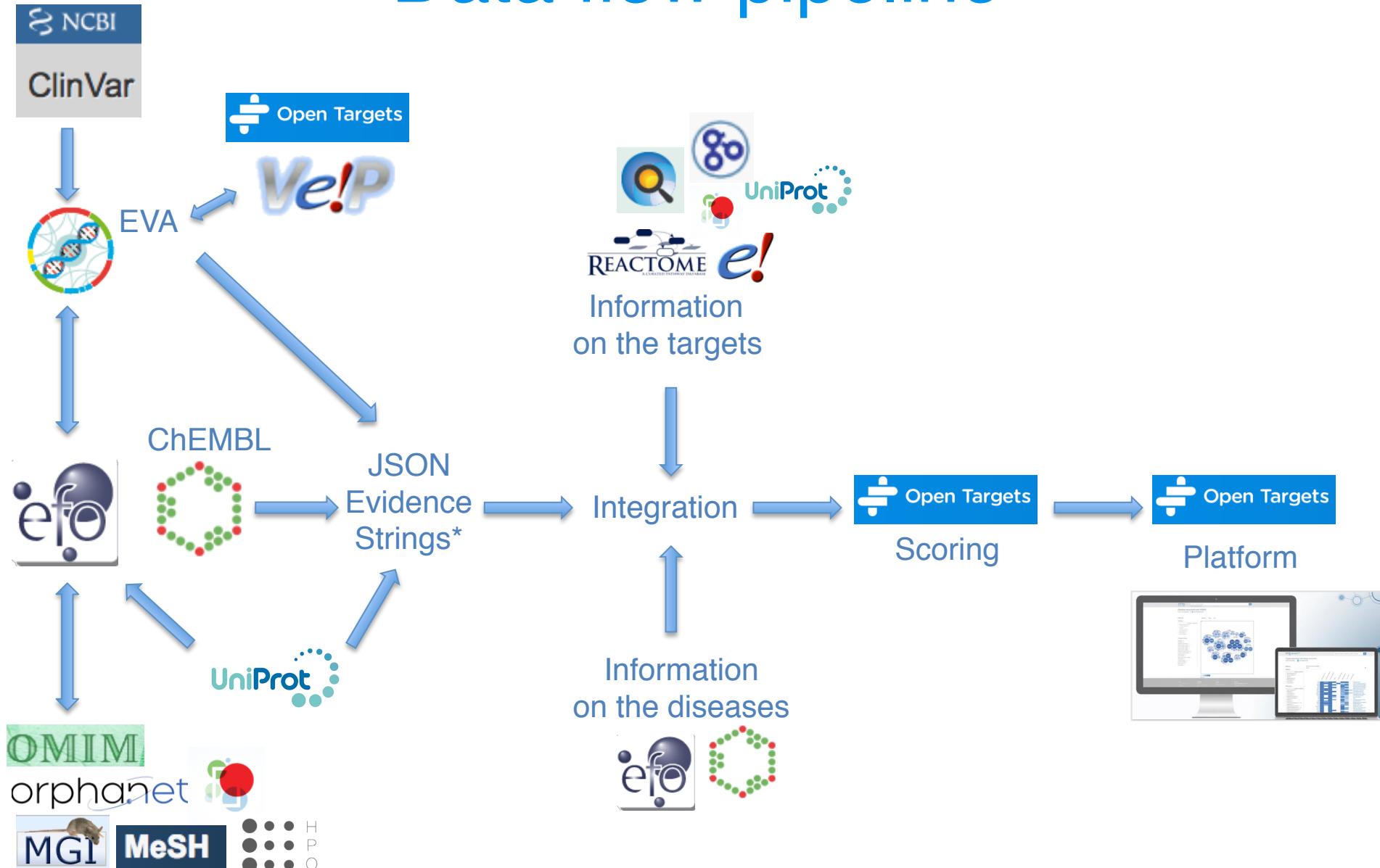
- Help scientists identify and prioritise relationships between targets and diseases

Platform integrates existing and new data



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

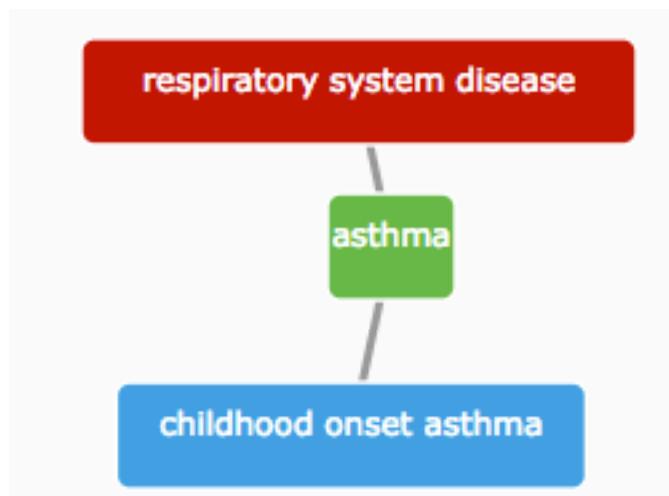
Data flow pipeline



*document = IDs (gene, disease, papers) + curation (e.g. manual) + evidence + source + stats for the score

Experimental Factor Ontology (EFO)

- Ontology: smart dictionary → relationships between entities
- EFO: way to organise experimental variables (e.g. diseases)



controlled vocabulary
+
hierarchy (relationship)

Increases the richness of annotation
Promotes consistency
Allow for easier and automatic integration

How do we associate diseases w/ targets?

Step 1: mine phenotypes and diseases from ChEMBL, UniProt and EVA (w/ ClinVar)

Step 2: map these to an ontology using EFO terms

Step 3: use genes as proxies for our targets

Step 4: create target-disease evidence JSON objects

Step 5: calculate for each evidence the likelihood of gene A being associated with disease B

Step 6: compute integrated target-disease scores at the data source, data type and overall level

Hypothetical scenario for a use case

The screenshot shows the header of the *Nature Genetics* website. The logo "nature genetics" is on the left. The main navigation menu includes "Home", "Current issue", "Comment", "Research", "Archive", "Authors & referees", and "About the journal". Below the menu, a breadcrumb trail shows the path: "home > archive > issue > letter > full text".

[home](#) > [archive](#) > [issue](#) > [letter](#) > [full text](#)

NATURE GENETICS | LETTER



Distinct genetic architectures for syndromic and nonsyndromic congenital heart defects identified by exome sequencing

Alejandro Sifrim, Marc-Phillip Hitz, Anna Wilsdon, Jeroen Breckpot, Saeed H Al Turki, Bernard Thienpont, Jeremy McRae, Tomas W Fitzgerald, Tarjinder Singh, Ganesh Jawahar Swaminathan, Elena Prigmore, Diana Rajan, Hashim Abdul-Khalil, Siddharth Banka, Ulrike M M Bauer, Jamie Bentham, Felix Berger, Shoumo Bhattacharya, Frances Bu'Lock, Natalie Canham, Irina-Gabriela Colgiu, Catherine Cosgrove, Helen Cox, Ingo Daehnert, Allan Daly
+ et al.

Nature Genetics 48, 1060–1065 (2016) | doi:10.1038/ng.3627

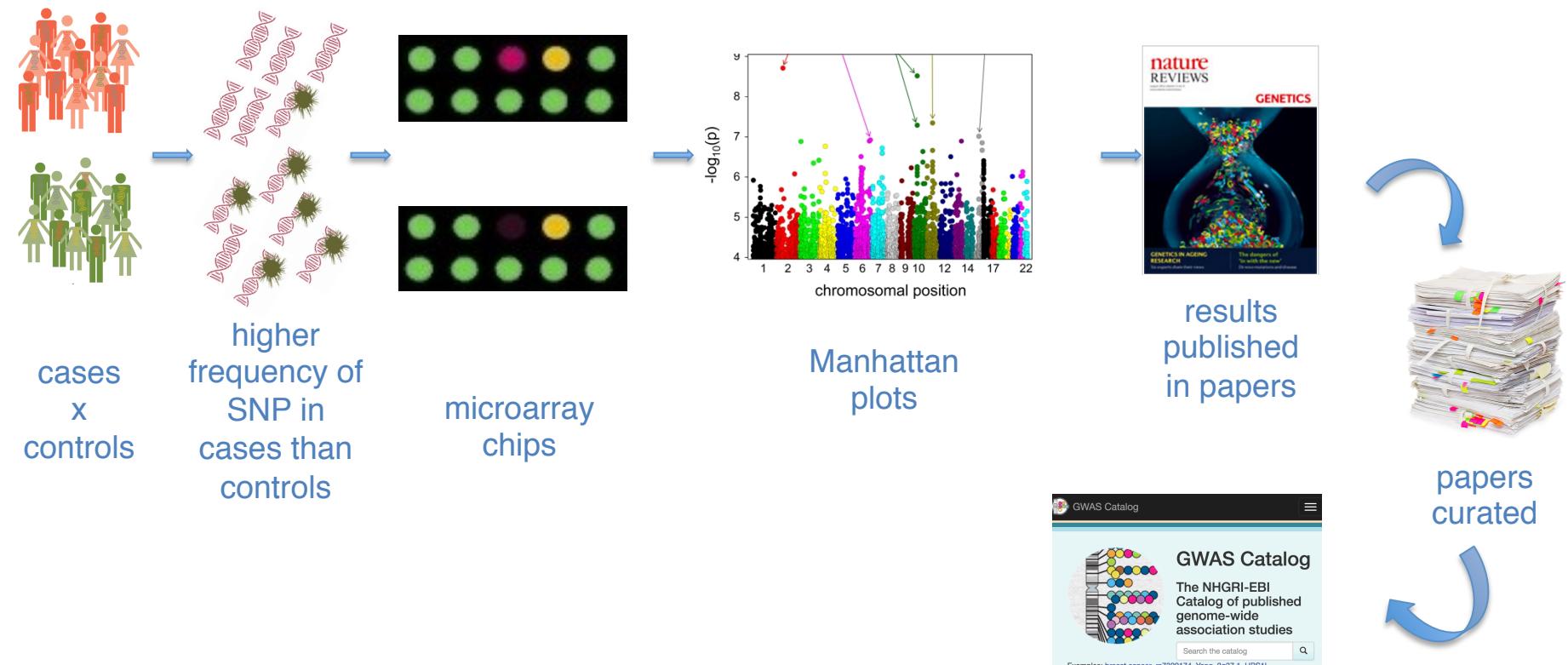
Received 23 December 2015 | Accepted 24 June 2016 | Published online 01 August 2016

Congenital heart disease (CHD)

- How many targets are associated with CHD?
- Can you filter this number to get the targets based on Genetic associations only?
- Which data sources were used to support this genetic association?

Data sources: GWAS catalog

- GenomeWide Association Studies (www.nature.com/nrg/series/gwas/index.html)
- Array-based chips → genotyping 100,000 SNPs genomewide

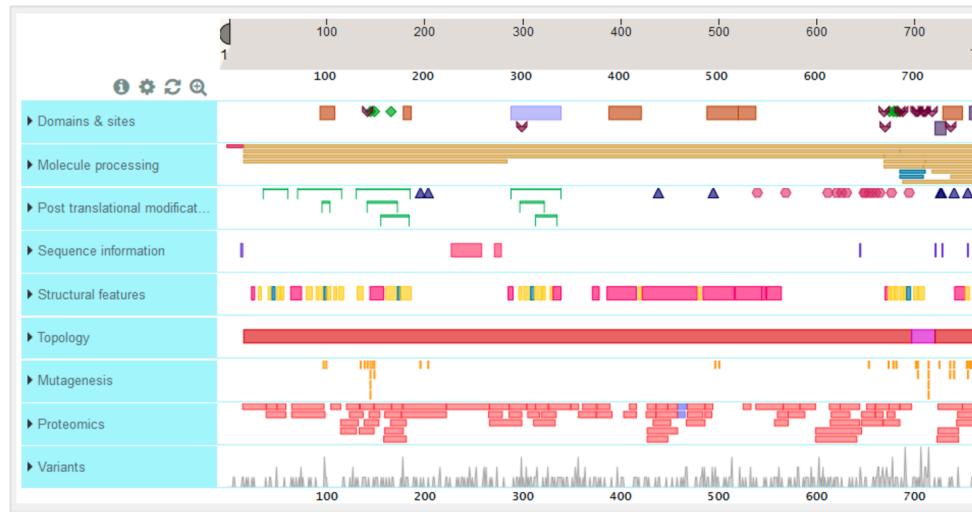


<https://www.ebi.ac.uk/gwas/>

SNP-trait associations
Published in the GWAS catalog

Data sources: UniProt* and UniProt literature**

- Catalog of protein information (sequence, annotation, function)



* Manual curation of variants in the coding region, seen in patients

** Associations between target and disease, no specific mutation

Data sources: EVA

- Catalog of genetic variants (SNPs, CNVs; germline or somatic)
- Clinical information from ClinVar available: rare diseases

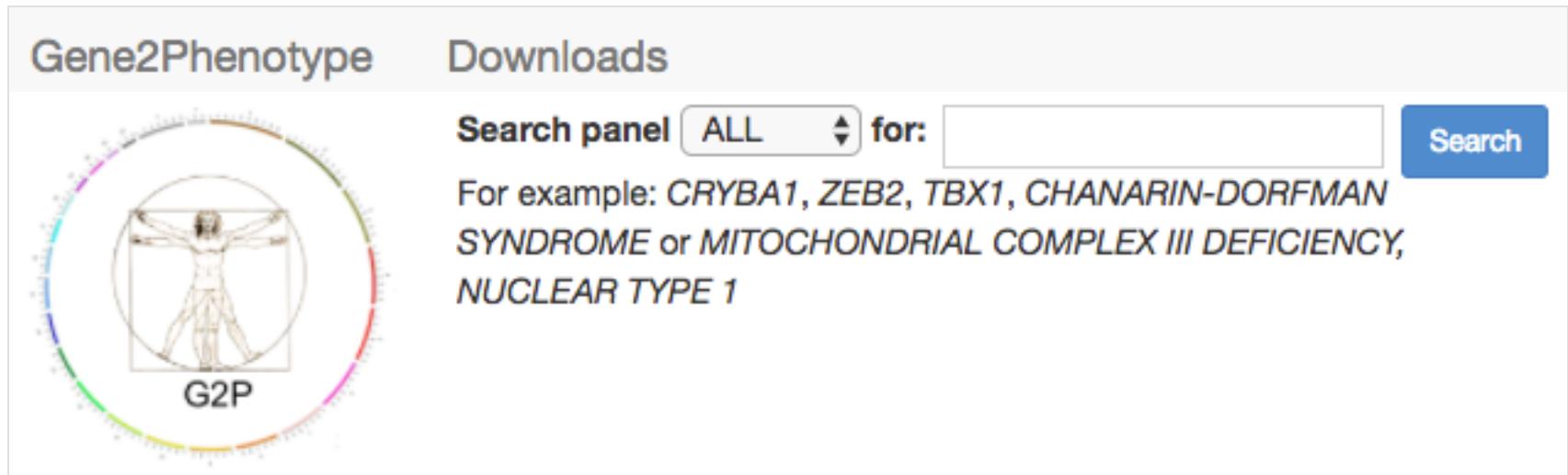
The screenshot shows the European Variation Archive (EVA) website. The header features the EVA logo and the text "European Variation Archive". Below the header is a navigation bar with links: Home, Submit Data, Study Browser, Variant Browser, Clinical Browser (which is highlighted in blue), GA4GH, API, FAQ, and Feedback.

The main content area is titled "ClinVar Browser" with a help icon. On the left, there is a "Filter" sidebar. The "Position" filter is set to "Assembly : GRCh37". The "Filter By:" dropdown is set to "Chromosomal", and the "Chromosome" dropdown shows "2:48000000-49000000". The "Consequence" filter has a "search" input field.

The main table displays 10 records out of 960, showing clinical variant details:

...	Posi...	Affecte... i	A...	Most Severe Consequence...	Trait	Clinical Significance	ClinVar ...
2	480...	MSH6	T/G	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	G/A	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	C/T	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	C/T	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	G/T	5_prime_UTR...	Lynch synd...	Uncertain s...	RCV000...
2	480...	MSH6	G/T	5_prime_UTR...	Hereditary ...	conflicting ...	RCV000...
2	480...	MSH6	C/T	5_prime_UTR...	Lynch synd...	Uncertain s...	RCV000...
2	480...	MSH6	C/T	5_prime_UTR...	Hereditary ...	conflicting ...	RCV000...
2	480...	MSH6	G/T	5_prime_UTR...	Hereditary ...	Benign	RCV000...
2	480...	MSH6	G/T	5_prime_UTR...	Hereditary ...	conflicting ...	RCV000...

Data sources: Gene2Phenotype



Gene2Phenotype

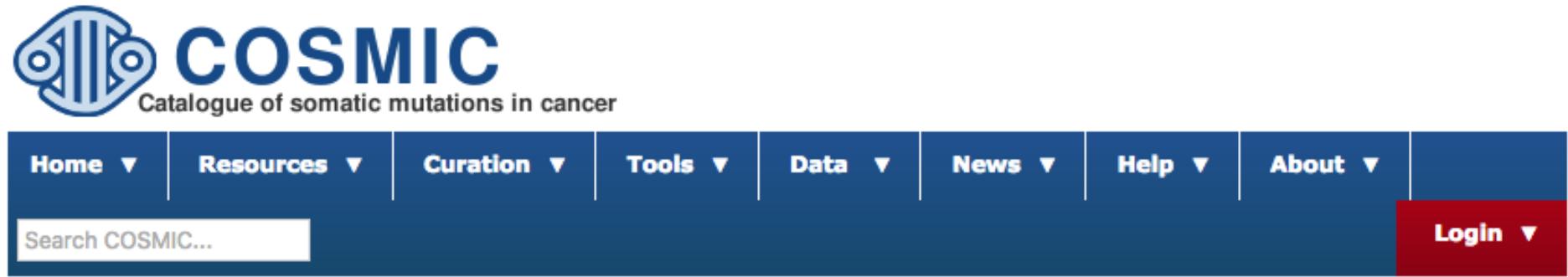
Downloads

Search panel ALL for: Search

For example: *CRYBA1, ZEB2, TBX1, CHANARIN-DORFMAN SYNDROME or MITOCHONDRIAL COMPLEX III DEFICIENCY, NUCLEAR TYPE 1*

- Catalog of variants, genes, phenotypes
- Developmental disorders
- Literature curation → consultant clinical geneticists in the UK

Data sources: The Cancer Gene Census



The screenshot shows the COSMIC website homepage. At the top left is the COSMIC logo, which consists of a stylized blue eye-like icon followed by the word "COSMIC" in a bold, blue, sans-serif font. Below the logo is the tagline "Catalogue of somatic mutations in cancer". A horizontal navigation bar follows, featuring eight items: "Home ▾", "Resources ▾", "Curation ▾", "Tools ▾", "Data ▾", "News ▾", "Help ▾", and "About ▾". To the right of this bar is a red "Login ▾" button. Below the navigation bar is a search bar containing the placeholder text "Search COSMIC...".

- catalog of genes for which mutations have been causally implicated in cancer
- genes associated with specific plus other cancers associated with that gene

Data sources: IntOGen

The screenshot shows the homepage of the IntOGen website. At the top is a navigation bar with links for Search, Downloads, Analysis, and About, along with a Sign In button. Below the navigation bar is the IntOGen logo, which consists of a stylized orange 'i' icon followed by the word 'intOGen' in lowercase. To the right of the logo is the text 'Integrative Onco Genomics'. Below the logo is a search bar containing the placeholder text 'e.g. Mutation frequency of VHL'. To the right of the search bar is a microphone icon. Below the search bar are links for 'Search example' and 'Show more examples'.

intOGen

Search Downloads Analysis About Sign in

e.g. Mutation frequency of VHL

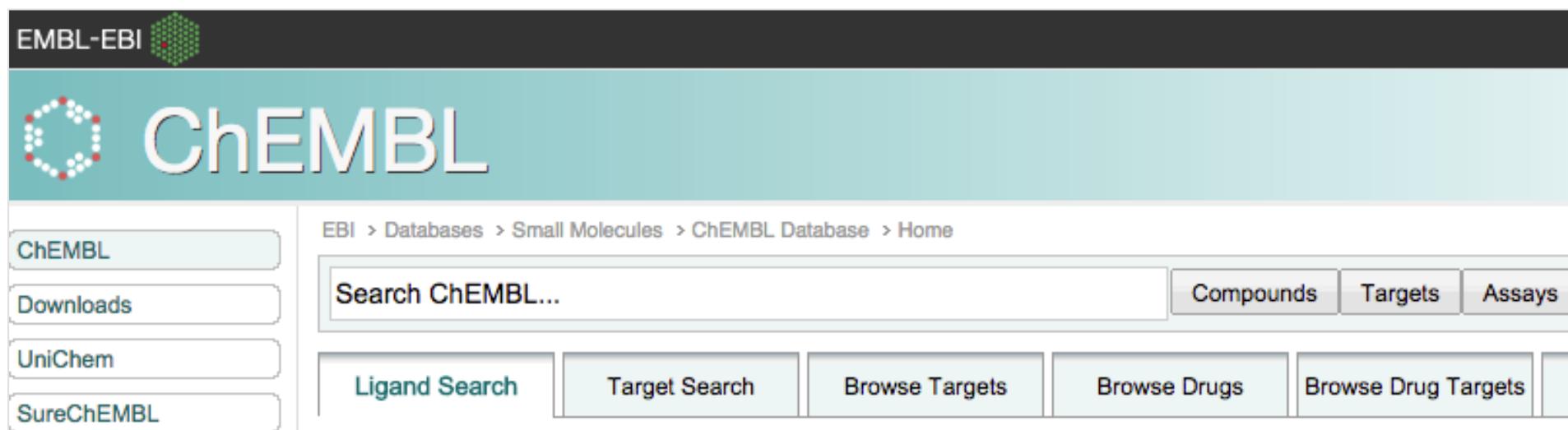
Integrative
Onco
Genomics

Search example | Show more examples

- catalog of genes and somatic mutations
- involvement in tumorigenesis

<https://www.intogen.org/search>

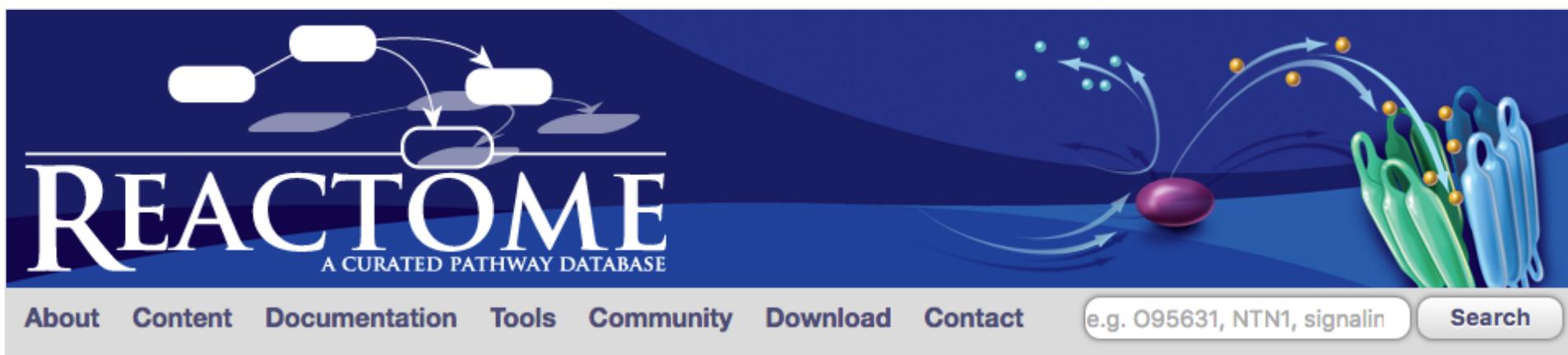
Data sources: ChEMBL



The screenshot shows the ChEMBL database homepage. At the top left is the EMBL-EBI logo. The main header features the ChEMBL logo (a stylized circular pattern) and the word "ChEMBL". Below the header is a navigation bar with links to "ChEMBL", "Downloads", "UniChem", and "SureChEMBL". To the right of the navigation bar is a search bar containing the placeholder "Search ChEMBL...". Above the search bar is a breadcrumb trail: "EBI > Databases > Small Molecules > ChEMBL Database > Home". To the right of the search bar are three buttons: "Compounds", "Targets", and "Assays". Below the search bar are five buttons: "Ligand Search", "Target Search", "Browse Targets", "Browse Drugs", and "Browse Drug Targets".

- Catalog of known drugs linked to a disease and a known target
- Drugs → FDA approved for marketing or clinical trials

Data sources: Reactome

The image shows the Reactome homepage. At the top, there is a large blue banner featuring a molecular interaction diagram with nodes and arrows. Below the banner, the word "REACTOME" is written in large, white, serif capital letters, with "A CURATED PATHWAY DATABASE" in smaller letters underneath. Below the title, there is a navigation bar with links: "About", "Content", "Documentation", "Tools", "Community", "Download", and "Contact". To the right of the navigation bar is a search bar containing the placeholder text "e.g. O95631, NTN1, signalin" and a "Search" button.

- Catalog of biochemical reactions and pathways
- Manual curation of pathways affected by mutations

Data sources: Expression Atlas

EMBL-EBI 

Services Research Training About us

 Expression Atlas

Enter gene query...
Examples: [ASPM](#), [Apoptosis](#), [ENSMUSG00000021789](#), [zinc finger](#)

Search

Home Release notes FAQ Download Help Licence About Feedback

Expression Atlas: Differential and Baseline Expression

The Expression Atlas provides information on gene expression patterns under different biological conditions. Gene expression data is re-analysed in-house to detect genes showing interesting baseline and differential expression patterns. [Read more about Expression Atlas.](#)

- Catalog of patterns of gene expression
- Baseline expression for human genes
- Differential expression (healthy versus diseases tissues)

Data sources: Europe PMC

The screenshot shows the Europe PMC website. At the top, there is a navigation bar with links for "About", "Tools", "Developers", "Help", and "Europe PMC plus". To the left of the navigation bar is the Europe PMC logo, which consists of three overlapping colored circles (blue, green, and red) followed by the text "Europe PMC". Below the navigation bar is a search bar with the placeholder text "Search worldwide, life-sciences literature". To the right of the search bar is a blue "Search" button with a magnifying glass icon. Further to the right is a link to "Advanced Search". Below the search bar, there is a text input field containing the example query "E.g. "breast cancer" HER2 Smith J".

- Text mining → association between targets and diseases
- Titles, abstracts, full text (but supplementary tables) are mined
- Co-occurrence in the same sentence of target and disease names (or synonyms)

Data sources: PhenoDigm

The screenshot shows the homepage of the PhenoDigm database. At the top, there is a dark header bar with the Wellcome Trust Sanger Institute logo on the left. To the right of the logo is a blue navigation bar containing links for "ABOUT" (with a dropdown arrow), "Who we are", "Careers", "Study", "Sex in Science", "Groups", and "Campus". On the far right of the blue bar is a magnifying glass icon representing a search function. Below the header, the main title "Welcome to PhenoDigm (PHENOtype comparisons for Disease and Gene Models)" is displayed in large, bold, black font. Underneath the title, there is a horizontal menu bar with three items: "Diseases" (which is highlighted in blue and underlined), "Tissue phenotype associations", and "Secondary phenotypes". Below this menu, a large text block reads: "Analyzing curated phenotype annotations to associate animal models with human diseases".

Welcome to PhenoDigm (PHENOtype comparisons for Disease and Gene Models)

Diseases Tissue phenotype associations Secondary phenotypes

Analyzing curated phenotype annotations to associate animal models with human diseases

- Semantic approach to map between clinical features observed in humans and annotations of phenotypes in mouse models
- PMID: 23660285

<http://www.sanger.ac.uk/resources/databases/phenodigm/>

Data sources and types

- Similar data sources are grouped for the score calculation

Data sources	Data type
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

- Do you have a favourite data you would like us to have?

Congenital heart disease (CHD)

- Let's focus on the top gene in the list, i.e. *GDF1*
- Can you get a list of genetic variants (i.e. mutations) that associate this target with CHD?
- How many papers support the association through text mining?
- Which tissues does this gene seem to be highly expressed according to the GTEx project?
- Are there other cardiovascular diseases associated with this target? How strong is this association?

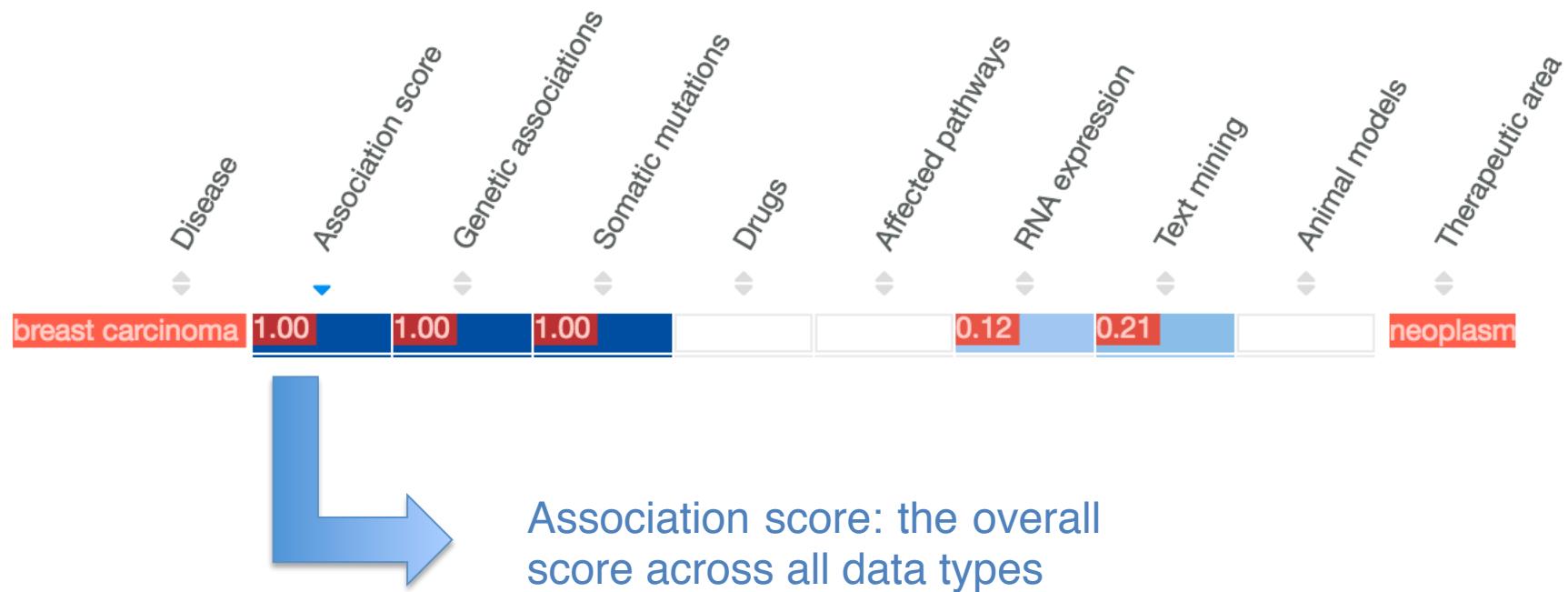
How confident can you be of the target-disease associations in Open Targets?

We've developed a scoring scheme*

- A) per evidence
- B) per data source (e.g. GWAS catalog)
- C) per data type (e.g. Genetic associations)
- D) overall

* https://github.com/CTTV/association_score_methods

Ranking the target-disease association



- Based on the data sources
- Different weight applied:

genetic association = drugs = mutations = pathways > RNA expression > animal models = text mining

How strong are the associations?

- Look for our score and the 5 shades of blue!



PIK3CD	1.00	1.00						0.03	0.18		
PIK3R1											

- No evidence to support the association: score is 0
- Sources providing their own score:  

Disclaimer: score, dos and don'ts

- It's a ranking of target-disease associations
- It shows how confident we are in the association
- It's based on data sources, publicly available

Maximum score → high quality source of data

Maximum score → several medium quality source of data

- It can help you to design your null hypotheses
- It can NOT be used to say:

gene A should be targeted to treat **disease Y**

Drugs marketed and in clinical trials

One of the targets in the paper that is associated with CHD is *PRKD1*.

- What are the drugs currently in clinical trials and targeting this gene?
- Can you list a couple of cancer types where this gene has been targeted at?

Exercises and Answers

<https://github.com/deniseOme/training>



Wrap up

Open Targets Platform is the place!

Identify and prioritise targets for drug discovery

Target-disease associations: different sources

Integrated information on target and diseases

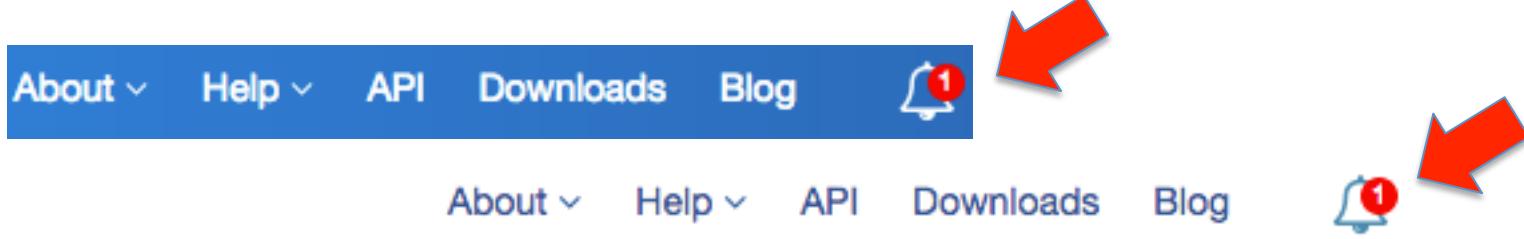
Oh Yes!
And all is 100% free
and open source



Open Targets

Open Targets Platform

- Intuitive and easy-to-use web interface
- Constantly updated: new data, new web features*



- Improvements driven by our user communities

* <https://www.targetvalidation.org/release-notes>

We support decision-making

A) Which targets are associated with a disease?

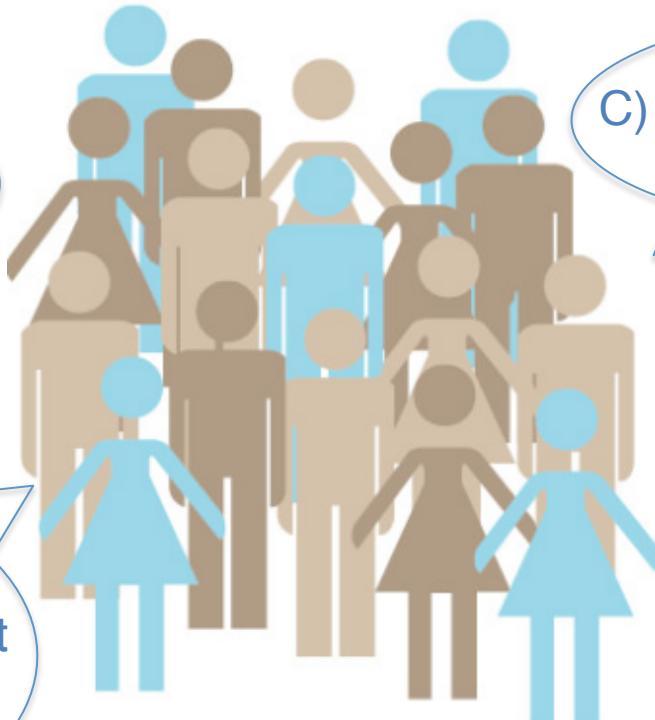
B) What evidence supports this target-disease association?

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?



Some impressive numbers

- Latest release: September 2016

30K
targets

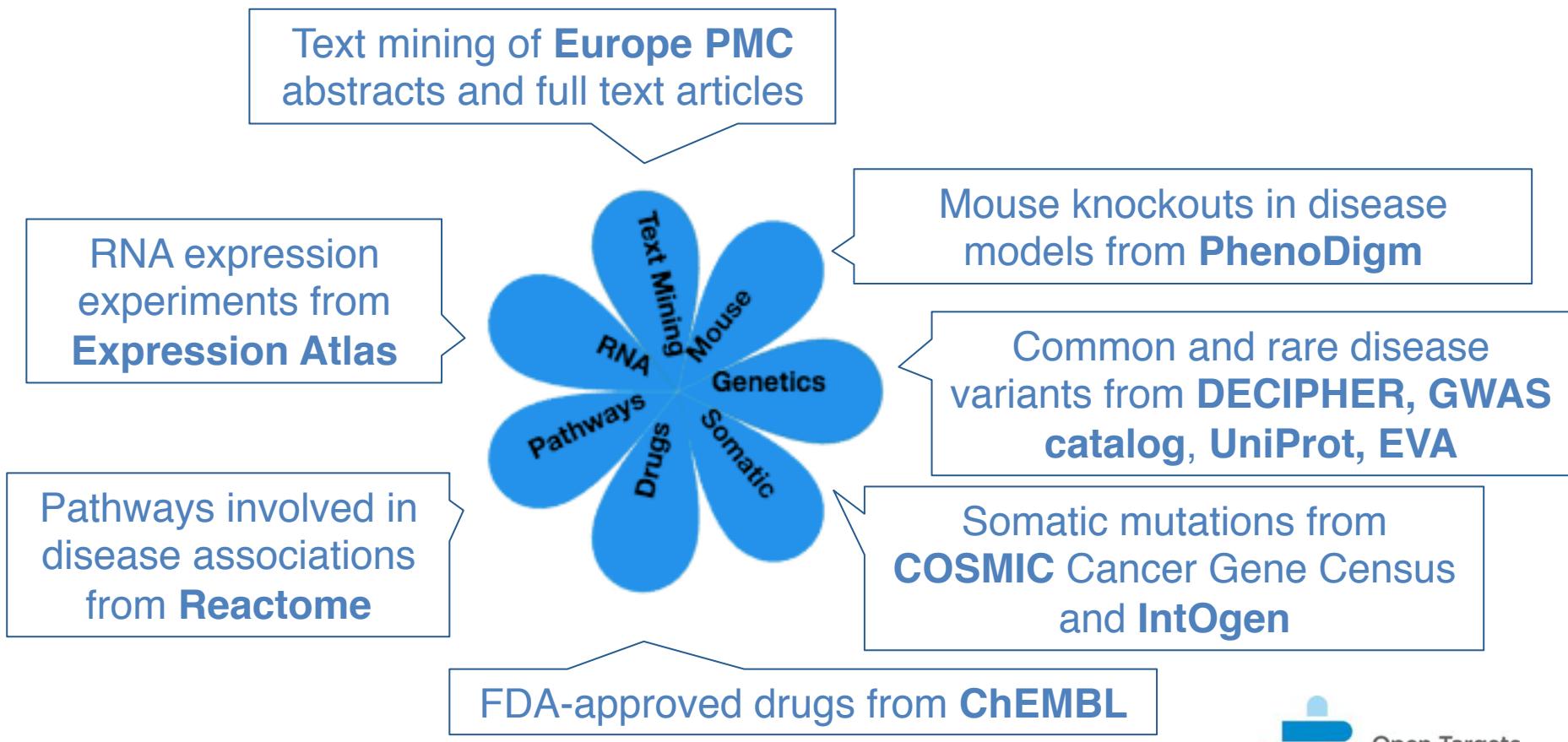
2.4M
associations

9.4K
diseases



> 2 million associations

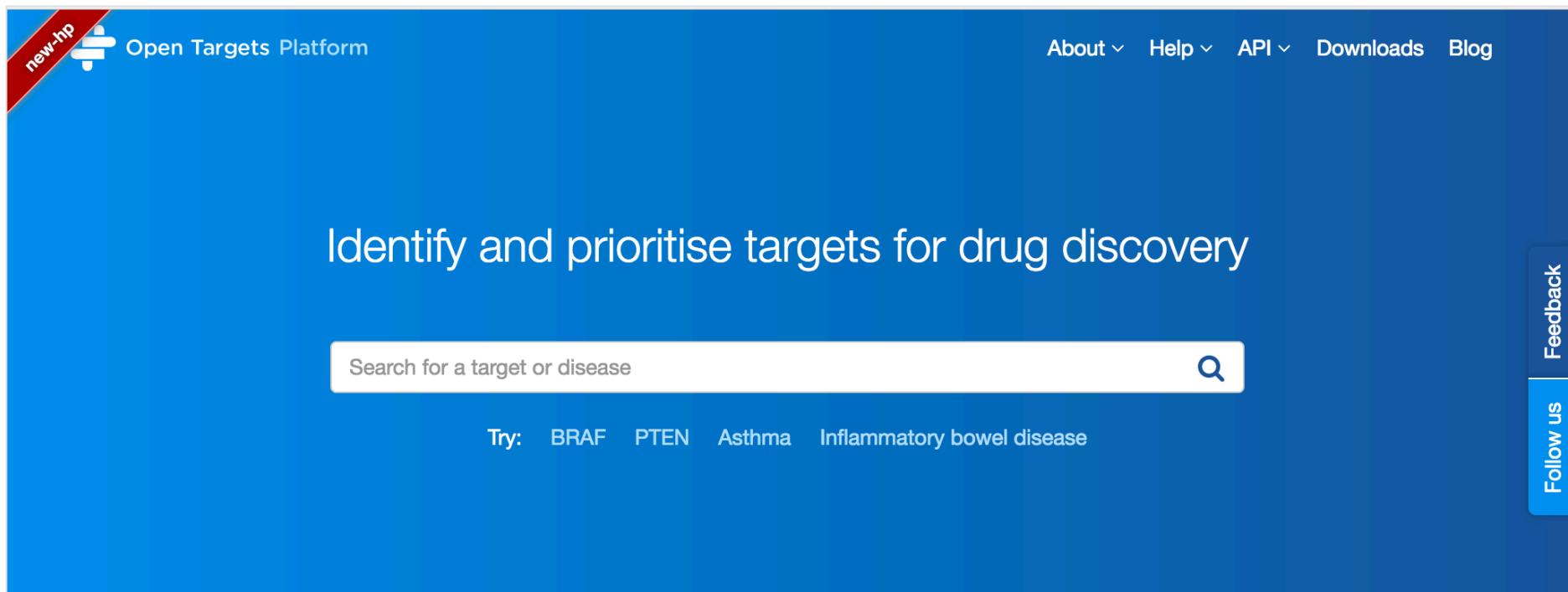
Supported by publicly available data: the evidence



Open Targets

Coming up: Open Targets Platform

New release, new look, new and updated data



The screenshot shows the homepage of the Open Targets Platform. At the top left is a red ribbon with the text "new-hp" and a small icon. To its right is the "Open Targets Platform" logo. On the right side of the header are navigation links: "About", "Help", "API", "Downloads", and "Blog". The main title "Identify and prioritise targets for drug discovery" is centered above a search bar. The search bar contains the placeholder text "Search for a target or disease" and a magnifying glass icon. Below the search bar, there is a "Try:" button followed by a list of terms: BRAF, PTEN, Asthma, and Inflammatory bowel disease. A vertical sidebar on the right edge features the text "Follow us" and "Feedback".

new-hp

Open Targets Platform

About ▾ Help ▾ API ▾ Downloads Blog

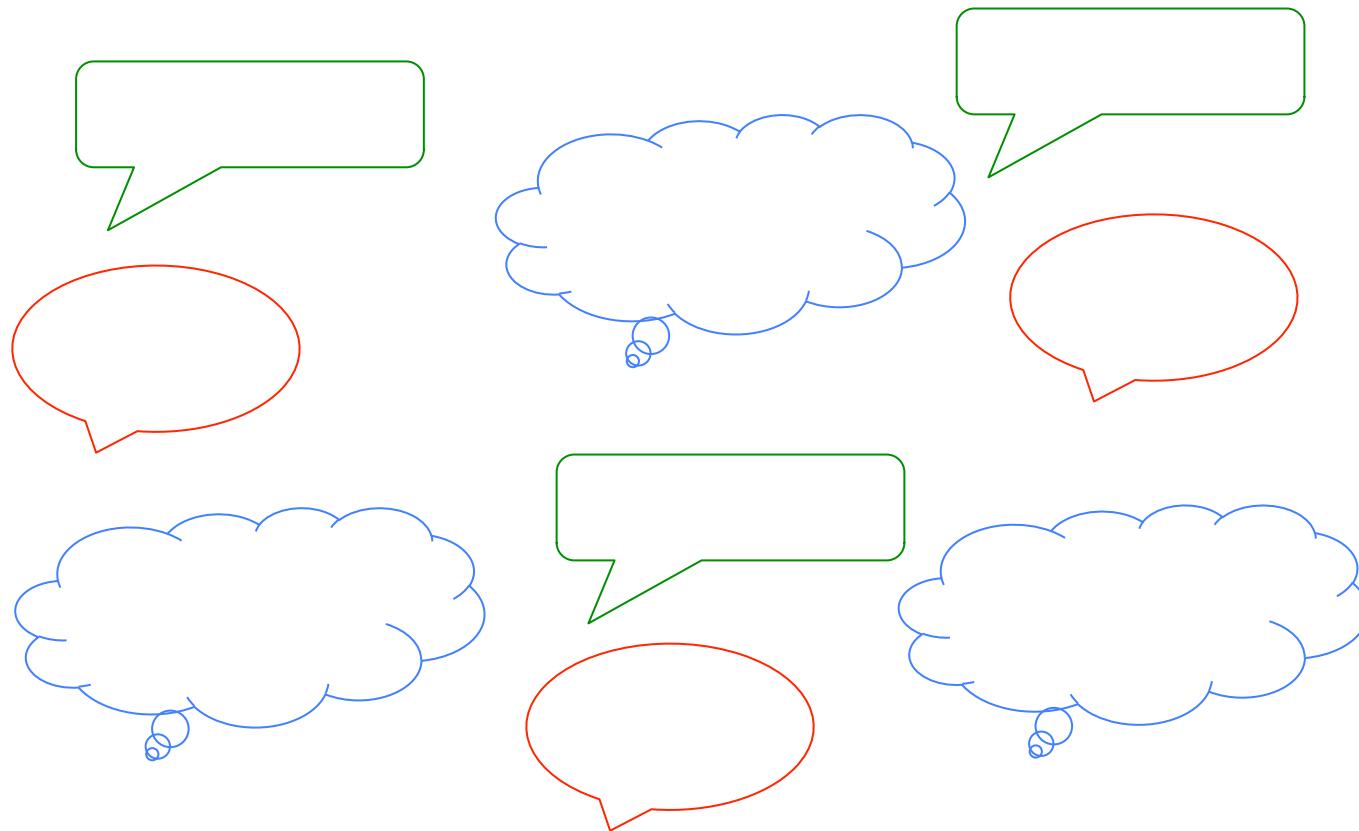
Identify and prioritise targets for drug discovery

Search for a target or disease

Try: BRAF PTEN Asthma Inflammatory bowel disease

Follow us Feedback

Your take home message



Open Targets

Short feedback survey

<http://tinyurl.com/manc-221116>

Help and documentation

Get in touch



@targetvalidate



support@targetvalidation.org



www.facebook.com/OpenTargets/

The Target Validation Platform:

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

Frequently Asked Questions:

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

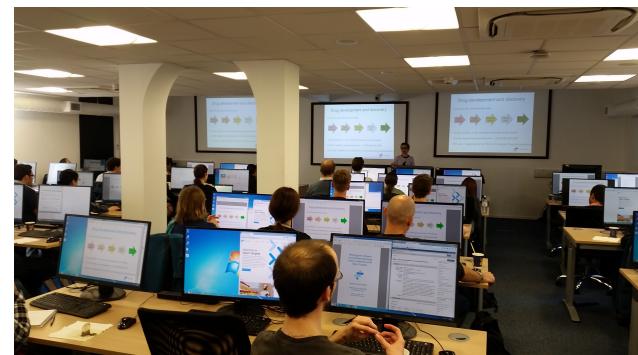
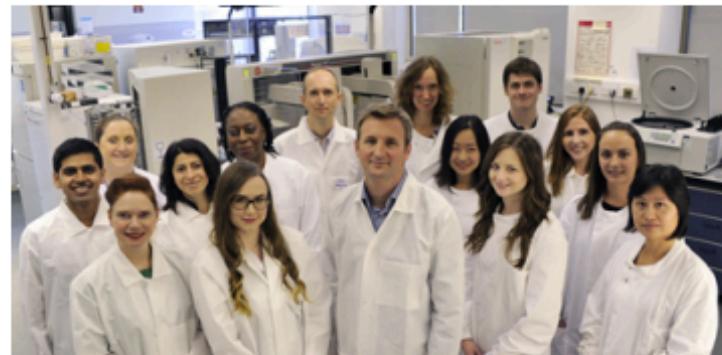
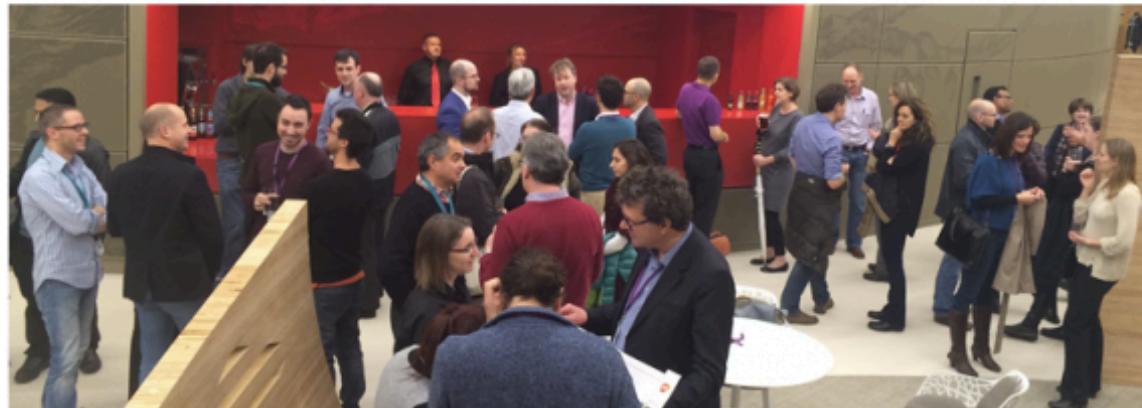
Open Targets Blog

blog.opentargets.org/



Open Targets

Acknowledgements



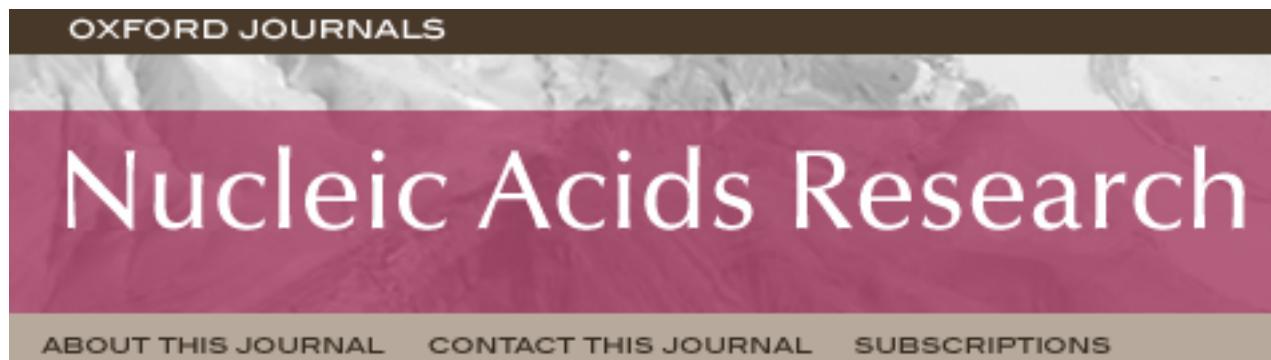
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Open Targets

How to cite us

Keep an eye out for our 2017 paper:



Database issue

For the time being, include our URL:

www.targetvalidation.org

Advanced use of Open Targets to help validate targets

Your user cases

Alternative ways to access the data

Looking for our entire datasets?

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

- All target-disease associations: 179 MB
- All evidence: 1.7 GB

Looking for extracts of our datasets?

- API: REST calls, Python client
- R client: maintained by community

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

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



Open Targets

GET

/public/association



Implementation notes

After integrating all evidence connecting a target to a specific disease, we compute an association score by mean of an harmonic sum. This association score provides an indication of how strong the evidence behind each connection is and can be used to rank genes in order of likelihood as drug targets. The association id is constructed by using the ensembl id of the gene and the EFO id for the disease (eg. ENSG00000073756-EFO_0003767). The method returns an association object, which contain data and summary on each evidence type included in the calculation of the score, as well as the score itself.

Parameters

Parameter	Value	Description	Parameter type	Data type
id	ENSG00000073756-EFO_0003767	an association ID usually in the form of TARGET_ID-DISEASE_ID	query	string

Response messages

HTTP status code	Reason	Model
200	Successful response	

[Try it out!](#)[Hide response](#)

Request URL

https://www.targetvalidation.org/api/latest/public/association?id=ENSG00000073756-EFO_0003767



Response body

```
{  
  "from": 0,  
  "facets": null,  
  "took": 6,  
  "therapeutic_areas": [],  
  "total": 1,  
  "data": [  
    {  
      "target": {  
        "gene_info": {  
          "symbol": "PTGS2",  
          "ensembl_id": "ENSG00000073756",  
          "name": "PTGS2",  
          "chromosome": 12, "start": 123456789, "end": 123456789},  
        "evidence": [{"source": "Ensembl", "score": 100, "type": "Gene-Disease"}, {"source": "OMIM", "score": 80, "type": "Gene-Disease"}],  
        "disease": {"id": "EFO_0003767", "name": "Prostaglandin synthase 2 deficiency", "ontology": "Disease", "category": "Phenotypic trait"},  
        "score": 100, "p_value": 0.001, "method": "Harmonic sum"}  
    }  
  ]  
}
```

- 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)

Python and R clients for the REST API

opentargets
latest

Search docs

Tutorial
High Level API
Low Level API
Code Documentation
Changelog

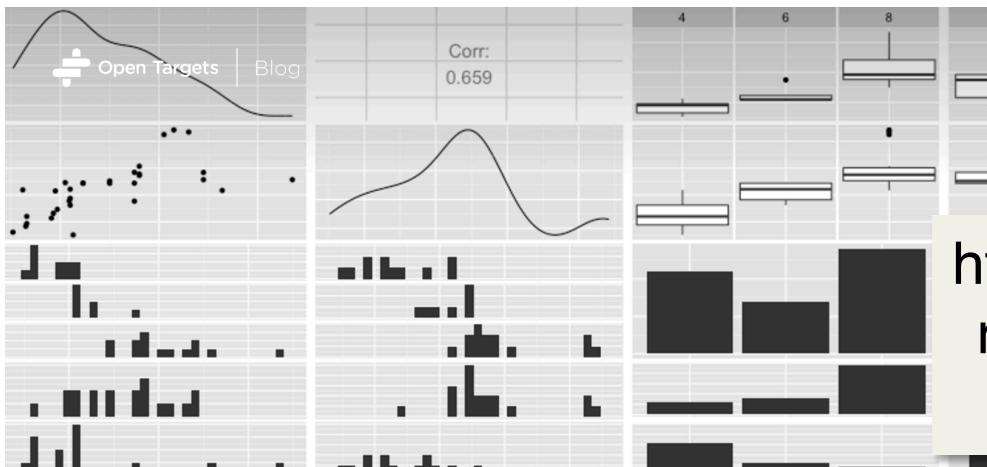
Docs » opentargets - Python client for targetvalidation.org

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/)

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