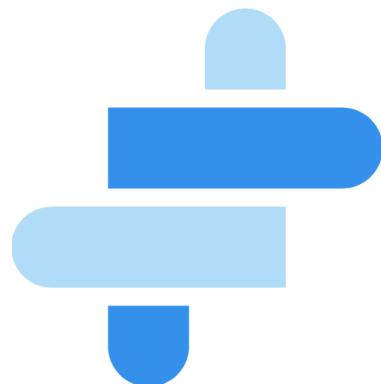


# Mining gene and disease associations with Open Targets



## Coursebook

University of Dundee  
Drug Discovery Unit  
10<sup>th</sup> May 2017

Denise Carvalho-Silva

Open Targets  
Wellcome Genome Campus  
Hinxton, United Kingdom

## Notes

This course is based on the February 2017 release of our Open Targets Platform.

Some useful links:

1) About the Open Targets Consortium

[www.opentargets.org/about](http://www.opentargets.org/about)

2) About the Open Targets Platform

[www.targetvalidation.org/about](http://www.targetvalidation.org/about)

3) Our publication

[www.bit.ly/OpenTargets](http://www.bit.ly/OpenTargets)

4) Details on the latest Platform release

<https://blog.opentargets.org/our-latest-release-is-out-its-all-about-data/>

Feel free to tackle questions relative to your own research instead of following the ones provided in this coursebook.

Questions or Feedback?  
[support@targetvalidation.org](mailto:support@targetvalidation.org)

## **TABLE OF CONTENTS**

<b>OVERVIEW.....</b>	<b>4</b>
<b>INTRODUCTION TO OPEN TARGETS.....</b>	<b>5</b>
<b>OPEN TARGETS PLATFORM: LIVE DEMOS.....</b>	<b>8</b>
Demo 1.....	9
Demo 2.....	16
Demo 3.....	28
<b>HANDS-ON EXERCISES PART I .....</b>	<b>26</b>
Exercise 1.....	26
Exercise 2.....	26
<b>HANDS-ON EXERCISES 3 AND 4.....</b>	<b>33</b>
Exercise 3.....	33
Exercise 4.....	34
<b>QUICK GUIDE TO DATABASES .....</b>	<b>35</b>

## **OVERVIEW**

Open Targets is a public-private initiative to generate evidence on the validity of therapeutic targets based on genome-scale experiments and analysis. We are working to create an R&D framework that applies to a wide range of human diseases, and we want to share this data openly with the scientific community.

The consortium was launched in March 2014 under the name of Centre for Therapeutic Open Targets (CTTV) and started with GlaxoSmithKline (<http://www.gsk.com/>), the Wellcome Trust Sanger Institute (<http://www.sanger.ac.uk/>) and the European Bioinformatics Institute (<http://www.ebi.ac.uk/>). In February 2016, a forth institution namely Biogen (<https://www.biogen.com/>) joined the initiative and the consortium was rebranded to Open Targets in April 2016.

In the process of drug discovery, the *validation* of a target refers to the creation of a specific entity that modulates that target's activity to provide therapeutic benefit to individuals with a disease. The ultimate validation of a target is the creation of an effective therapeutic molecule. This is a long and costly endeavour with more failures than successes. The goal of Open Targets is to transform this process by predicting if the modulation of a target is likely to provide therapeutic benefit. This would be done much earlier in the drug discovery process than is currently possible and far in advance of having a final, approved medicine.

Points covered in this workshop:

- The projects of Open Targets consortium
- An introduction to the Open Targets Platform
- Browsing the Platform
- Pointing to alternative ways to access the data

## **INTRODUCTION TO OPEN TARGETS**

Open Targets employs large-scale human genetics and genomics data to change the way drug targets are identified and validated. We have established a set of projects to develop both the data and analytical processes that implicate targets as valid, and the core platform to provide the information to a diverse audience of users.

The core bioinformatics team develops pipelines and a database to integrate existing target data. The core also designed, created and maintains the Open Targets Platform, a public web portal to serve the integrated data and views.

Our experimental projects focus on providing insights in the identification of targets relevant to key therapeutic areas namely:

- Oncology
- Inflammatory bowel diseases (IBD)
- Respiratory disease
- Inflammation and immunity
- Neurodegenerative diseases

We also aim to develop standard epigenome profiles of cell models in use within the pharmaceutical industry and academia and establish a systematic approach for the determination of human biological and disease relevance.

More details can be found in our [Projects](#) page.

### **Retrieving data from Open Targets with our Platform**

The Open Targets Platform is a web application that integrates and displays publicly available biological data to foster the discovery and prioritisation of targets for new therapies. We use data sources as diverse as Gene2Phenotype, IntOGen, GWAS, UniProt, ChEMBL, Expression Atlas, Cancer Census, Reactome and EuropePMC as pieces of evidence to support target-disease associations. The associations are scored using objective statistical and computational techniques.

In our release (December 2016), the Platform provides information on 31,071 targets; 8,659 diseases; 4.9 million evidence; and 2.5 million target-disease associations.

In addition to the web application, we include the data dumps, a REST API and a Python client.

The Open Targets Platform is aimed at users from both academia and industry, whether they want to browse a target on a gene by gene (or disease by disease) basis, carry out more complex queries using the API, or download all evidence and association objects for downstream analyses.

### **Synopsis: what can I do with the Open Targets Platform?**

- Find out which targets are associated with a disease
- Explore the evidence supporting this target-disease association
- Export a table with the FDA drugs currently in clinical trials
- Discover if there other diseases associated with a given target
- Get the association of a target with diseases from different therapeutic areas
- Find target specific information, such as baseline expression, protein structure, alternatively spliced transcripts, gene trees
- Get disease target specific information, such as a classification based on the ontology of the disease and the drugs mapped to it

## **Help documentation and support**

- ?
- [Data sources](#) in the Open Targets Platform
- ?
- View our [FAQs](#)
- ?
- [Email us](#)

## **Connect with us**

- ❖ [Open Targets Blog](#)
- ❖ Follow us on [Twitter](#)
- ❖ Check our page on [Facebook](#) and [LinkedIn](#)

## **Further reading**

Koscielny, G. *et al.* Nucleic Acids Res (2017 Database Issue):

<http://nar.oxfordjournals.org/content/early/2016/11/29/nar.gkw1055>

A breakthrough article from Nucleic Acids Research:

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

## **OPEN TARGETS PLATFORM: LIVE DEMOS**

We will guide you through the website using multiple sclerosis, as an example and exploring the *CD86* gene.

The following points will be addressed during the walkthrough:

- How to find targets associated with multiple sclerosis
- How to filter down the number of targets based on specific type of evidence
- How to find the data sources used to support the target-disease association
- How to look for other diseases (than multiple sclerosis) associated with a given target
- How to visualise a target in a browser-like view
- How to find out how strong the association between a target and a disease is
- How to find drugs currently in clinical trials
- How to filter **our** associations by **your** list of target genes

## Demo 1

Go to [www.targetvalidation.org](https://www.targetvalidation.org) and search for multiple sclerosis.

The screenshot shows the Open Targets Platform homepage. At the top, there is a navigation bar with links for Survey, About, Help, API, Downloads, and Blog. Below the navigation bar is the platform's logo, "Open Targets Platform", and a tagline "Find new targets for drug discovery". There is a search bar with the placeholder "Search for a target or disease" and a magnifying glass icon. Below the search bar, there is a "Try:" button followed by suggestions: BRAF, PTEN, Asthma, and Inflammatory bowel disease. On the right side of the page, there are two call-to-action boxes: "Feedback" and "Follow us". A large callout box on the right says "Follow us on social media". The main content area displays search results for "multiple scler".

Select the first (best) hit:

The screenshot shows the search results for "multiple scler". The search bar at the top contains "multiple scler". The first result is "multiple sclerosis" with the subtitle "2735 targets associated". It has a "Disease" section with a brief description: "An autoimmune disorder mainly affecting young adults and characterized by destruction of myelin in the central nervous system. Pathologic findings include multiple sharply demarcated areas of demyelination throughout the white matter of the central nervous system. Clinical manifestations include vis...". Below this, there is a "Targets" section listing "MBP myelin basic protein". Further down, there is a "Diseases" section listing "relapsing-remitting multiple sclerosis" and "experimental autoimmune encephalomyelitis".

You will see a page like this:

## Total number of targets associated with multiple sclerosis

Help API Downloads Blog

Search for a target or disease



2735 targets associated with multiple sclerosis

[View disease profile](#)

Filter the results

Filter by

Datatype

- Genetic associations (168)
- Somatic mutations (1)
- Drugs (152)
- Affected pathways (0)
- RNA expression (1k)
- Text mining (1k)
- Animal models (4)

Data types  
(Genetic Associations  
Drugs, etc)

Showing 1 to 50 of 2,735 targets

Search:



Pathway types

- Immune System (618)
- Signal Transduction (489)
- Metabolism (351)

Target symbol	Association score	Genetic associations	Somatic mutations	Drugs	Affected pathways	RNA expression	Text mining	Animal models	Target name
IL2RA									interleukin 2 receptor sub...
TNFRSF1A									TNF receptor superfamily ...
MS4A1									membrane spanning 4-do...
KCNB2									potassium voltage-gated ...
VDR									vitamin D (1,25- dihydroxy...
PTGS2									prostaglandin-endoperoxi...
S1PR1									sphingosine-1-phosphate...
NR3C1									nuclear receptor subfamili...
IFNAR1									interferon alpha and beta ...
CD52									CD52 molecule

The current release of the Open Targets Platform (February 2017 lists 2735 targets associated with multiple sclerosis.

The data types supporting these results are based on Genetic association, Drugs, RNA expression, Text mining, and Animal models.

Check our help page to find out more about our data sources:  
[https://targetvalidation.org/data\\_sources](https://targetvalidation.org/data_sources).

You can filter the number of associations by 'Data types', 'Pathway types', 'Target class' and by uploading 'Your target list':

### A) Data types

- Genetic associations (e.g. GWAS catalog)
- Somatic mutations (e.g. Cancer Gene Census, EVA)
- Drugs (from ChEMBL)
- Affected Pathways (from Reactome)
- RNA expression (from Expression Atlas)
- Text mining (from EuropePMC)
- Animal models (from PhenoDigm)

### B) Pathway types

- Signal Transduction
- Metabolism

...

### C) Target class

Enzyme

Membrane receptor

...

### D) Your target list

Upload your own list of genes (in official gene symbols from HGNC or Ensembl Gene IDs)

## What are Data types, Pathway types and Target class?

We collect data from various sources and combine them into categories called Data types. Example of data sources are GWAS catalog and UniProt, both combined into Data types. Note that data from an individual source can contribute to different Data types, e.g. data from EVA is observed in two data types, Genetic associations and Somatic mutations.

'Pathway types' are defined by Reactome:

<http://www.reactome.org/>

whereas the categories within 'Target class' are defined by ChEMBL

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

Let's now filter the data to focus on 'Genetic associations' (Data type) only. The number of targets goes down to 168:



These are targets associated with multiple sclerosis based on genetic variants only. Genetic variants are SNPs (single nucleotide polymorphisms or mutations, or short indels) from the GWAS catalog, UniProt and EVA (European Variation Archive) sources only.

The table is sorted by default with the best hit on the top of the table i.e. *IL2RA*. The best hit is the target that contains the highest (overall) association score. Different weight is given to different data types when computing the score:

From highest to lowest weight of all data types:

Genetic association = somatic mutations = drugs = pathways

RNA expression

Animal models = Text mining

You can sort the table by alphabetical order of the list of targets, or by the association score (either overall or per data type e.g. Genetic associations, Drugs, Text mining, etc). The association score varies from 0 to 1, the closer to 1 the stronger the association. This score is computed for each piece of evidence that is used to support the association. Individual scores within data sources and data types are combined to give the overall score ('Association score' column in the table below):

Showing 1 to 50 of 168 targets									
Target symbol	Association score	Genetic associations	Somatic mutations	Drugs	Affected pathways	RNA expression	Text mining	Animal models	Target name
IL2RA									interleukin 2 receptor sub...
TNFRSF1A									
KCNB2									

Click here to sort the results by alphabetical order of the gene symbols

Click on the arrows to sort the results by score values of individual data types e.g. Text mining.

To see which drugs are used in the clinical trials with patients with multiple sclerosis (or children terms of this disease), click on the 'View disease profile':

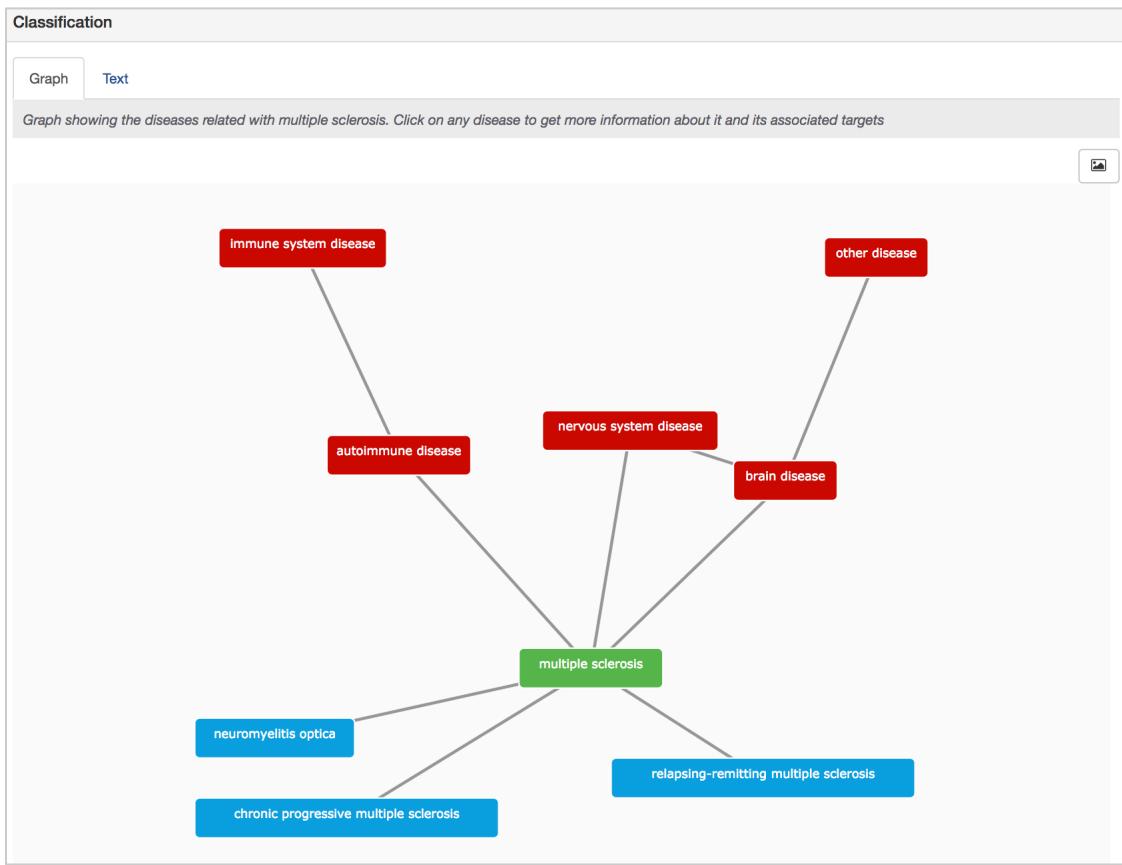
## 168 targets associated with multiple sclerosis

 [View disease profile](#)

Let's now expand the tab 'Drugs' to get a list of all drugs (n = 32 unique drugs in the December release) in different phases of clinical trials. You can filter (and sort) the table by disease, phase of clinical trial (e.g. IV, the most advanced phase), class of the target (e.g. membrane receptor), etc. You can also download this table in csv (comma separated value):

Drugs																																																	
Source: CHEMBL																																																	
Found 32 unique drugs: ALEMTUZUMAB BACLOFEN BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX CHOLECALCIFEROL CORTICOTROPIN DACLIZUMAB DALFAMPRIDINE DICLOFENAC DIMETHYL FUMARATE DULOXETINE ECULIZUMAB ERGOCALCIFEROL FINGOLIMOD INTERFERON BETA-1A INTERFERON BETA-1B LAMOTRIGINE MEMANTINE METHYLPREDNISOLONE MIRABEGRON MITOXANTRONE MYCOPHENOLATE MOFETIL NALTREXONE NATALIZUMAB OCRELIZUMAB OFATUMUMAB PEGINTERFERON BETA-1A PREDNISOLONE PREDNISONE RITUXIMAB SIMVASTATIN Siponimod TERIFLUONIMIDE																																																	
Showing 1 to 10 of 1,000 entries																																																	
Search: <input type="text"/>																																																	
<table border="1"> <thead> <tr> <th colspan="2">Drug Information</th> <th colspan="8">Gene-Drug Evidence</th> </tr> <tr> <th>Disease</th> <th>Drug</th> <th>Phase</th> <th>Status</th> <th>Type</th> <th>Mechanism of action</th> <th>Activity</th> <th>Target class</th> <th>Evidence source</th> <th></th> </tr> </thead> <tbody> <tr> <td>multiple sclerosis</td> <td>DICLOFENAC</td> <td>Phase IV</td> <td>Completed</td> <td>Small molecule</td> <td>Cyclooxygenase inhibitor 1 publication FDA</td> <td>antagonist</td> <td>Oxidoreductase</td> <td>Curated from Clinical Trials Information</td> <td></td> </tr> <tr> <td>multiple sclerosis</td> <td>DALFAMPRIDINE</td> <td>Phase IV</td> <td>Completed</td> <td>Small molecule</td> <td>Voltage-gated potassium channel blocker 1 publication FDA</td> <td>antagonist</td> <td>Voltage-gated potassium channel</td> <td>Curated from Clinical Trials Information</td> <td></td> </tr> </tbody> </table>										Drug Information		Gene-Drug Evidence								Disease	Drug	Phase	Status	Type	Mechanism of action	Activity	Target class	Evidence source		multiple sclerosis	DICLOFENAC	Phase IV	Completed	Small molecule	Cyclooxygenase inhibitor 1 publication FDA	antagonist	Oxidoreductase	Curated from Clinical Trials Information		multiple sclerosis	DALFAMPRIDINE	Phase IV	Completed	Small molecule	Voltage-gated potassium channel blocker 1 publication FDA	antagonist	Voltage-gated potassium channel	Curated from Clinical Trials Information	
Drug Information		Gene-Drug Evidence																																															
Disease	Drug	Phase	Status	Type	Mechanism of action	Activity	Target class	Evidence source																																									
multiple sclerosis	DICLOFENAC	Phase IV	Completed	Small molecule	Cyclooxygenase inhibitor 1 publication FDA	antagonist	Oxidoreductase	Curated from Clinical Trials Information																																									
multiple sclerosis	DALFAMPRIDINE	Phase IV	Completed	Small molecule	Voltage-gated potassium channel blocker 1 publication FDA	antagonist	Voltage-gated potassium channel	Curated from Clinical Trials Information																																									

Scroll down to view the disease ontology (disease relationship) in the 'Classification' tab. The data on the relationship of diseases comes from the EFO (Experimental Factor Ontology).



Multiple sclerosis is the disease of interest in this tutorial, and is represented in green. Red nodes correspond to parental terms in relation to multiple sclerosis, whereas its children terms (e.g. chronic progressive multiple sclerosis) are shown in blue. Click on any of disease names to get the targets associated with them:

---

relapsing-remitting multiple sclerosis

**relapsing-remitting multiple sclerosis**

EFO code EFO\_0003929

**226 genes associated (Showing the first 10)**

<b>CD52</b>	<a href="#">See Evidence</a>
<b>S1PR1</b>	<a href="#">See Evidence</a>
<b>S1PR4</b>	<a href="#">See Evidence</a>
<b>ITGB7</b>	<a href="#">See Evidence</a>
<b>KEAP1</b>	<a href="#">See Evidence</a>
<b>S1PR5</b>	<a href="#">See Evidence</a>
<b>S1PR2</b>	<a href="#">See Evidence</a>
<b>ITGB1</b>	<a href="#">See Evidence</a>
<b>IFNAR2</b>	<a href="#">See Evidence</a>
<b>IFNAR1</b>	<a href="#">See Evidence</a>

Help | [FAQ](#) | [Submit](#) | [GSK](#)

privacy | [Email](#)

By using the EFO parent-child (subclass of) relationships, we derive new associations that may not have direct evidence. For instance, IBD is an autoimmune disease and the direct evidence of targets associated to IBD are propagated to the higher autoimmune level to allow users to find common targets across groups of related diseases (e.g. Ulcerative Colitis, Crohn's disease and IBD). In EFO, 'asthma' is a 'respiratory system disease' and 'childhood onset asthma' is a subclass of 'asthma'. Both evidence from 'asthma' and 'childhood onset asthma' are propagated to 'respiratory system disease'.

## Demo 2

Let's now explore the evidence used to associate *CD86* and multiple sclerosis. We've chosen this target for follow up based on the availability of information for different data types.

Click on any row corresponding to *CD86* in the table below:

Showing 1 to 50 of 168 targets

Search:



Target symbol	Association score	Genetic associations	Somatic mutations	Drugs	Affected pathways	RNA expression	Text mining	Animal models	Target name
IL2RA	1.00	0.70				0.07			interleukin 2 receptor sub...
TNFRSF1A	1.00	1.00				0.07			TNF receptor superfamily ...
KCNB2	1.00	0.07			1.00				potassium voltage-gated ...
<b>CD86</b>	0.89	0.82			0.25	0.01	0.05		<b>CD86 molecule</b>



The data types that support this association are (check the flower and the coloured petals):

Genetic association

Drugs

RNA expression

Text mining



**Note:** If you wish to suggest data types or resources we could/should incorporate into our Platform, please get in touch:

[support@targetvalidation.org](mailto:support@targetvalidation.org)

The genetic evidence that supports the association (*CD86* – multiple sclerosis) comes from the GWAS catalog. They are all known in public databases i.e. dbSNP (hint: the rsID such as rs9282641, rs4308217, rs2255214, and rs2681424).

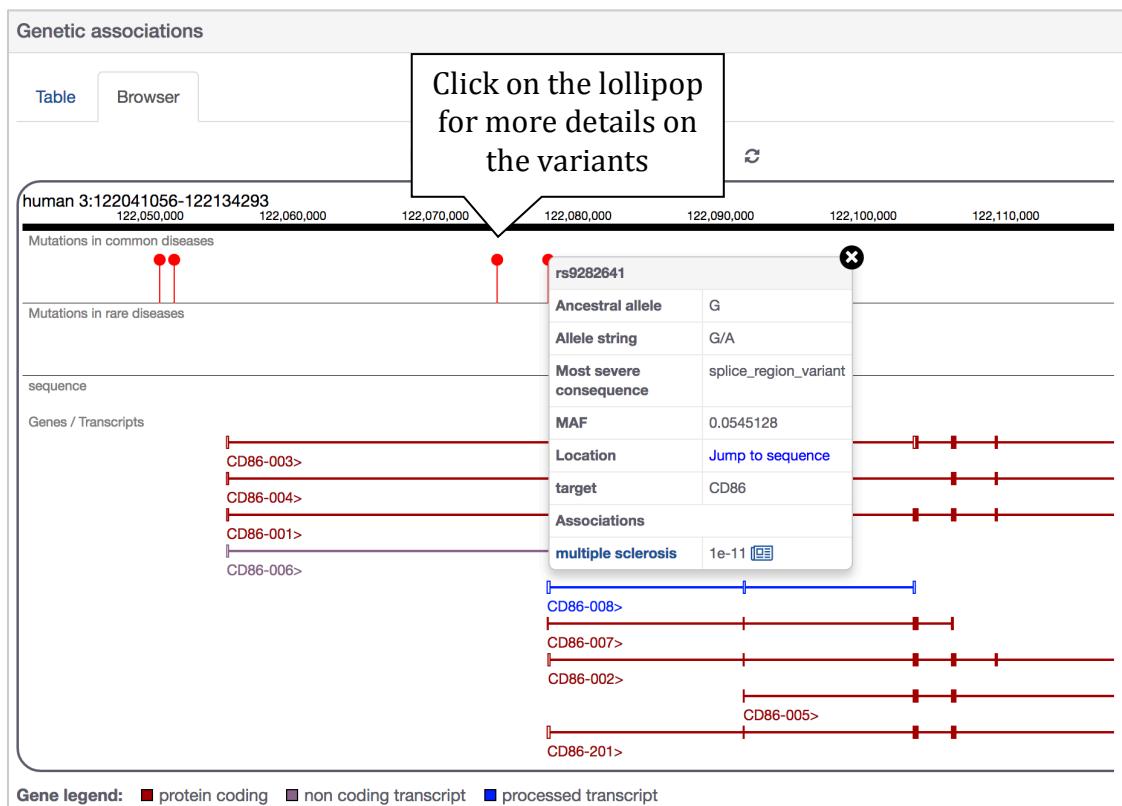
Genetic associations						
Common diseases		Gene-Variant Evidence				
Disease	Variant	Variant type	Evidence source	Variant-Disease Evidence	P-Value	Publications
multiple sclerosis	<a href="#">rs9282641</a>	splice region variant	Open Targets pipeline	<a href="#">gwas catalog</a>	1e-11	<a href="#">1 publication</a>
multiple sclerosis	<a href="#">rs4308217</a>	intron variant	Open Targets pipeline	<a href="#">gwas catalog</a>	6e-8	<a href="#">1 publication</a>
multiple sclerosis	<a href="#">rs2255214</a>	upstream gene variant	Open Targets pipeline	<a href="#">gwas catalog</a>	5e-8	<a href="#">1 publication</a>
multiple sclerosis	<a href="#">rs2681424</a>	upstream gene variant	Open Targets pipeline	<a href="#">gwas catalog</a>	2e-7	<a href="#">1 publication</a>
Show	10	entries			Previous	1 Next

In addition to the table above, you can also explore the ‘Genetic associations’ data in a Browser view.

In the Browser view, you can zoom in and out, scroll along the genome and find out more about the gene (s), transcript (s), and the genetic variants (represented as lollipops) in the genomic region depicted.

**Note:** The assembly we use is human assembly GRCh38, also known as hg38.

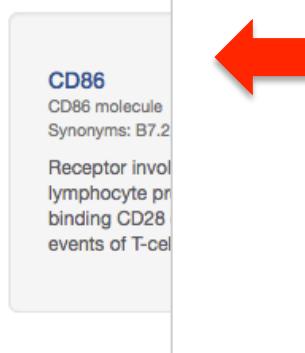
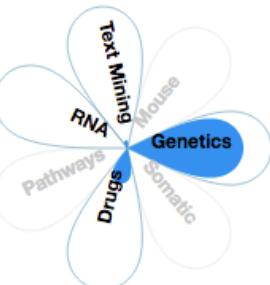
We also provide links to Ensembl.



To find out if there are drugs currently in clinical trials targeting *CD86* in patients with multiple sclerosis, let's expand the 'Drugs' tab. There is just one drug (i.e. ABATACEPT) on phase II of clinical trials.

We can now scroll back to the top of the page and click on the 'CD86' link (next to the flower) to explore this target in more details, such as to find out its RNA expression levels across several tissues and whether or not it is associated with other diseases of the nervous system.

## Evidence for CD86 in multiple sclerosis



You will land on a page like this:

CD86  
CD86 molecule | View associated diseases

Receptor involved in the costimulatory signal essential for T-lymphocyte proliferation and interleukin-2 production, by binding CD28 or CTLA-4. May play a critical role in the early events of T-cell activation and costimulation of naive T-cells, such as deciding between immunity and anergy that is made by T-cells within 24 hours after activation. Isoform 2 interferes with the formation of CD86 clusters, and thus acts as a negative regulator of T-cell activation.

Synonyms: B7.2 B7-2 CD28LG2 B70 FUN-1 Activation B7-2 antigen T-lymphocyte activation antigen CD86 CTLA-4 counter-receptor B7.2 B-lymphocyte antigen B7-2 BU63

Protein Information (from UniProt)

Variants, isoforms and genomic context

Protein baseline expression

RNA baseline expression

Gene Ontology

Protein Structure

Pathways

Drugs

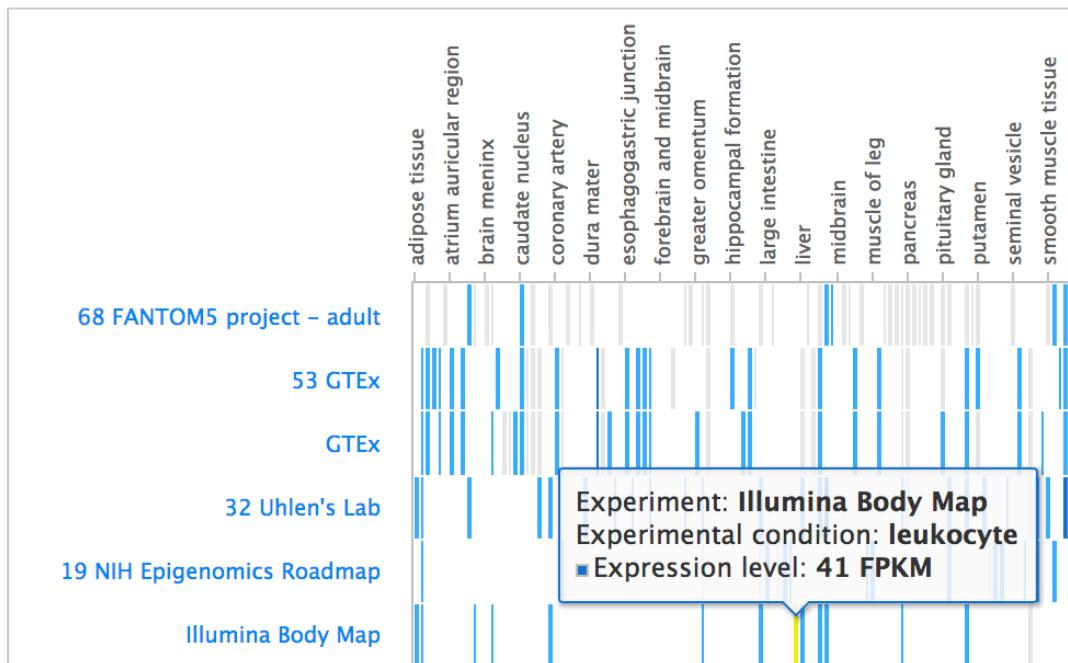
Gene tree

Bibliography

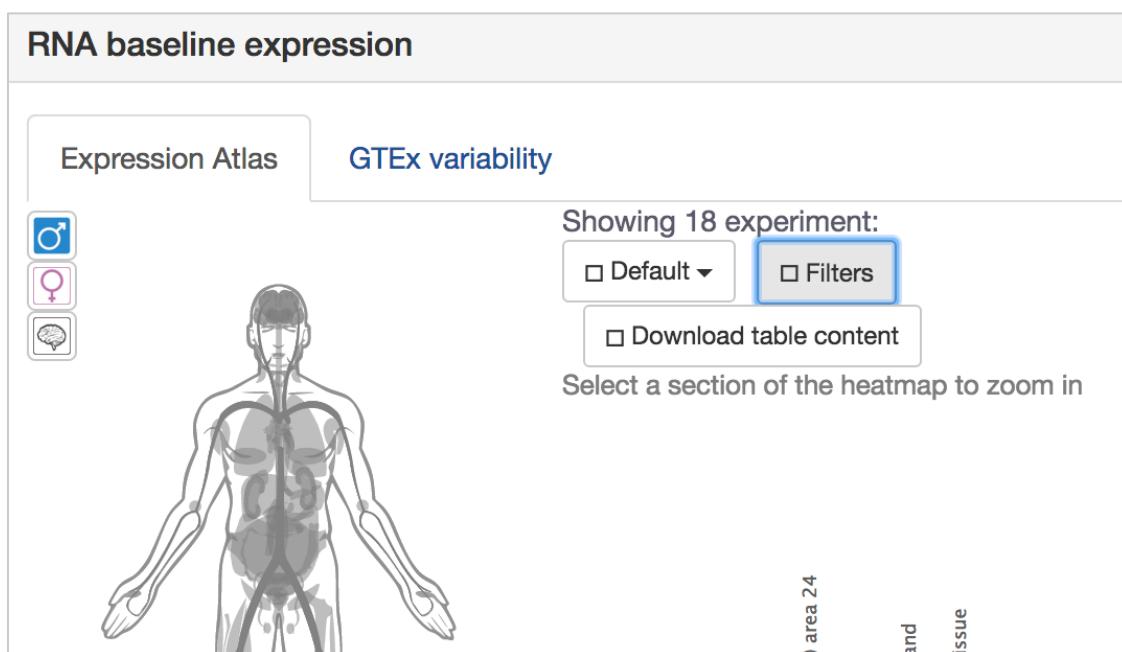
Expand the 'RNA baseline expression' to find out in which tissues *CD86* is highly expressed.

You will find two tabs in there: one with Expression Atlas data (with data from several projects including the Illumina Body Map), and one with GTEx data only:

According to the Illumina Body Map data, leukocytes are the cells with the highest expression level for the *CD86* gene:



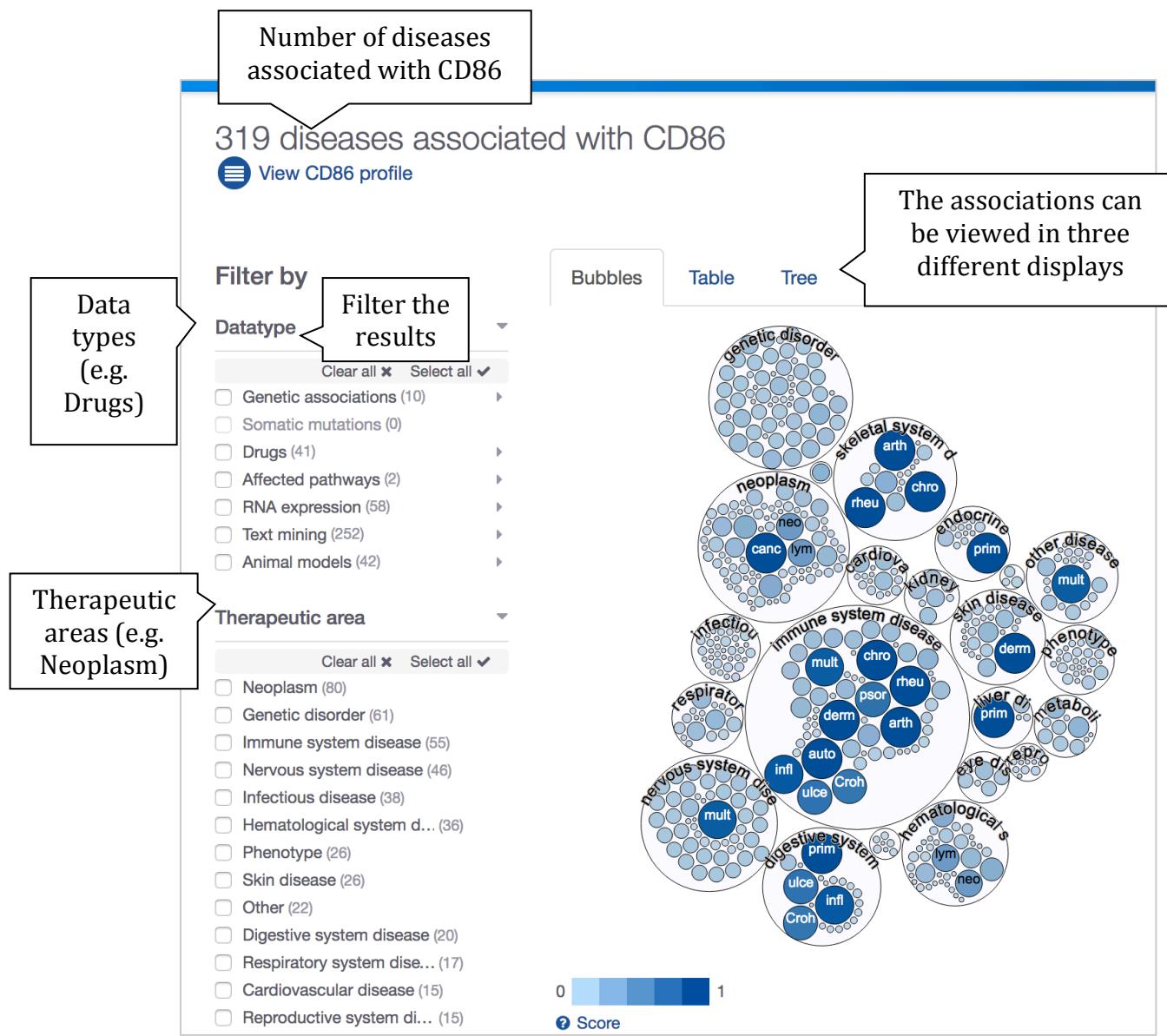
You can zoom this view in and out and apply filters such as 'Expression Value' (below cutoff, low, medium or high) and Anatomical Systems.



Let's now click on 'View associated diseases' to find out all diseases associated with the *CD86* (not only multiple sclerosis):

The screenshot shows the Open Targets Platform interface for the molecule *CD86*. At the top, there is a blue header bar with the Open Targets logo and a 'About' dropdown menu. Below the header, the text 'CD86' is prominently displayed, followed by 'CD86 molecule' and a 'View associated diseases' button with a grid icon.

You will land on a page like this:



There are three different displays that can be used to view the diseases associated with any given target:

- Bubble view

In this view, we group diseases into 'bubbles' based on the disease ontology. Large bubbles correspond to a therapeutic area and consist of smaller bubbles representing diseases within this area. A disease can belong to several therapeutic areas and therefore can appear within more than one large bubble. The strength of the association between the target and a disease is represented by the size of the bubble and the shade of its blue colour; the larger the bubble and the darker the blue, the stronger the association.

- Table view

In this view, we list all diseases associated with a target, ordered by the association score, which is colour coded. When there is no evidence to support the association, the cells in this table are coloured in white (score of zero). You can show the 10 first entries and get the pagination for the remaining entries.

Bubbles Table Tree

Showing 1 to 10 of 46 entries

Search:



Disease	Association score	Genetic associations	Somatic mutations	Drugs	Affected pathways	RNA expression	Text mining	Animal models	Therapeutic area
multiple sclerosis									immune system disease, ...
relapsing-remitting multipl...	0.20								immune system disease, ...
Charcot-Marie-Tooth dise...	0.15						0.15		nervous system disease, ...
Hereditary spastic paraple...	0.15					0.03	0.14		nervous system disease, ...
Charcot-Marie-Tooth dise...	0.15						0.15		nervous system disease, ...
Charcot-Marie-Tooth dise...	0.15						0.15		nervous system disease, ...
Charcot-Marie-Tooth dise...	0.15						0.15		nervous system disease, ...
Charcot-Marie-Tooth dise...	0.15						0.15		nervous system disease, ...
Autosomal dominant inter...	0.15						0.15		nervous system disease, ...
Autosomal dominant Char...	0.15						0.15		nervous system disease, ...

Show 10 entries

Previous 1 2 3 4 5 Next

No data

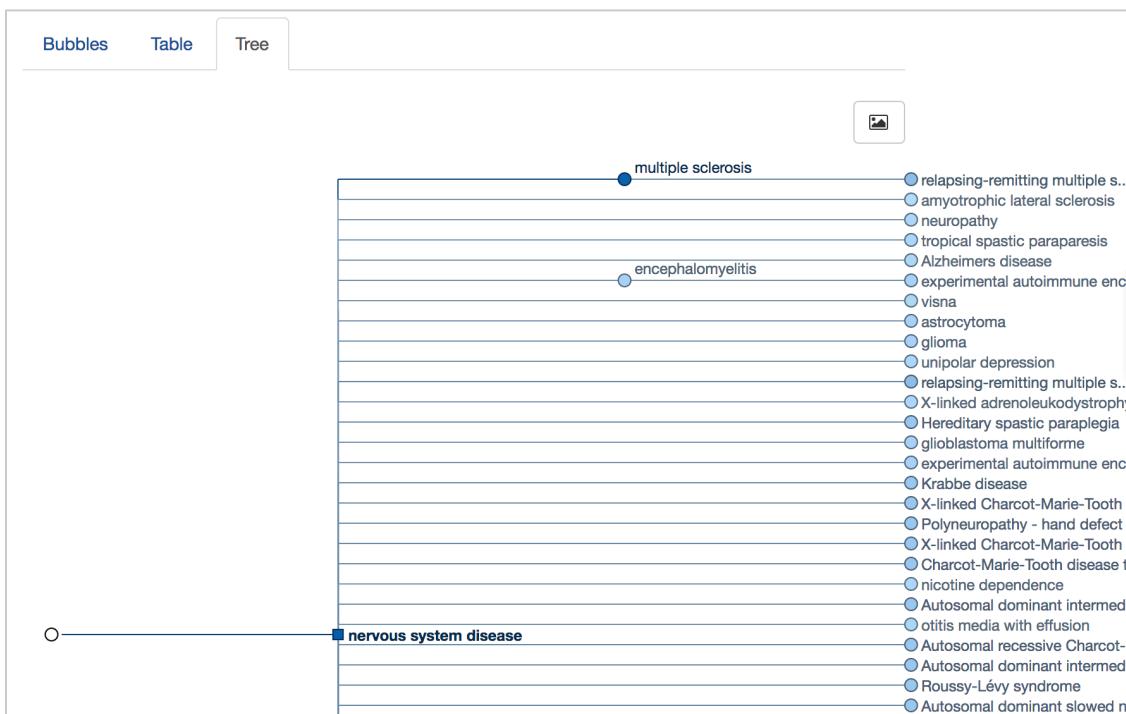
Score

This table can be exported in csv format (look for the download button).

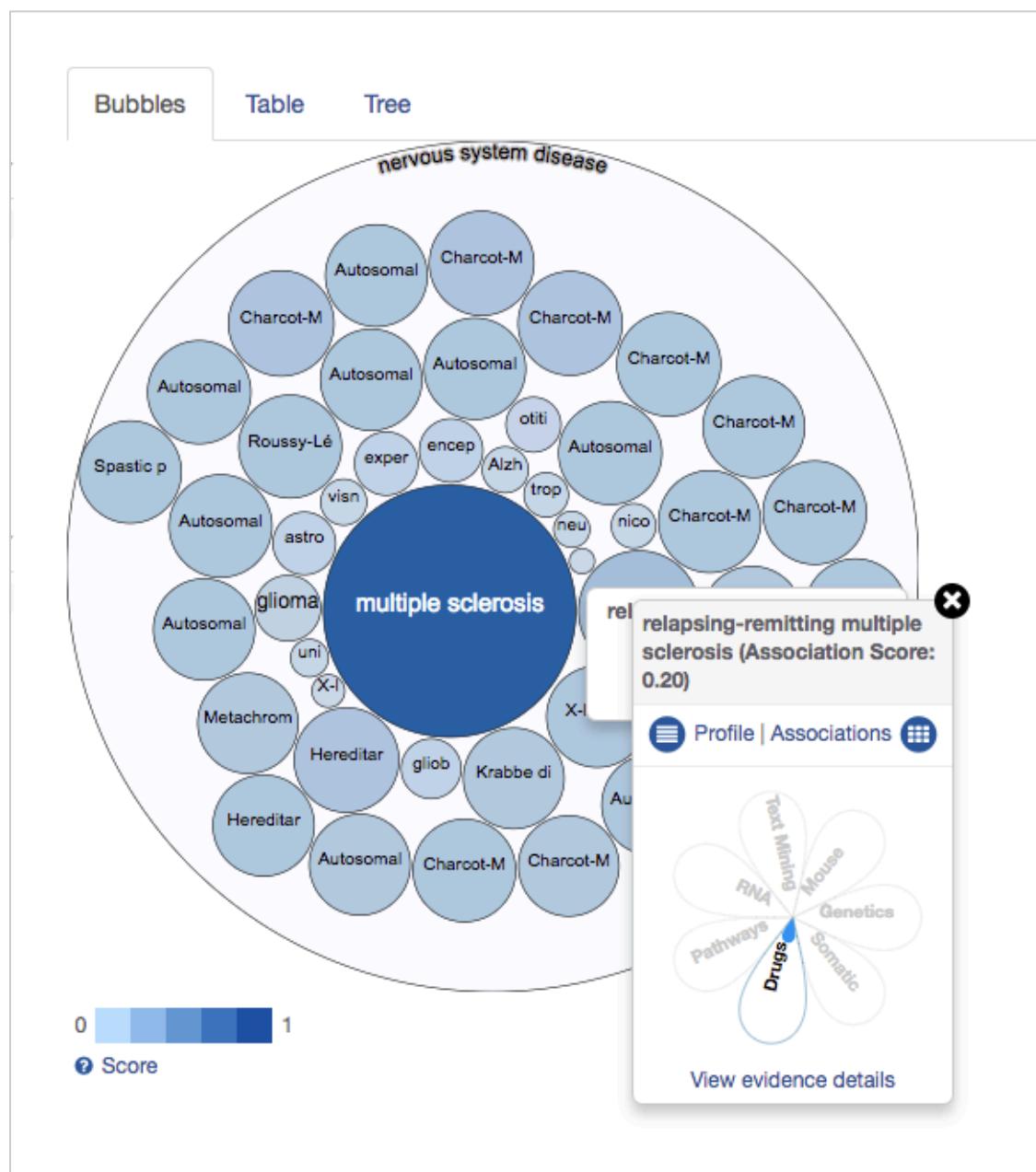
*Tip: We colour code the cells in the table in different shade of blue as a visual way to convey the strength of the association (strongest association is coloured in dark blue). The score varies from 0 to 1. Hover over the cells in the table to view the numbers. Alternatively, you can select the cells in the table so that you can view the numerical values.*

- Tree view

In the Tree view, you can visualise the evidence across the therapeutic areas in a tree format that represents the relationships of diseases. Therapeutic areas have a square symbol (e.g. Genetic disorders), while the diseases (e.g. ovarian carcinoma) are represented as circles. The squares and circles are colour coded in blue, and the darker the blue, the stronger the association:



Regardless the view you choose to explore, you can filter the data to find out if there are other “Nervous system” diseases associated with this target. There are 46 of them (e.g. Hereditary spastic paraplegia, amyotrophic lateral sclerosis and neuropathy). The scores vary from 0.01 to 0.20.



---

## **HANDS-ON EXERCISES PART I**

---

### **Exercise 1**

#### ***TRAF3IP2 in psoriasis***

##### **BACKGROUND**

The *TRAF3IP2* gene encodes a protein that is involved in regulating responses to cytokines by members of the Rel/NF-kappaB transcription factor family. These factors play a central role in innate immunity in response to pathogens, inflammatory signals and stress. Genome-wide association studies have identified a psoriasis susceptibility locus at *TRAF3IP2* (PMID:20953188, PMID: 20953186).

##### **QUESTIONS**

- a) Is this target associated with other skin diseases? If so, can you name three of them with the highest (overall) association score (> 0.70)?
  - b) Which types of data suggest such associations?
  - c) Can you name a few genetic variants that support the association between *TRAF3IP2* and psoriasis? Where does this evidence come from?
  - d) Can you view the genetic variants in a Browser view? What does the different colours represent in this view? In which human chromosome does this gene map to on the human genome? Is it a forward or reverse stranded gene?
  - e) How many research articles do currently support the association between *TRAF3IP2 in psoriasis*?
- 

### **Exercise 2**

#### **Aducanumab, antibody that may slow the progress of Alzheimer's disease**

## BACKGROUND

The most common cause of dementia, Alzheimer's disease is a brain disorder that leads to impairment of intellectual functions and social skills, resulting in significant disturbance of daily living activities. Dementia is caused by the destruction of cells in certain parts of the brain primarily involved in memory and mental function.

## SIGNIFICANCE

Alzheimer's disease is the 6<sup>th</sup> leading cause of death in the United States and it's expected 16 million Americans will be living with Alzheimer's by 2050 (source: alz.org).

Biogen in collaboration with Neurimmune has been conducting clinical studies investigating a potential new treatment (Aducanumab) for early Alzheimer's disease. Aducanumab is an antibody that binds to and may reduce amyloid plaques from the brain, potentially slowing the progress of the disease.

## QUESTIONS

- a) Which gene (s) does this drug match to?
- b) Can you name the biochemical pathways that this gene is involved in and that likely play a role in the pathogenesis of Alzheimer's?
- c) Are there other pathways that this gene can be mapped to, outside the context of any disease? Hint: these pathways are not related to Alzheimer's or other diseases. Click on the gene name to get to the profile page of the target (or gene).
- d) What is the human tissue with the highest RNA baseline expression for this target according to GTEx? Can you compare the RNA expression with the protein expression in this same human tissue?
- e) Is there a homologue to the human gene targeted by aducanumab in zebrafish? *Note: Zebrafish can be a useful animal model to focus on the roles of intracellular aggregate-prone proteins in the pathogenesis of AD and to help the identification of pathways, which can enhance the clearance of these toxic proteins. See more in the link below:*

<http://www.pdn.cam.ac.uk/directory/angeleen-fleming>

---

## Demo 3

Filter the target association table for Alzheimer's based on a list of known targets.

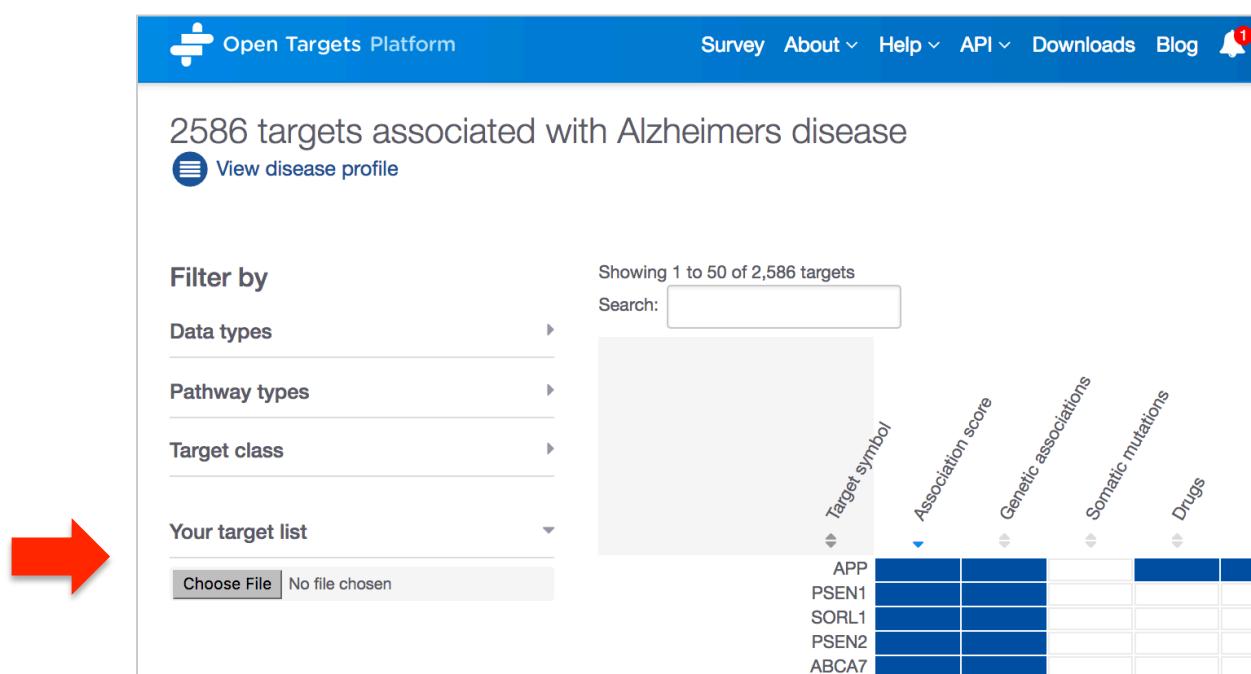
This is a list of several genes that seem to be associated with Alzheimer's based literature searches:

*HFE*  
*PSEN1*  
*TF*  
*APOE*  
*ADRB2*  
*PSEN2*  
*A2M*

Which information is available in the Open Targets Platform that could help you to choose and prioritise a target out of that list for follow up? We can input this data as a list (in .txt) to filter the associations for Alzheimer's in Open Targets.

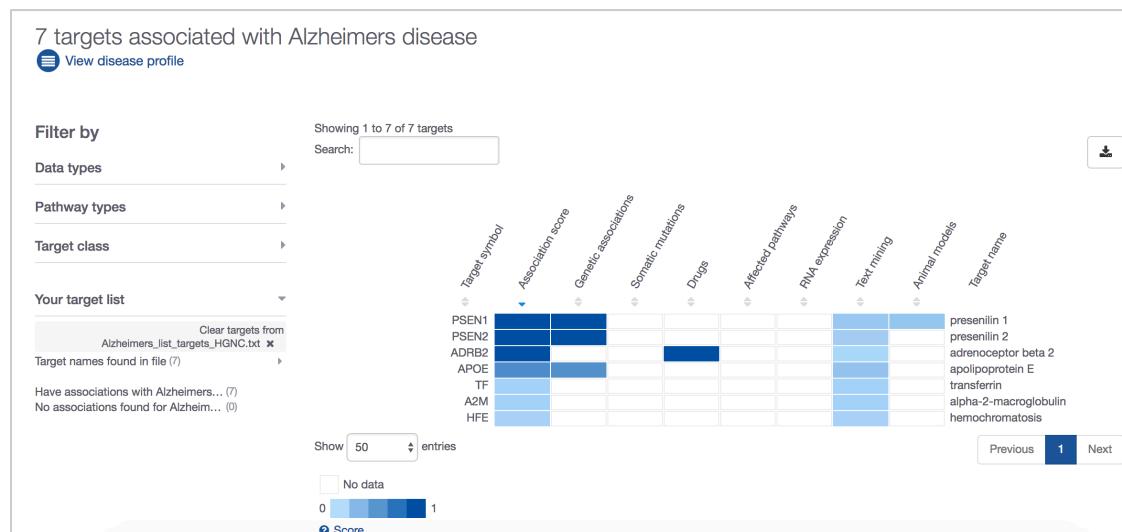
- a) Which of those seven genes have the strongest association w/ Alzheimer's?

Firstly, let's search for Alzheimer's and then upload our target list onto the Platform:



The screenshot shows the Open Targets Platform interface. At the top, there is a blue header bar with the logo and the text "Open Targets Platform". To the right of the logo are links for "Survey", "About", "Help", "API", "Downloads", "Blog", and a notification bell icon with a red "1" badge. Below the header, a message states "2586 targets associated with Alzheimers disease" and a link to "View disease profile". On the left, there is a sidebar titled "Filter by" with dropdown menus for "Data types", "Pathway types", "Target class", and "Your target list". The "Your target list" menu has a "Choose File" button and a placeholder "No file chosen". To the right of the sidebar, a table displays 50 targets out of 2,586. The columns are labeled "Target symbol", "Association score", "Genetic associations", "Somatic mutations", and "Drugs". The first five rows of the table show APP, PSEN1, SORL1, PSEN2, and ABCA7. A red arrow points to the "Choose File" button in the sidebar.

Now, we can upload a text file containing our list of genes (either as official gene symbols from HGNC e.g. *SOX3*, or Ensembl gene IDs e.g. ENSG00000134595). The filter 'Your target list' is at the left hand side of the association page (you will need to scroll down to see it):



The list should be uploaded and the resulting table will show the results of our analyses for your list of seven genes (i.e. targets). This will help you prioritise which targets to follow up.

b) Are there any targets, which are membrane receptors?

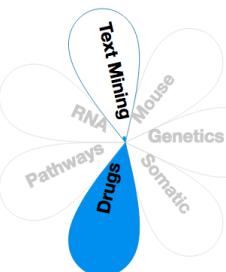
We can now use the filter 'Target class' to focus on membrane receptors only. There is only one target that is a membrane receptor, *ADRB2*.



c) Which amino acids of this membrane receptor correspond to the extracellular domain?

To explore more about the target itself, we can click on any cell of the resulting table then click on the target name, next to the flower:

## Evidence for ADRB2 in Alzheimers disease

**ADRB2**

adrenoceptor beta 2  
Synonyms: ADRBR, BAR, B2AR, ADRB2R  
Beta-adrenergic receptors mediate the catecholamine-induced activation of adenylate cyclase through the action of G proteins. The beta-2-adrenergic receptor binds epinephrine with an approximately 30-...



We will land on a page like this:

**ADRB2**adrenoceptor beta 2 |  View associated diseases

Beta-adrenergic receptors mediate the catecholamine-induced activation of adenylate cyclase through the action of G proteins. The beta-2-adrenergic receptor binds epinephrine with an approximately 30-fold greater affinity than it does norepinephrine.

Synonyms: ADRBR BAR B2AR ADRB2R Beta-2 adrenoceptor Beta-2 adrenoreceptor Beta-2 adrenergic receptor

## Protein Information (from UniProt)

## Variants, isoforms and genomic context

## Protein baseline expression

## RNA baseline expression

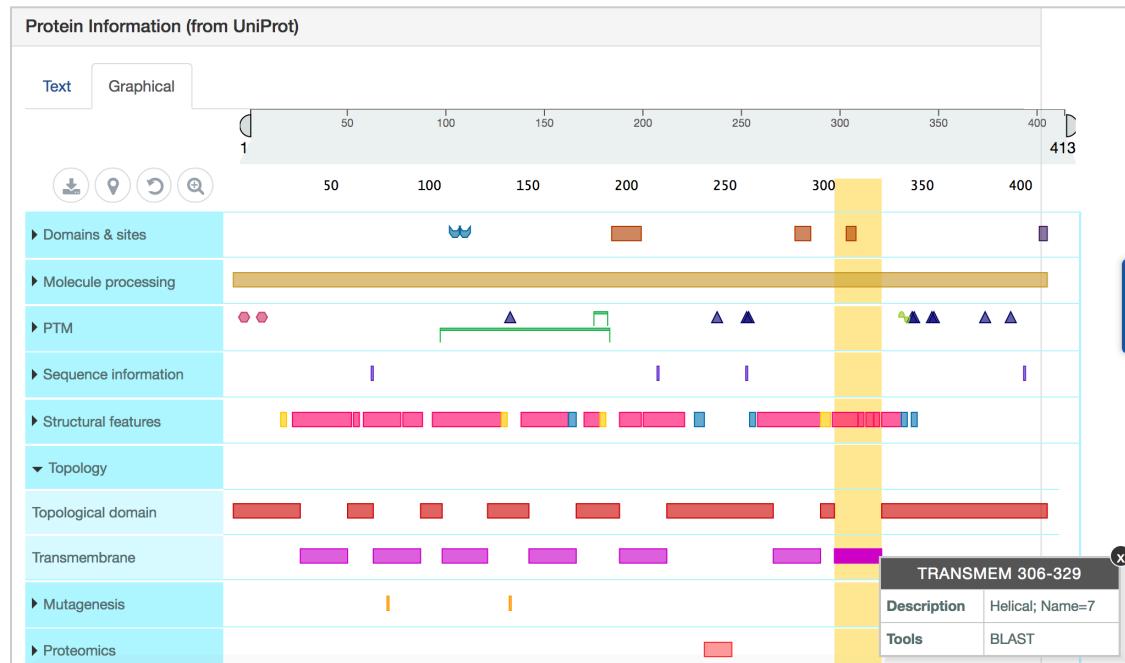
## Gene Ontology

## Protein Structure

## Pathways

## Drugs

To find what which amino acids of this membrane receptor correspond to the extracellular domain, we need to expand the tab ‘Protein Information (from UniProt)’, click on ‘Graphical’, then expand the ‘Topology’ section in the image:



This membrane receptor is a G-coupled transmembrane receptor, hence there are seven transmembrane domains. Click on the ‘purple-ish’ boxes in ‘Topology’ to get a pop up window with more information on which amino acids of the protein span the entirety of the cellular membrane.

---

---

## **HANDS-ON EXERCISES PART II**

---

### **Exercise 3**

#### ***IL6 as a possible target in the treatment of rheumatoid arthritis***

##### **BACKGROUND**

IL6 encodes a cytokine that functions in inflammation and the maturation of B cells. In addition, it has been shown to be an endogenous pyrogen capable of inducing fever in people with autoimmune diseases or infections. The protein implicated in a wide variety of inflammation-associated disease states, including systemic juvenile rheumatoid arthritis (PMID:9769329).

##### **QUESTIONS**

- a) How many diseases within the broader Therapeutic area 'Immune system disease' are associated with this target based on 'Drugs' as the only class of data type?
- b) In addition to the data type 'Drugs', are there other types of evidence supporting the association between *IL6* and rheumatoid arthritis?
- c) Can you describe some of the phenotypes in mice that seem to mimic the phenotype in patients with rheumatoid arthritis? What are the differences between the existing *Il6* knockout mouse models for this disease?

Let's now explore some disease information available for rheumatoid arthritis.

- d) What are the different subtypes (i.e. the children terms) of rheumatoid arthritis (RA)? Can you download the ontology tree of rheumatoid arthritis? Let's now have a look at one of the subtypes of RA i.e. chronic childhood arthritis.
- e) Can you list all drugs in phase III of clinical trials for the treatment of chronic childhood arthritis, which are still recruiting volunteers?

Let's now click on 'View associated targets' to see the targets associated with chronic childhood arthritis.

- f) Can you filter this list to show the results for the following targets only: *IL1B*, *JAK2*, *CXCR4*, *TNF* and *PTGS2* only? Are any of these genes a secreted class of target?
- 

## Exercise 4

### BACKGROUND

The Drug Discovery Unit at the University of Dundee translates biology research into novel drug targets and candidate drugs to address unmet medical need across, such as infectious affecting mainly the developing world.

These are some of the targets that have been selected for further investigation: *ODC1*, *GUCY1A2*, *GUCY1A1*, *CSF3R*, *CCR5*, *TLR7*, and *CD28*.

### QUESTIONS

- a) How can you search for all these targets in one go using the web interface of the Open Targets Platform?
  - b) Which diseases do these targets map to?
  - c) Can you list a few of the pathways these targets are involved in? Can you find out the diagram of the pathway that is enriched in this list of targets?
  - d) Can you list a few of the drugs targeting some of these genes? Can you find out the mechanism of action for one ACETAMINOPHEN?
  - e) Do any of these targets seem to be interacting with each other?
-

---

## **QUICK GUIDE TO DATABASES**

---

Here is a list of databases and projects that may be useful for you to explore:

### **PROTEINS**

**UniProtKB** – The “Protein knowledgebase” is a comprehensive set of protein sequences. It is divided into two parts: TrEMBL and Swiss-Prot. The later is manually annotated and reviewed, therefore provides a set of protein sequences of high quality.

<http://www.uniprot.org/>

### **GENE NOMENCLATURE COMMITTEES**

**HGNC** – The HUGO Gene Nomenclature Committee assigns unique names and symbols to every single human gene, whether they are coding or not. These gene names and symbols are the official ones for human genes.

<http://www.genenames.org/>

**MGI** – The HGNC counterpart for naming mouse genes and symbols.

<http://www.informatics.jax.org/>

### **GENETIC VARIANTS and SOMATIC MUTATIONS**

**GWAS catalog**– The catalog of Genome Wide Association Studies (GWAS) provides genetic variants (e.g. SNPs) that are associated with a disease.

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

**EVA** – The European Variation Archive (EVA) provides genetic variants and somatic mutations (associated with cancer).

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

**Cancer Gene Census** - A catalogue of genes for which mutations have been causally implicated in cancer. The Catalogue of Somatic Mutations in Cancer (COSMIC) at the Wellcome Trust Sanger Institute provides us with the set of genes associated with specific cancers in the Cancer Gene Census, in addition to other cancers associated with that gene in the COSMIC database.

[www.cancer.sanger.ac.uk/census/](http://www.cancer.sanger.ac.uk/census/)

**IntOGen** - It provides evidence of somatic mutations, genes and pathways involved in tumorigenesis from 6,792 samples across 28 cancer types.

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

**Gene2Phenotype** - The data in Gene2Phenotype (G2P) provides evidence of genetic variants that are manually curated from the literature by consultant clinical geneticists in the UK. This is provided by DECIPHER, a database of genomic variants and phenotypes in patients with developmental disorders.

<https://www.ebi.ac.uk/gene2phenotype>

## **DRUGS**

**ChEMBL** - The ChEMBL database at the EMBL-EBI provides evidence from known drugs that can be linked to a disease and a known target.

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

## **RNA EXPRESSION**

**Expression Atlas** - The Expression Atlas at EMBL-EBI provides information on genes that are differentially expressed between normal and disease samples, or among disease samples from different studies. In addition to differential expression, they provide baseline expression information for each gene.

<https://www.ebi.ac.uk/gxa/home>

## **AFFECTED PATHWAYS**

**Reactome** - The Reactome database at the EMBL-EBI contains pathway information on biochemical reactions sourced from manual

curation. It identifies reaction pathways that are affected by pathogenic mutations.

<http://www.reactome.org/>

### **ANIMAL MODELS**

**Phenodigm** - The Phenodigm resource at the Wellcome Trust Sanger Institute provides evidence on associations of targets and disease. It uses a semantic approach to map between clinical features observed in humans and mouse phenotype annotations.

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

### **TEXT MINING**

**Europe PMC** - The Europe PubMed Central at the EMBL-EBI mines the titles, abstracts and full text research articles from both PubMed and PubMed Central to provide evidence of links between targets and diseases.

<http://europepmc.org/>