Mining Gene and Disease Associations with the Open Targets Platform

Drug Discovery Unit
The University of Dundee

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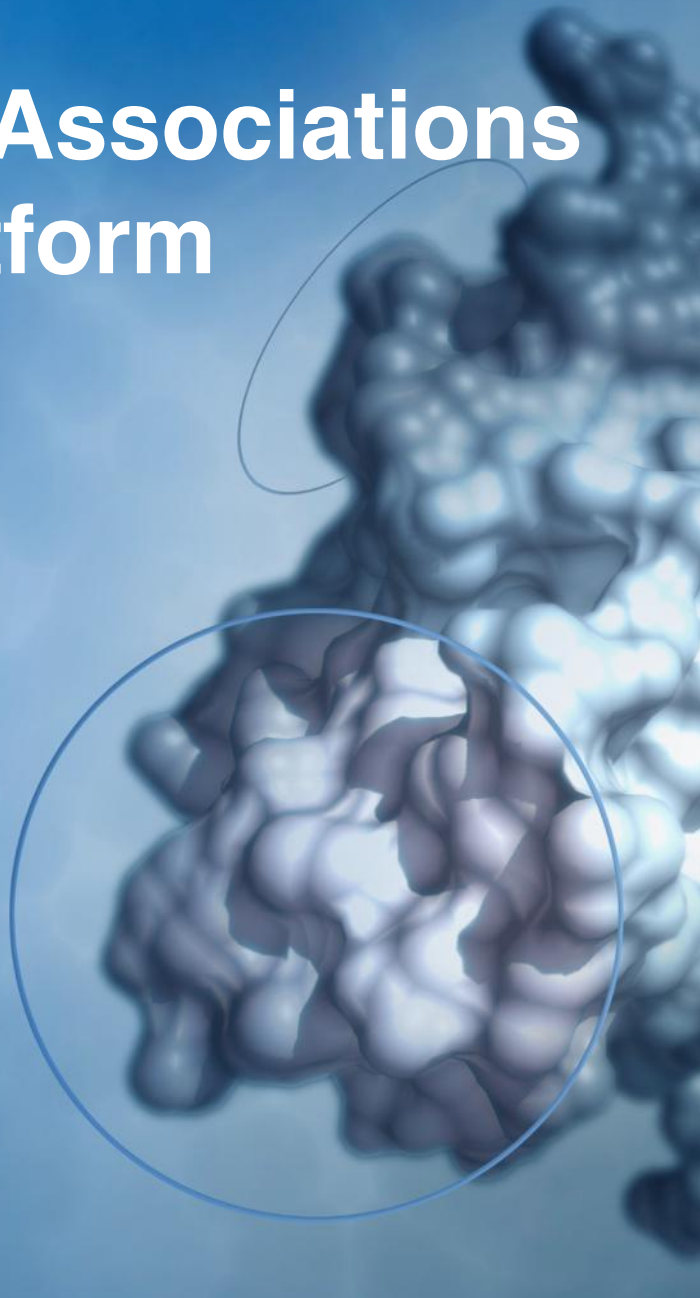
Open Targets Consortium
Core Bioinformatics team



Open Targets

Materials

https://github.com/deniseOme/training

DDU_presentation

DDU_coursebook

Course's objectives

What is the **Open Targets Platform**?

How does Open Targets **associate targets with diseases**?

How to **navigate** the Open Targets Platform?

How to **connect** with the Open Targets team

Outline

- The Open Targets Platform
- Live demos and hands-on
- Get in touch

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- Live demos and hands-on
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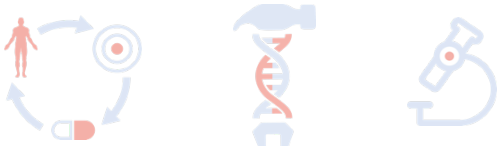
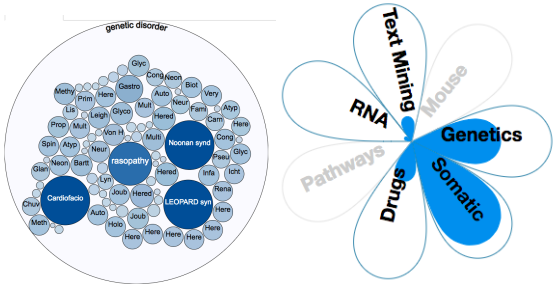
Two major areas of work in Open Targets

Experimental projects



Generate new evidence
CRISPR/Cas9, Organoids
(cellular disease models)

Core bioinformatics pipelines



Database for data integration
Web portal
REST API and data dumps

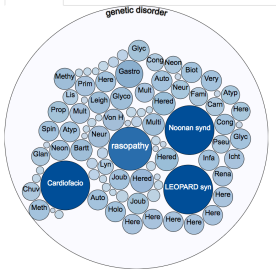
Concurrent
www.opentargets.org/projects

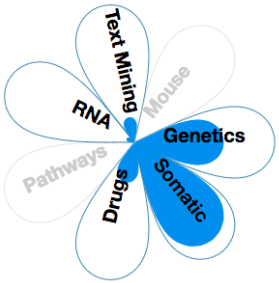
Open Targets

Open Targets Platform*

- Developed by the Core Bioinformatics team at EMBL-EBI
- Allow users to identify target and disease associations
- Improvements driven by you

https://www.targetvalidation.org/



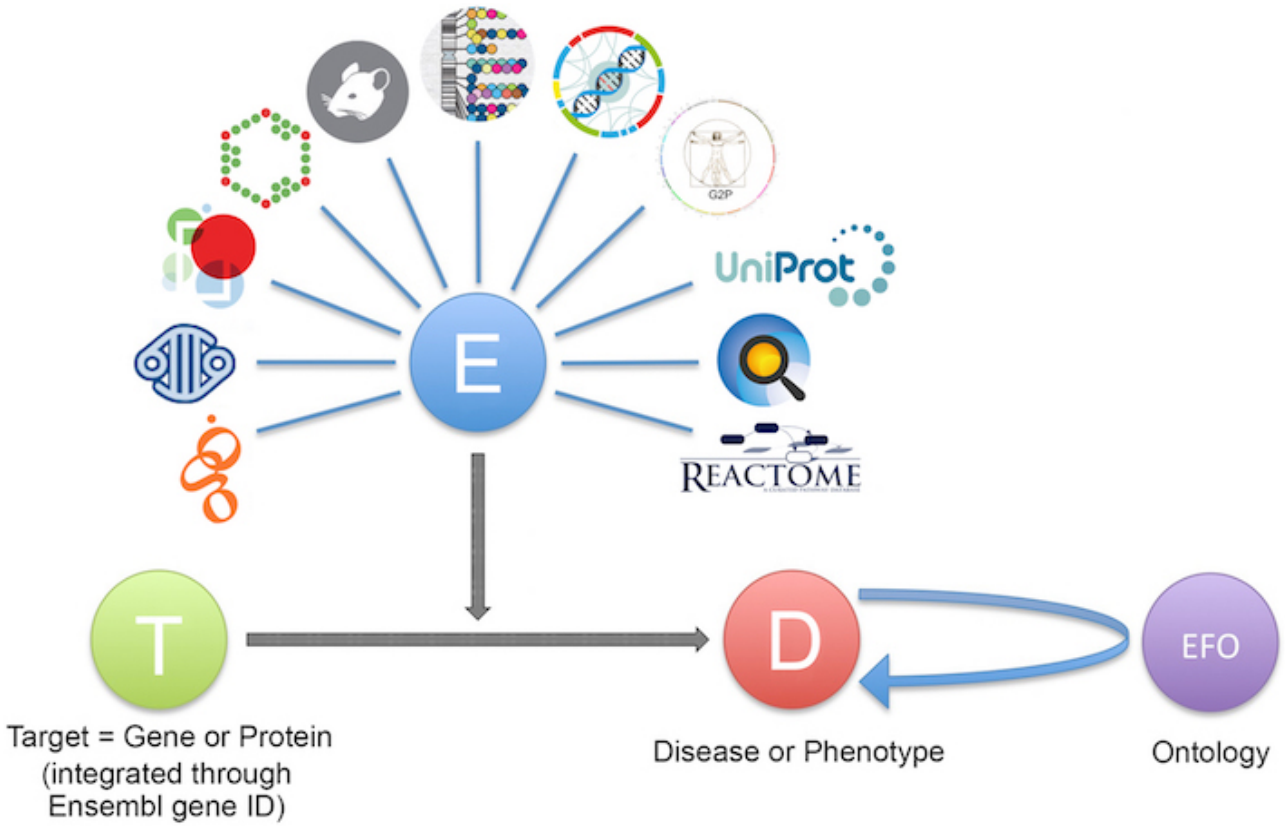


Open Targets

* First release: December 2015

Open Targets Platform

Evidence model for target and disease associations

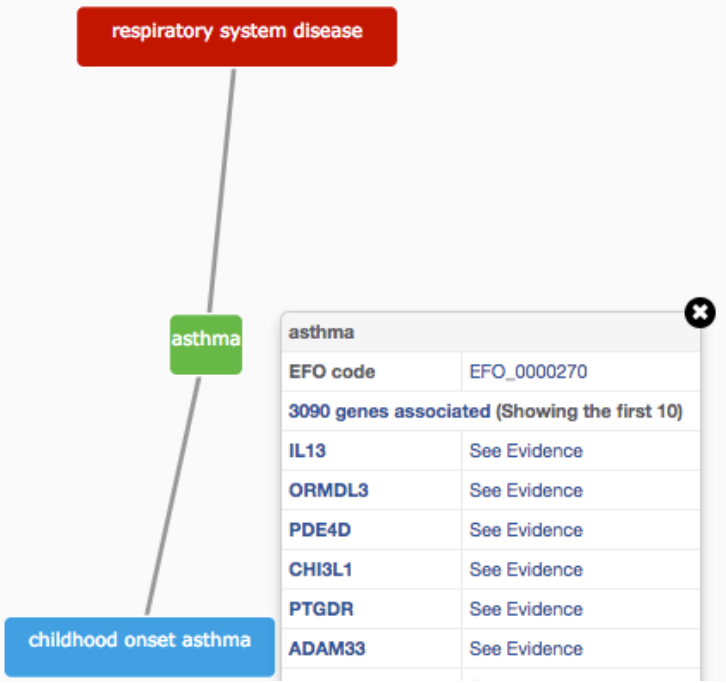


https://github.com/opentargets/json_schema/blob/master/doc/instructions.md

Open Targets

Experimental Factor Ontology* (EFO)

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



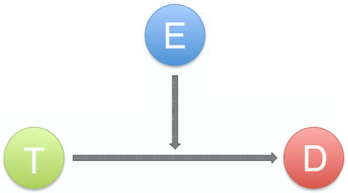
controlled vocabulary
+
hierarchy (relationship)

* https://www.ebi.ac.uk/efo/

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

Evidence from publicly available data

- Similar data sources are grouped into data types

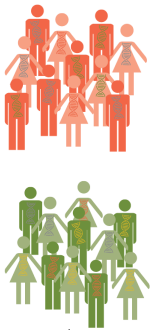


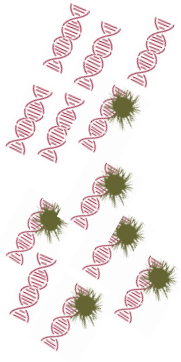
Data sources	Data types
GWAS catalog, UniProt, EVA, G2P	Genetic associations
Cancer Gene Census, EVA, IntOgen	Somatic mutations
Expression Atlas	RNA expression
ChEMBL	Drugs
Reactome	Affected pathways
Europe PMC	Text mining
PhenoDigm	Animal models
Your favourite data?	**Let us know!**

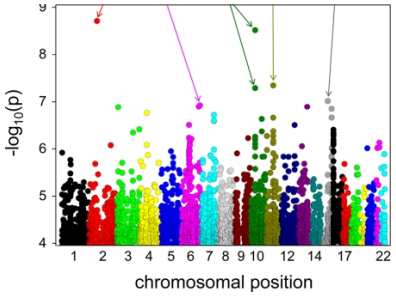
Open Targets

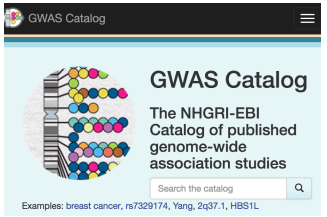
Data sources: GWAS catalog

- Genome Wide Association Studies
- Array-based chips → genotyping 100,000 SNPs genomewide









Open Targets

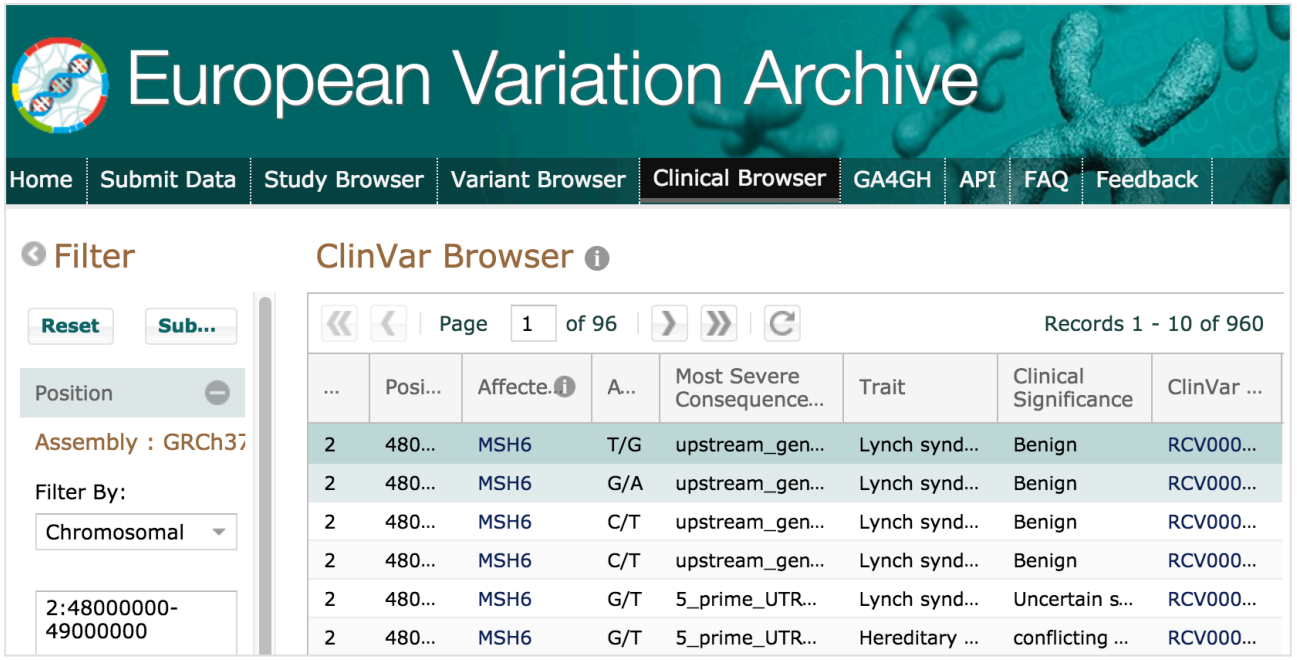
Data sources: UniProt

- Protein: sequence, annotation, function

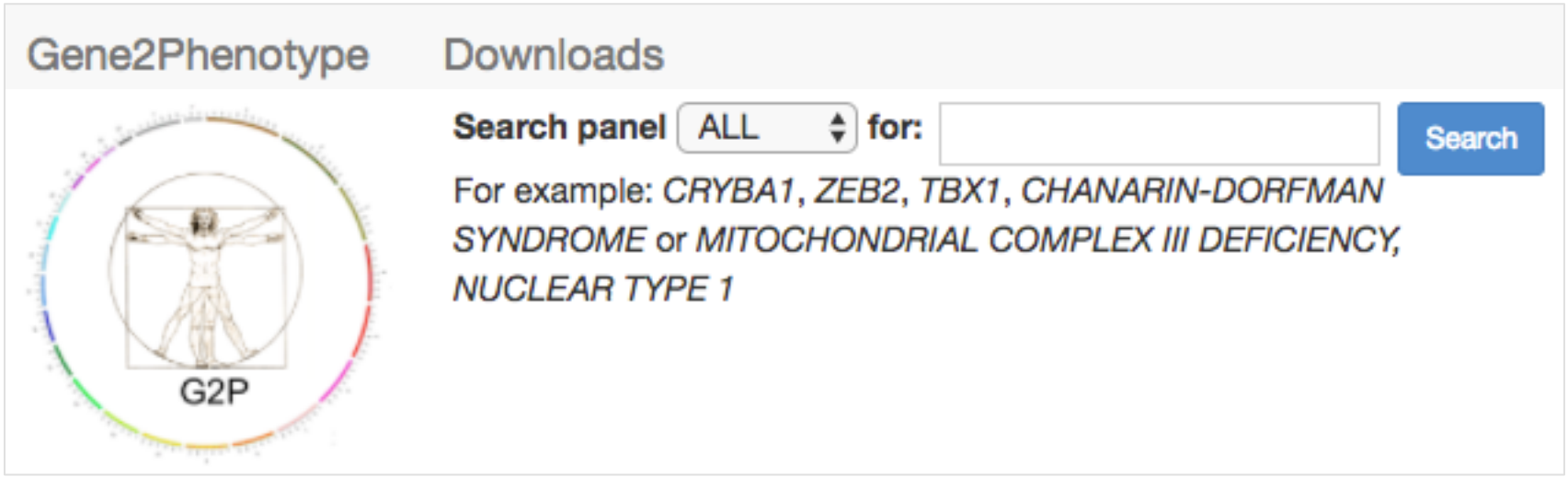
- Manual curation of coding variants in patients

Data sources: EVA

- Germline and somatic variants
- With ClinVar information for rare diseases



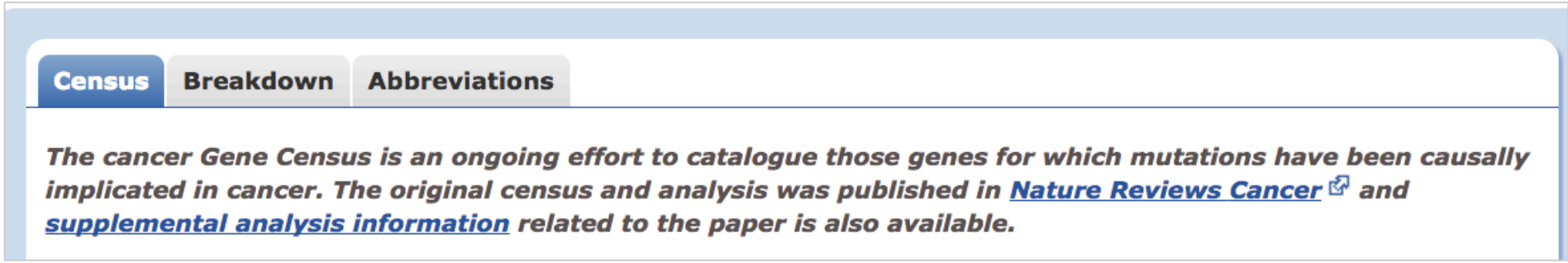
Data sources: Gene2Phenotype



- Variants, genes, phenotypes in rare diseases
- Literature curation → consultant clinical geneticists in the UK

Open Targets

Data sources: The Cancer Gene Census



- Genes with mutations causally implicated in cancer
- Gene associated with a cancer plus other cancers associated with that gene

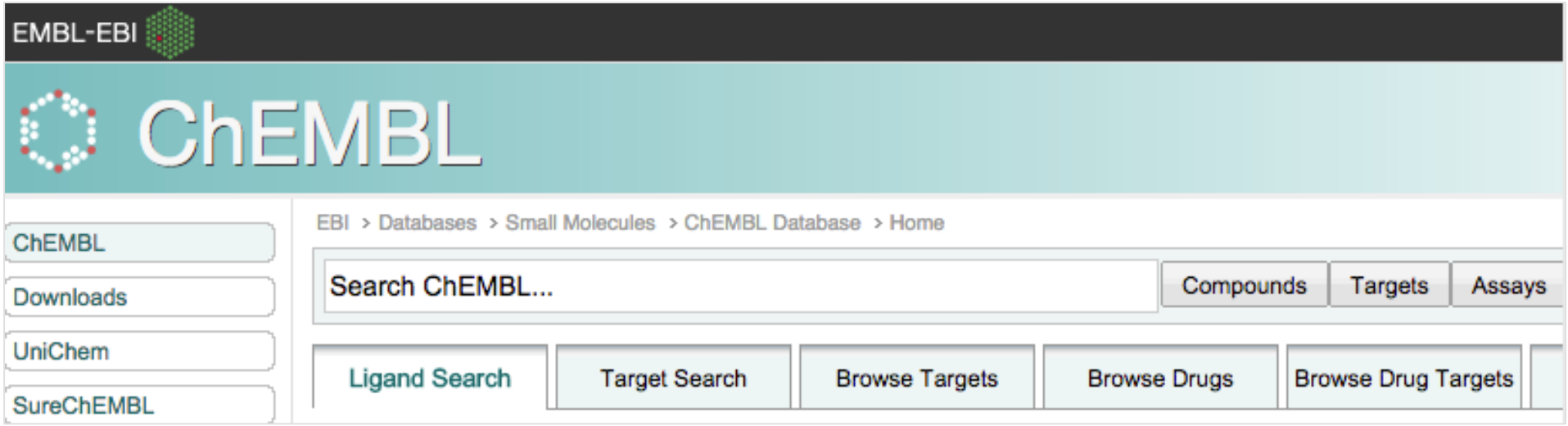
Open Targets

Data sources: IntOGen

- Genes and somatic (driver) mutations
- Involvement in cancer biology

Open Targets

Data sources: ChEMBL

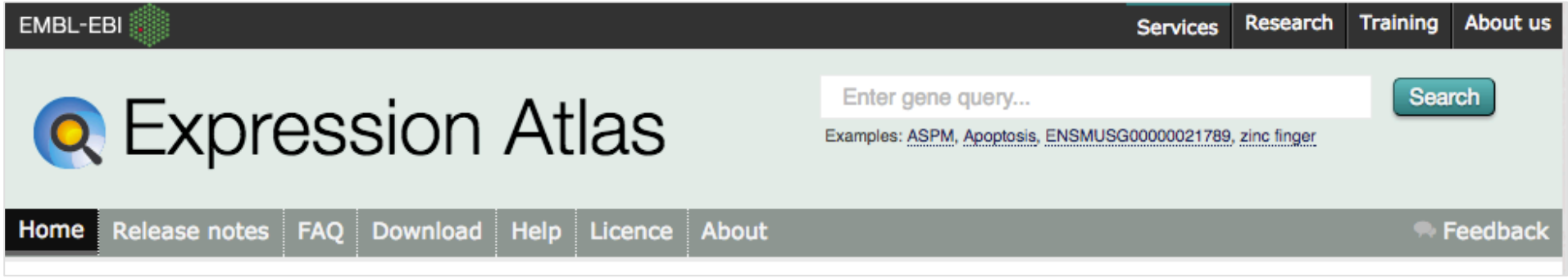


- Known drugs linked to a disease and a known target
- FDA approved for clinical trials or marketing

Data sources: Reactome

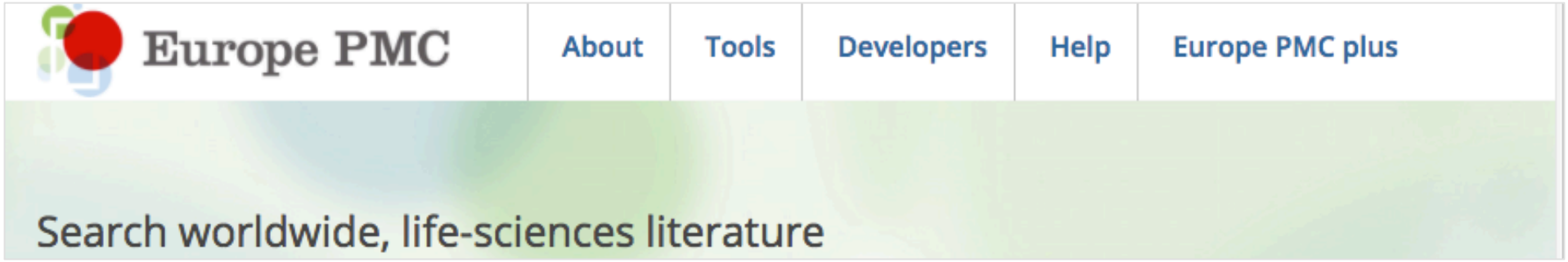
- Biochemical reactions and pathways
- Manual curation of pathways affected by mutations

Data sources: Expression Atlas



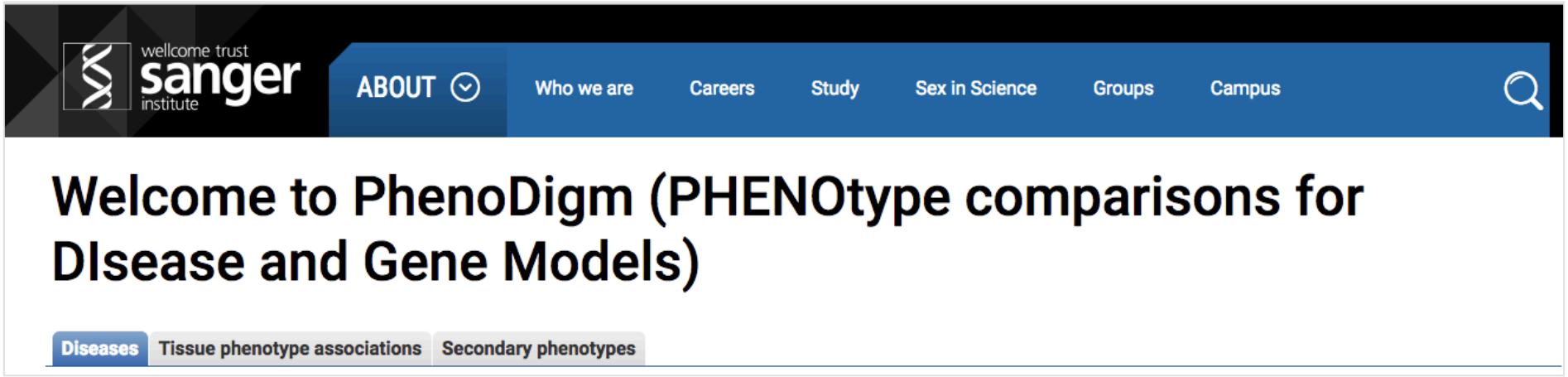
- Baseline expression for human genes
- Differential mRNA expression (healthy *versus* diseased)

Data sources: Europe PMC



- Mining titles, abstracts, full text in research articles
- Target and disease co-occurrence in the same sentence

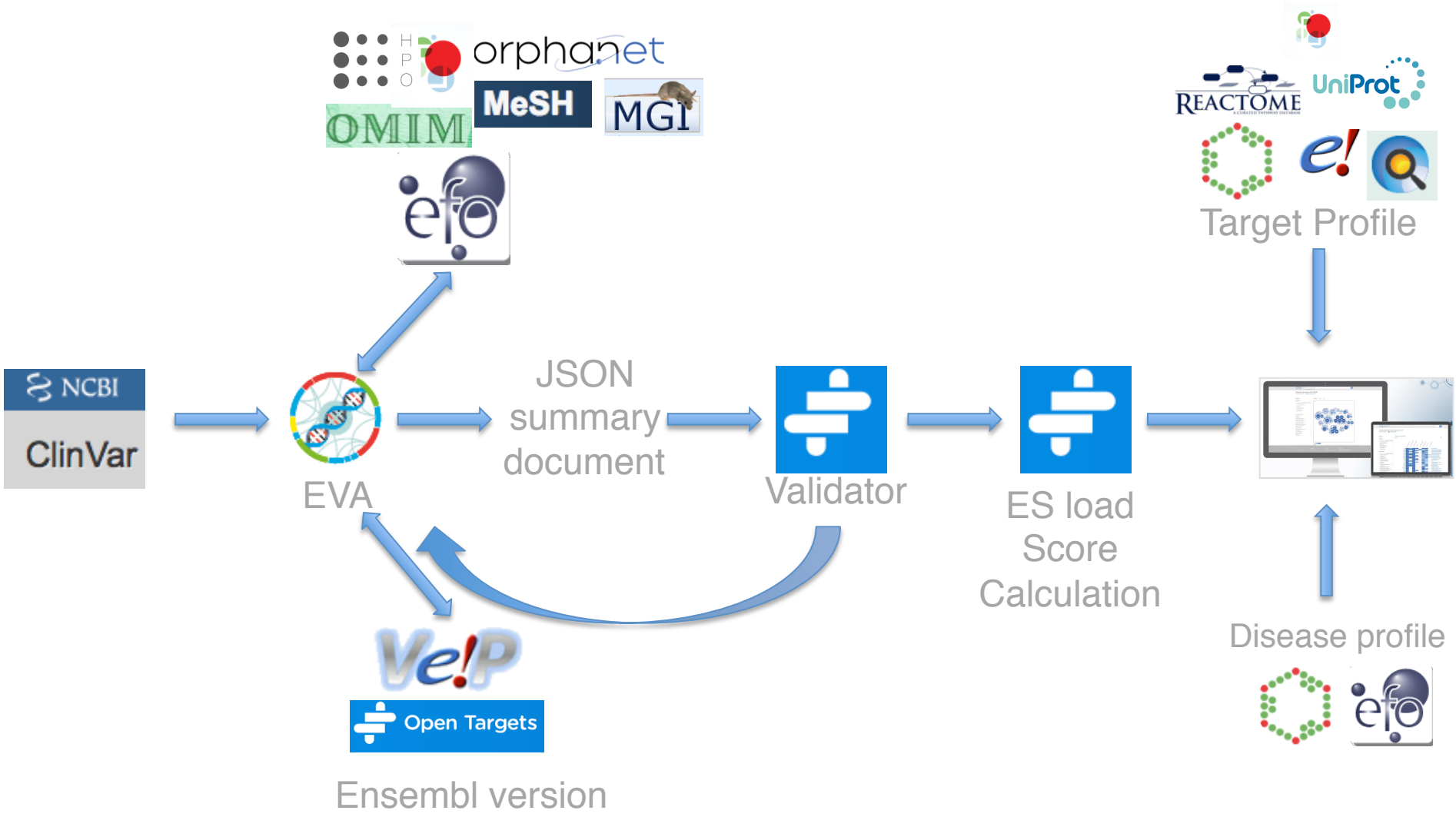
Data sources: PhenoDigm



- Semantic approach to associate mouse models with diseases

Open Targets

Data flow pipeline



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

JSON summary document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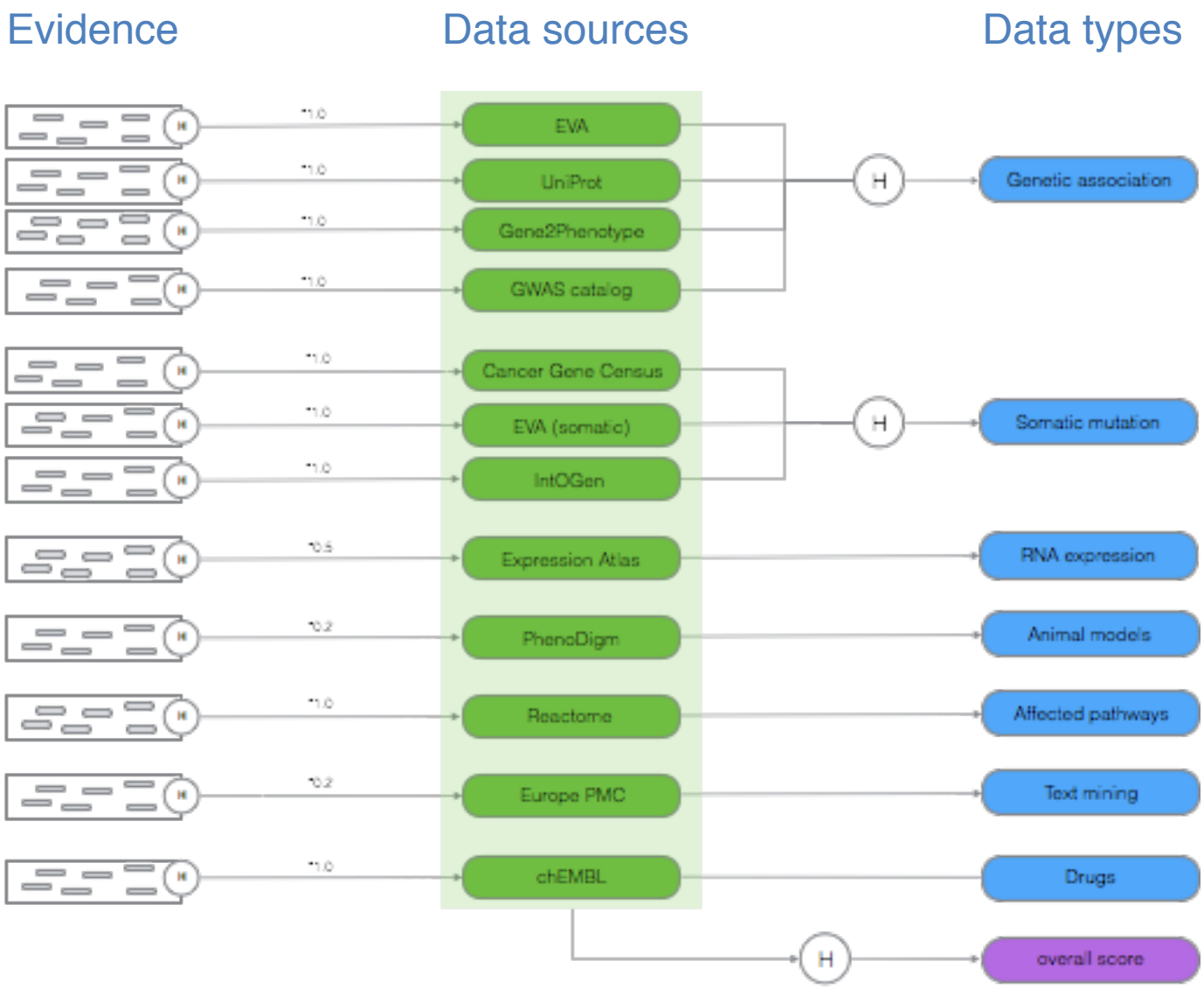
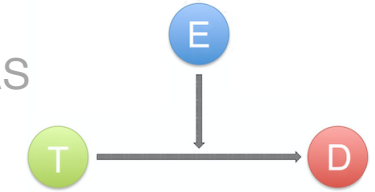
https://s3-eu-west-1.amazonaws.com/targetvalidation-dumps/16.12_evidence_data.json.gz

Score approach and aggregation



Evidence score e.g. $f * S * C$ (frequency x Severity x Confidence) for GWAS

$H = S_1 + S_2/2^2 + S_3/3^2 + S_4/4^2 + S_i/i^2$

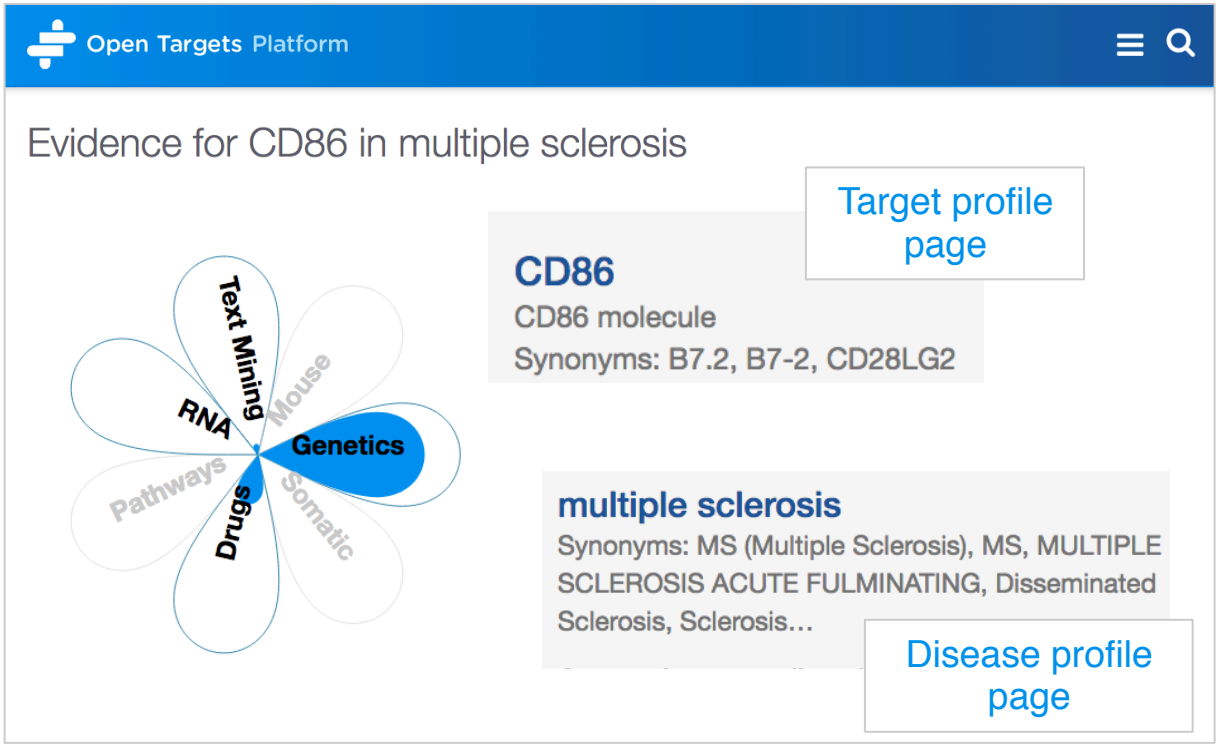


Outline

- The Open Targets Platform
- Live demos and hands on
- Get in touch

Demo 1: Evidence for a T-D association

What is the evidence for the association between *CD86* and multiple sclerosis?



https://www.targetvalidation.org/evidence/ENSG00000114013/EFO_0003885

Choose your favourite internet browser

Supported ones: Internet Explorer 11 (and above), Chrome, Firefox and Safari

Demo 2: Several targets to pursue

We have a list of 26 possible targets for IBD (inflammatory bowel disease).

How can we get all the data in Open Targets for all of them using the website?

https://www.targetvalidation.org/batch-search

Hands-on exercises

Pages 26-29

Hands-on exercises

Pages 26-29

Not enough time left today?

Email us with your questions

support@targetvalidation.org

Wrap up

Open Targets Platform:

- For drug target ID and selection in drug discovery
- Rank target-disease associations: di rces
- Integrated information o
- Intuitive graph

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

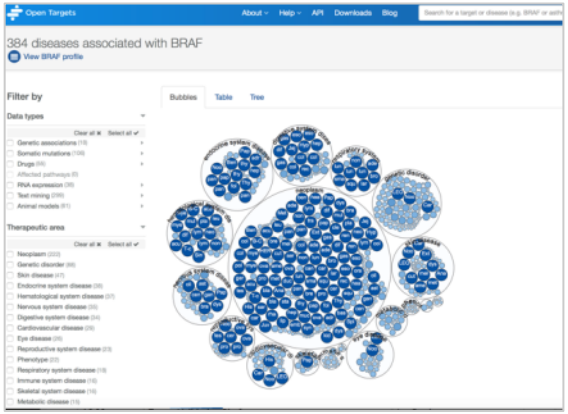
Currently: Integration of existing data

Public Databases and Pipelines

ChEMBL
UniProt
Europe PMC
REACTOME
IntAct
intOgen Integrative Onco Genomics
G2P

E
T
D

Open Targets Platform



Open Targets experimental data: NEW
Physiologically relevant and at scale

Oncology

Immunology

Neurodegeneration

Generated as we speak

Open Targets

We support decision-making

Can I find out about the mechanisms of the disease?

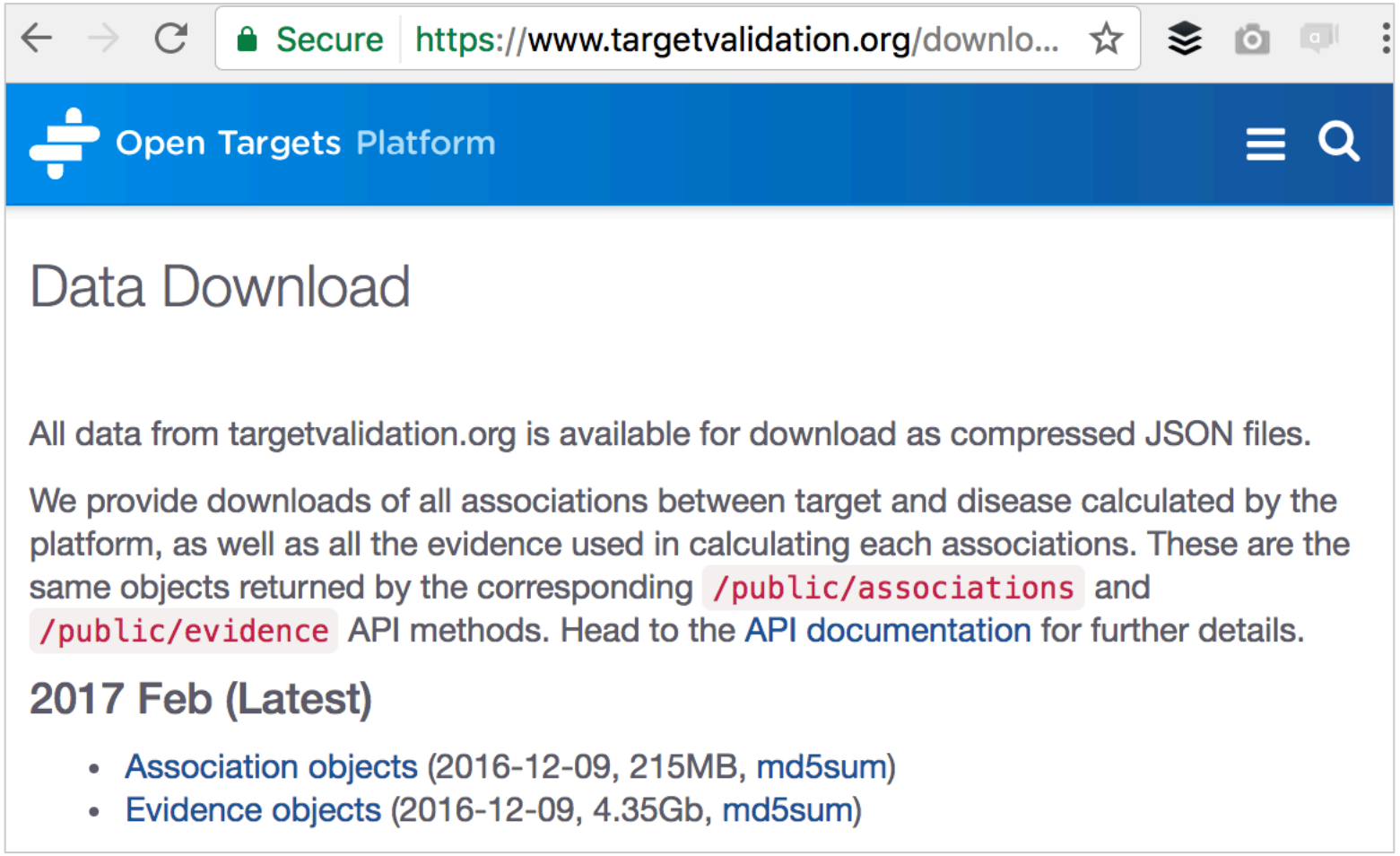
Are there FDA drugs for this association?

What else can I find out about my drug target?

…

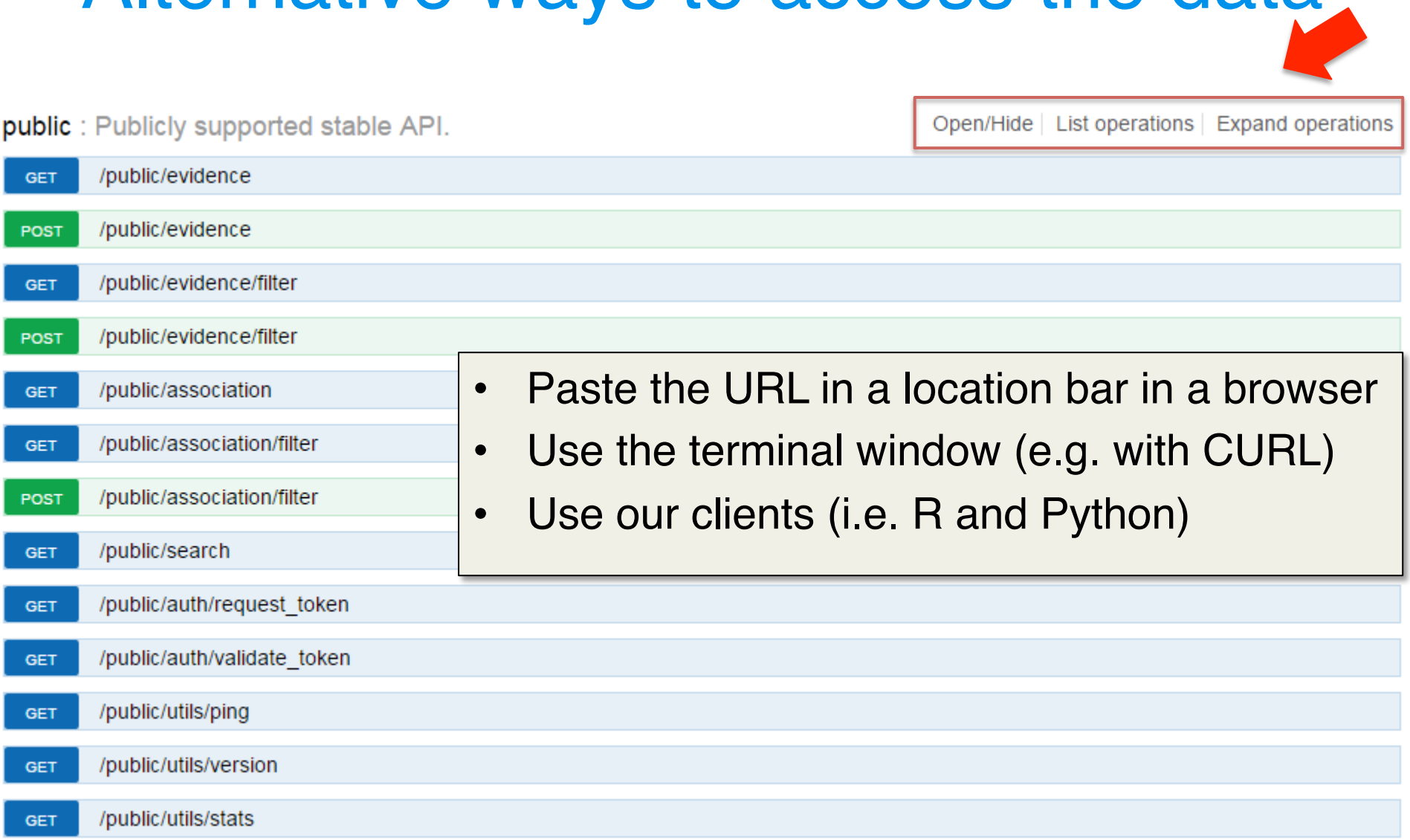
Open Targets

Alternative ways to access the data



Open Targets

Alternative ways to access the data



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

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

Open Targets

API calls: some examples

GET /public/search

http://targetvalidation.org/api/latest/public/search?q=EFO_0003767

GET /public/association/filter

http://www.targetvalidation.org/api/latest/public/association/filter?target=ENSG00000110324&direct=false&fields=is_direct&fields=disease.efo_info.label&size=100

GET /public/evidence/filter

https://targetvalidation.org/api/latest/public/evidence/filter?target=ENSG00000141867&disease=EFO_0000565&datatype=expression_atlas&size=100&format=json

blog.opentargets.org

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Open Targets

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Open Targets: a platform for therapeutic target identification and validation

Gautier Koscielny[1,2,*], Peter An[1,3], Denise Carvalho-Silva[1,4], Jennifer A. Cham[1,4], Luca Fumis[1,4], Rippa Gasparyan[1,3], Samiul Hasan[1,2], Nikiforos Karamanis[1,4], Michael Maguire[1,4], Eliseo Papa[1,3], Andrea Pierleoni[1,4], Miguel Pignatelli[1,4], Theo Platt[1,3], Francis Rowland[1,4], Priyanka Wankar[1,3], A. Patrícia Bento[1,4], Tony Burdett[1,4], Antonio Fabregat[1,4], Simon Forbes[1,5], Anna Gaulton[1,4], Cristina Yenyxe Gonzalez[1,4], Henning Hermjakob[1,4,6], Anne Hersey[1,4], Steven Jupe[1,4], Şenay Kafkas[1,4], Maria Keays[1,4], Catherine Leroy[1,4], Francisco-Javier Lopez[1,4], Maria Paula Magarinos[1,4], James Malone[1,4], Johanna McEntyre[1,4], Alfonso Munoz-Pomer Fuentes[1,4], Claire O'Donovan[1,4], Irene Papatheodorou[1,4], Helen Parkinson[1,4], Barbara Palka[1,4], Justin Paschall[1,4], Robert Petryszak[1,4], Naruemon Pratanwanich[1,4], Sirarat Sarntivijal[1,4], Gary Saunders[1,4], Konstantinos Sidiropoulos[1,4], Thomas Smith[1,4], Zbyslaw Sondka[1,5], Oliver Stegle[1,4], Y. Amy Tang[1,4], Edward Turner[1,4], Brendan Vaughan[1,4], Olga Vrousgou[1,4], Xavier Watkins[1,4], Maria-Jesus Martin[1,4], Philippe Sanseau[1,2], Jessica Vamathevan[4], Ewan Birney[1,4], Jeffrey Barrett[1,4,5] and Ian Dunham[1,4,*]

[1]Open Targets, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SD, UK, [2]GSK, Medicines Research Center, Gunnels Wood Road, Stevenage, SG1 2NY, UK, [3]Biogen, Cambridge, MA 02142, USA, [4]European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SD, UK, [5]Wellcome Trust Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SA, UK and [6]National Center for Protein Research, No. 38, Life Science Park Road, Changping District, 102206 Beijing, China

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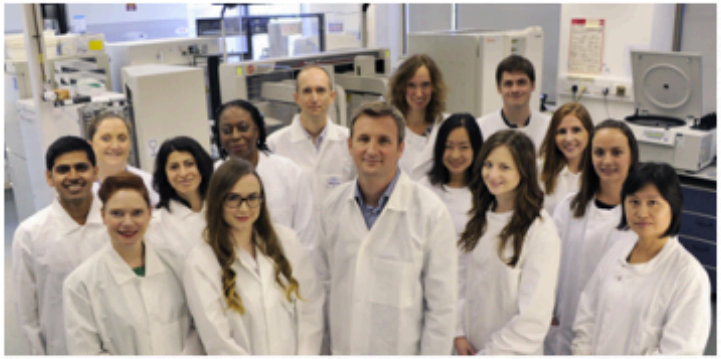
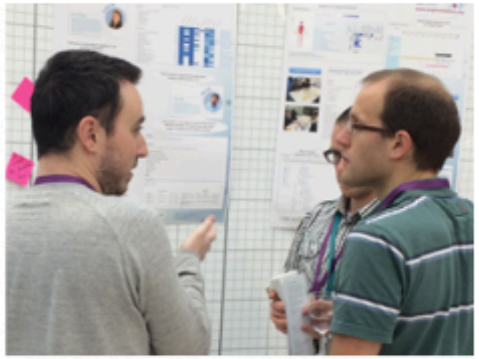
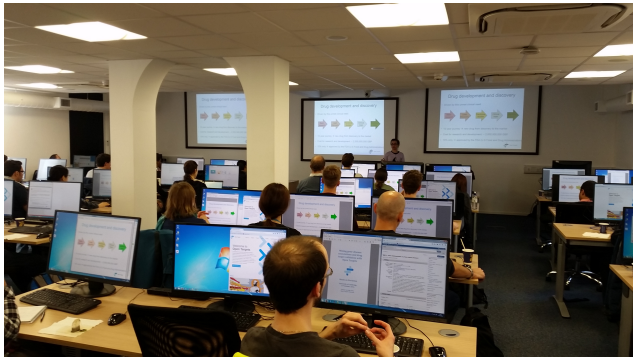




support@targetvalidation.org

Open Targets

Feedback survey

http://bit.ly/2q1aXWc

Open Targets

Extra Extra Extra
(slides)

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

Statistical integration, aggregation and scoring*

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

bit.ly/OpenTargets

Factors affecting the relative strength of an evidence

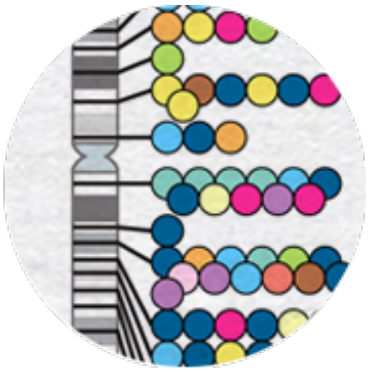
e.g. GWAS Catalog

$$S = f * s * c$$

f, relative occurrence of a target-disease evidence

s, strength of the effect described by the evidence

c, confidence of the observation for the target-disease evidence



f = sample size (cases and controls)

s = predicted functional consequence

c = *p* value reported in the paper

Aggregating scores across the data

- Using a mathematical function, the harmonic sum*

$$S_{1..i} = S_1 + \frac{S_2}{2^2} + \frac{S_3}{3^2} + \frac{S_4}{4^2} \ldots + \frac{S_i}{i^2}$$

where S1,S2,...,Si are the individual sorted evidence scores in descending order

- Advantages:
  A) account for replication
  B) deflate the effect of large amounts of data e.g. text mining

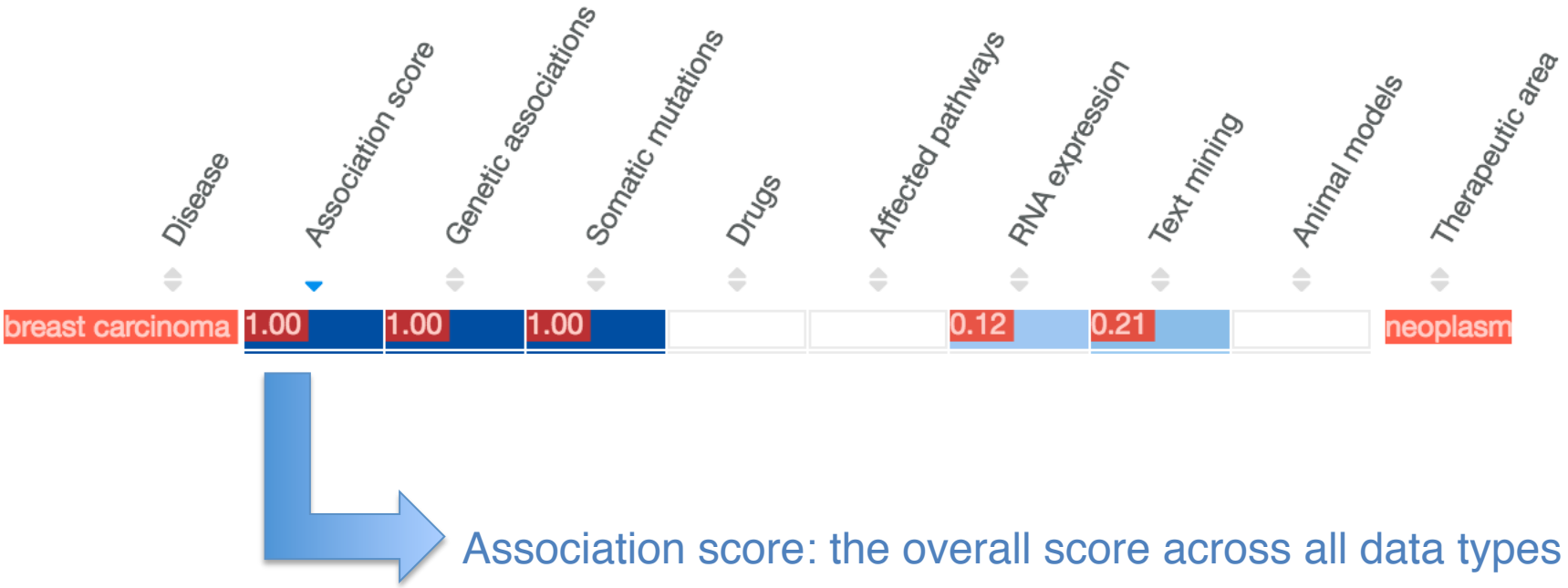
* PMID: 19107201, PMID: 20118918

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

- It can help you to design your null hypothesis
- It can help you to decide which target to pursue
- It is NOT sufficient on its own (use it in combination with…)

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 do we associate diseases and phenotypes w/ targets?

1. ChEMBL, UniProt, EVA (w/ ClinVar) curate diseases and phenotypes
2. Map disease/phenotypes to an ontology using EFO and HPO terms
3. Use genes as proxies for our targets
4. Create target-disease evidence JSON objects
5. Calculate for each supporting evidence the likelihood of gene A being associated with disease B
6. Compute integrated target-disease scores at the levels of data source, data type and overall score