

Open Targets: identifying drug targets in a pre-competitive framework

BSPR meeting 2019

July 2nd 2019

Denise Carvalho-Silva, PhD

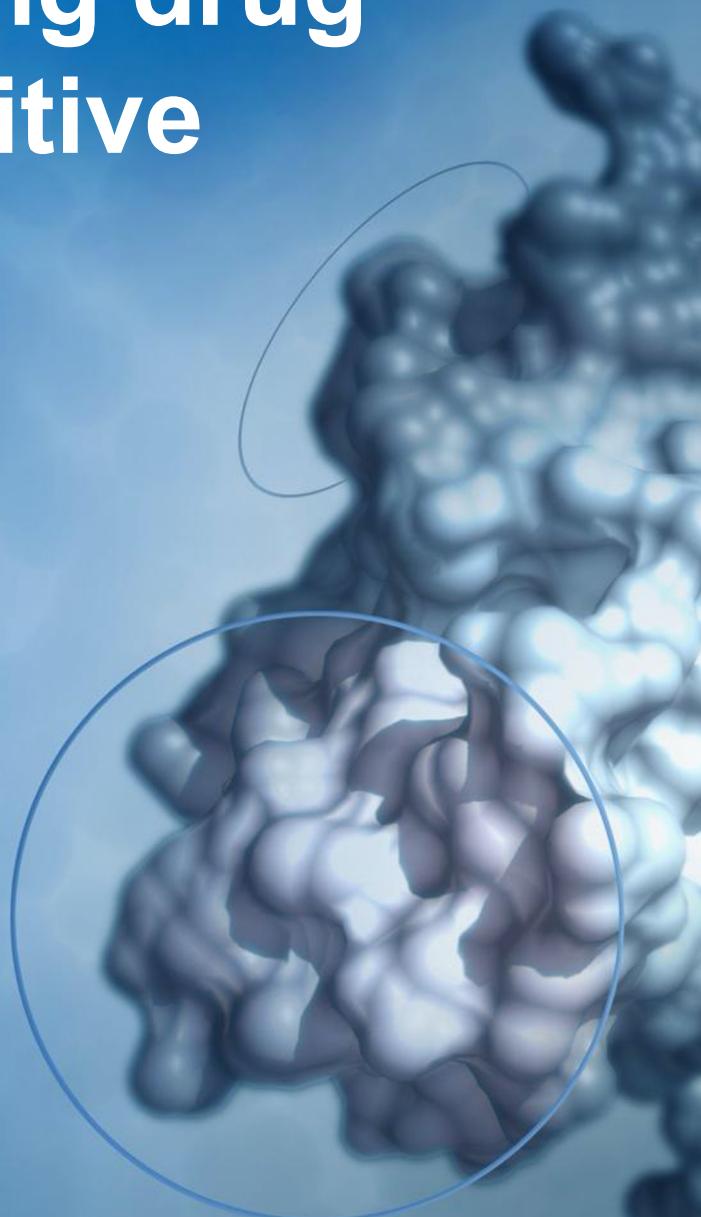
EMBL-EBI | Open Targets

Wellcome Genome Campus

United Kingdom



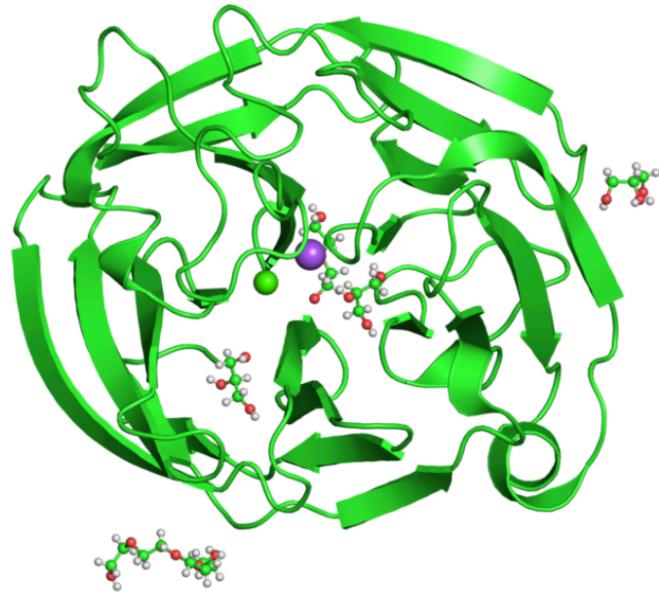
Open Targets



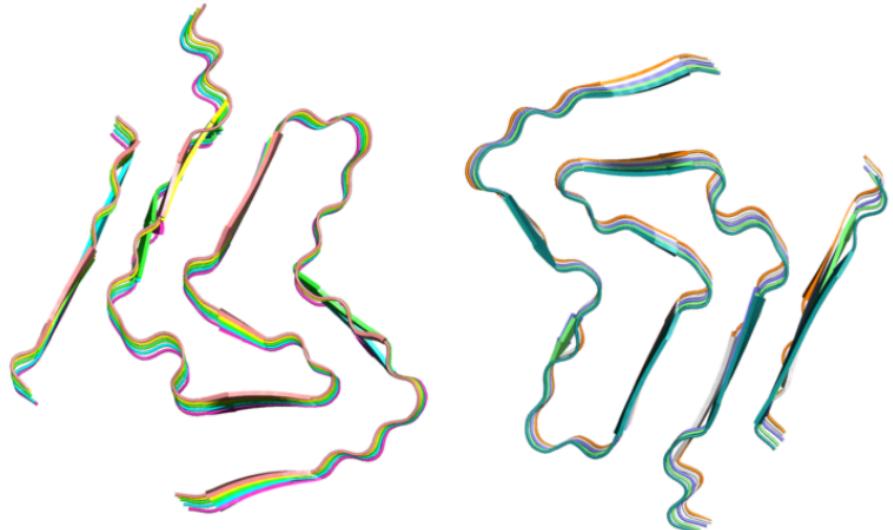
Acknowledgements



Most drug targets are proteins



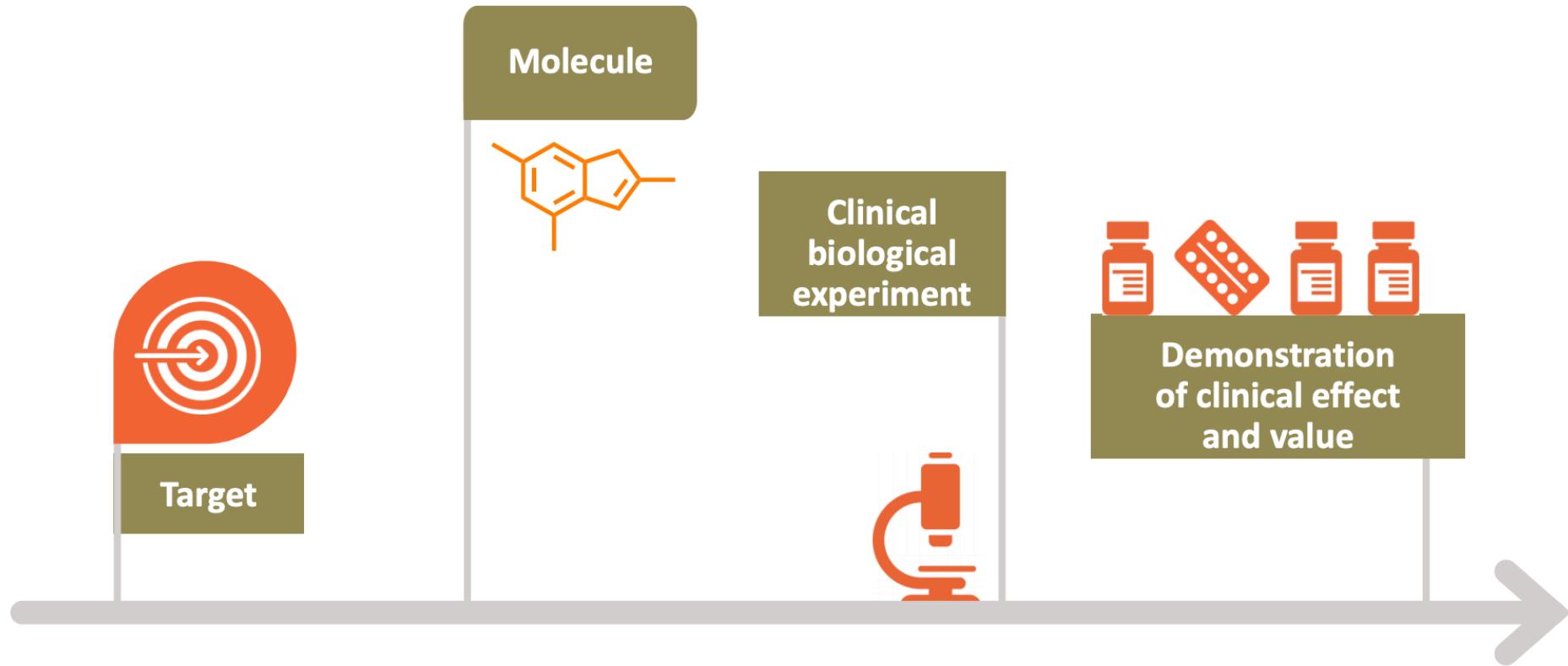
MYOC - glaucoma
(PDBe 4wx5)



SNCA - Parkinson's
(PDBe 6rt0)

Genetic variants → protein structure → diseases

Selecting the right target

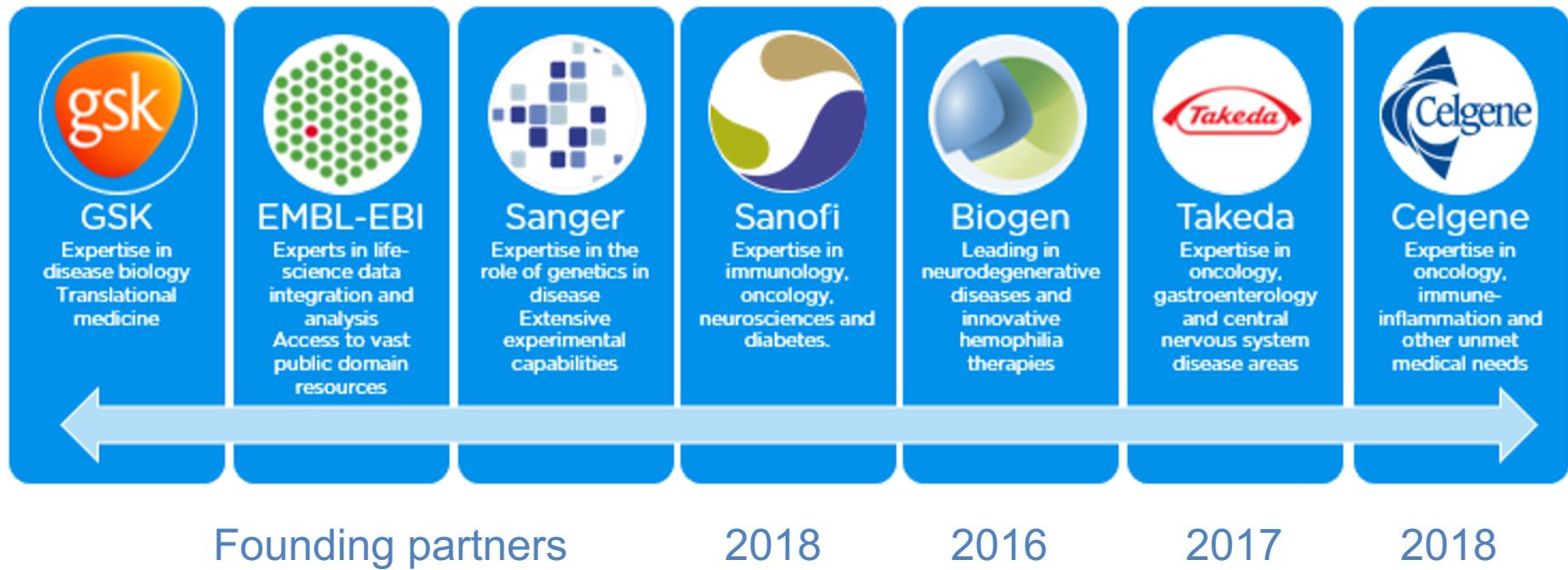


Drug discovery is challenging

Open Targets

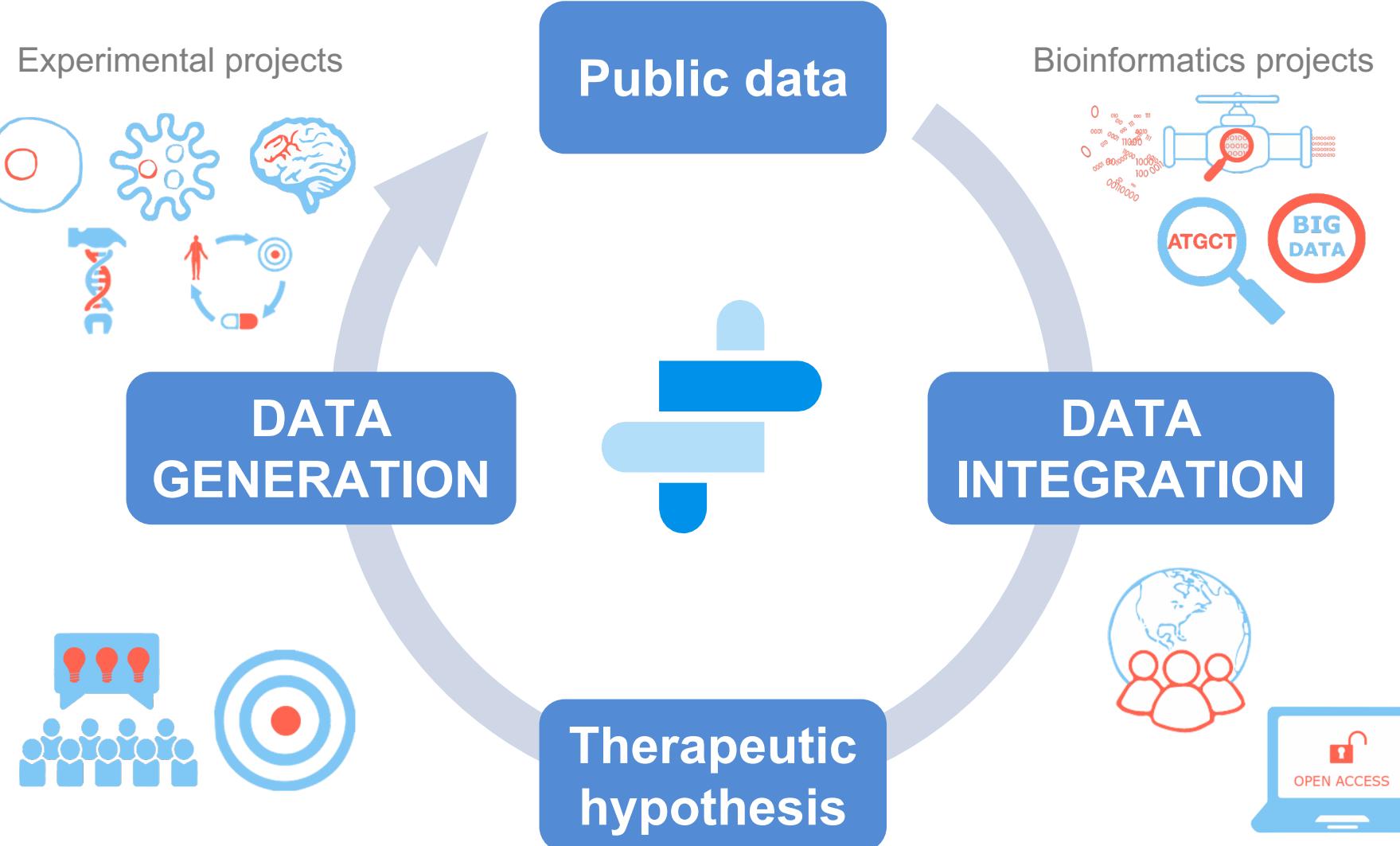
A partnership to transform drug discovery

Founded in 2014

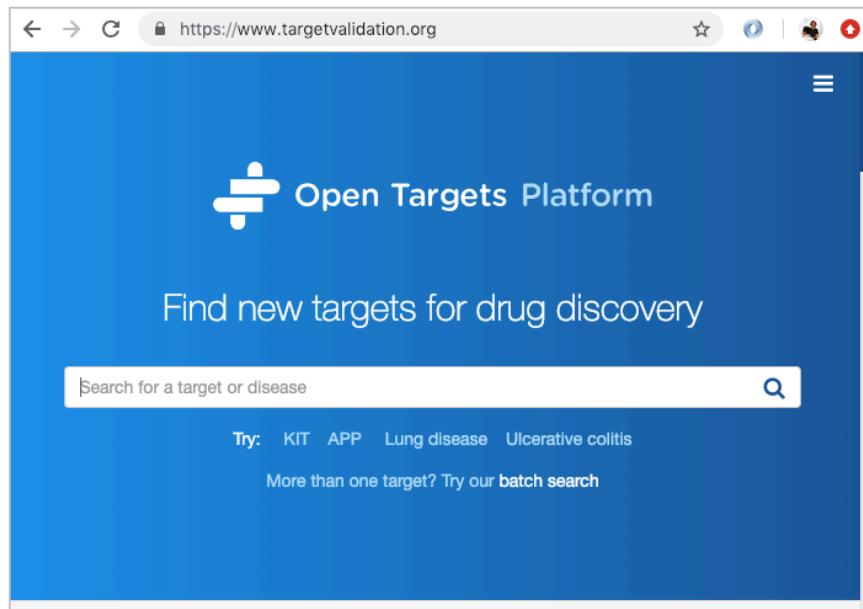


Systematic identification and prioritisation of targets

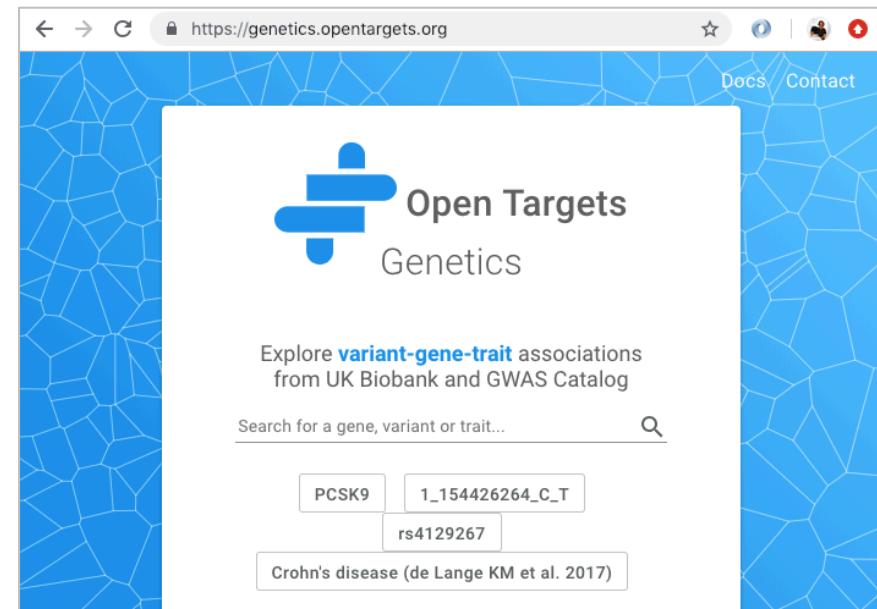
Knowledge cycle



Data integration: informatics



The screenshot shows the homepage of the Open Targets Platform. The URL in the address bar is <https://www.targetvalidation.org>. The page has a dark blue header with the "Open Targets Platform" logo and a search bar. Below the header, there's a large white area with the text "Find new targets for drug discovery". A search bar contains the placeholder "Search for a target or disease" with a magnifying glass icon. Below the search bar, there are suggestions: "Try: KIT APP Lung disease Ulcerative colitis". A link "More than one target? Try our batch search" is also present.



The screenshot shows the homepage of the Open Targets Genetics website. The URL in the address bar is <https://genetics.opentargets.org>. The page has a light blue header with the "Open Targets Genetics" logo and a search bar. Below the header, there's a large white area with the text "Explore variant-gene-trait associations from UK Biobank and GWAS Catalog". A search bar contains the placeholder "Search for a gene, variant or trait..." with a magnifying glass icon. Below the search bar, there are three highlighted results: "PCSK9", "1_154426264_C_T", and "rs4129267". At the bottom, there's a link "Crohn's disease (de Lange KM et al. 2017)".

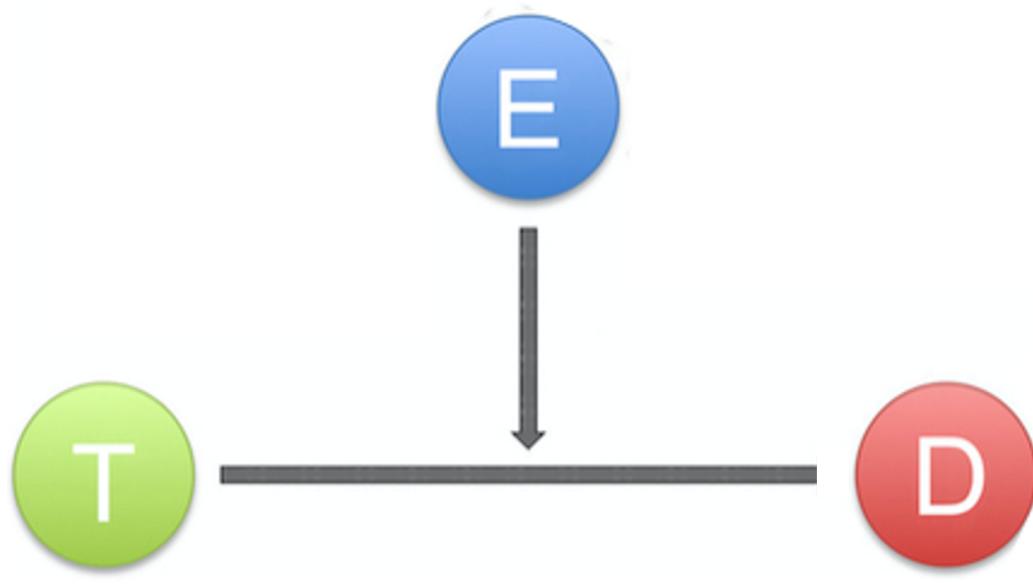
<https://www.targetvalidation.org>

<https://genetics.opentargets.org>

Open Targets Platform: data model

Evidence

(variants, drugs, literature, etc)



Target

(protein and non-protein coding genes)

Disease

(rare and common)

<https://www.targetvalidation.org>

Is my protein associated with a disease?

Filter by

Table

Bubbles

Tree

Data type

selected

- Genetic associations (8)
- Somatic mutations (0)
- Drugs (0)
- Pathways & systems b... (0)
- RNA expression (0)
- Text mining (37)
- Animal models (13)

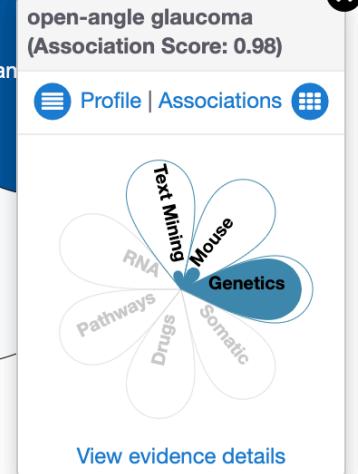
Therapeutic area

selected

- Genetic disorder (7)
- Eye disease (7)
- Immune system disease (3)
- Nervous system disease (3)
- Measurement (2)
- Phenotype (1)
- Biological process (1)

Filter by
data types

Diseases associated with MYOC
from two therapeutic areas

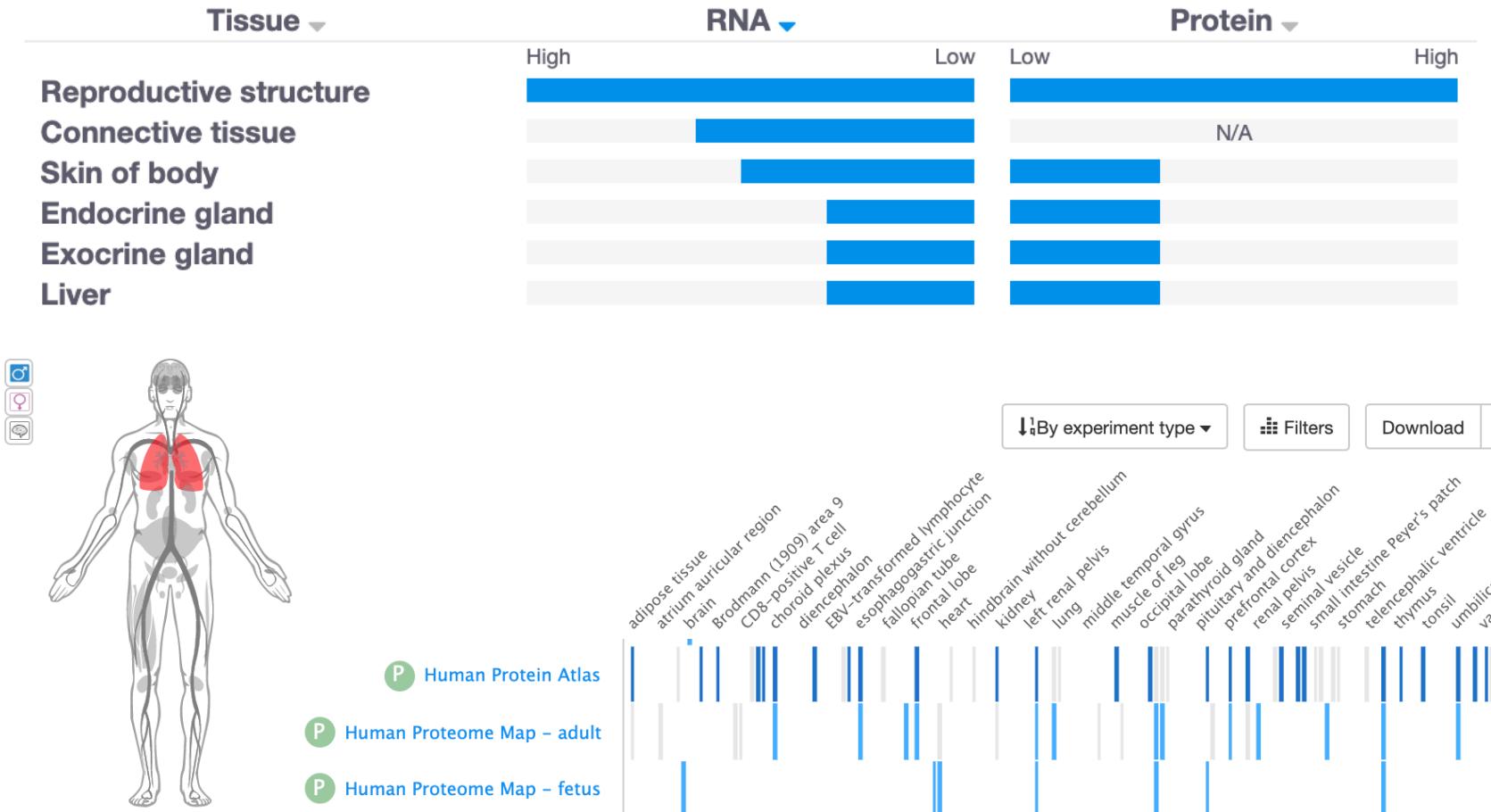


Associations for a target

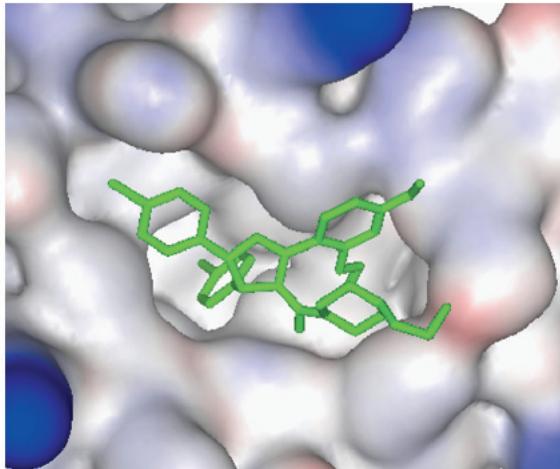
0 1
Score

Feedback

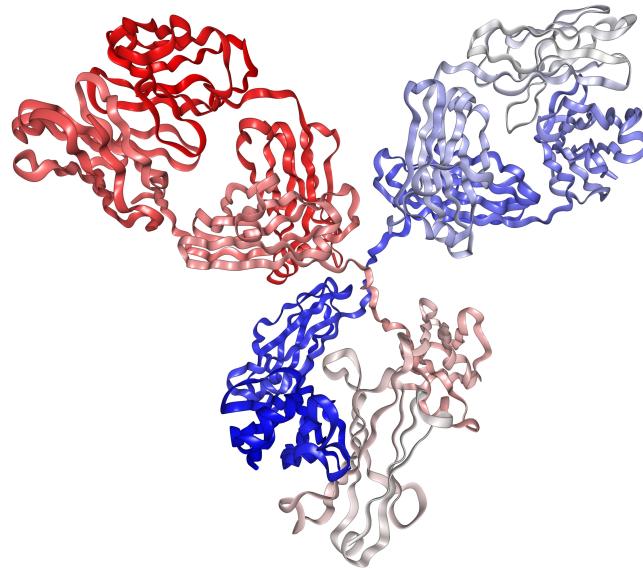
Is my target expressed in the relevant tissue?



Is my target tractable?



DOI:10.1517/17460441.34.391



Antibody

Small molecule

Clinical precedence Discovery precedence

Phase 4 Phase 2 or 3 Phase 0 or 1

PDB targets with ligands Active compounds in ChEMBL

Predicted tractable

DrugEBIliy score > 0.7

DrugEBIliy score 0 to 0.7

Clinical precedence

Phase 4 Phase 2 or 3 Phase 0 or 1

Predicted tractable - high confidence

UniProt location - high confidence

GO cell component - high confidence

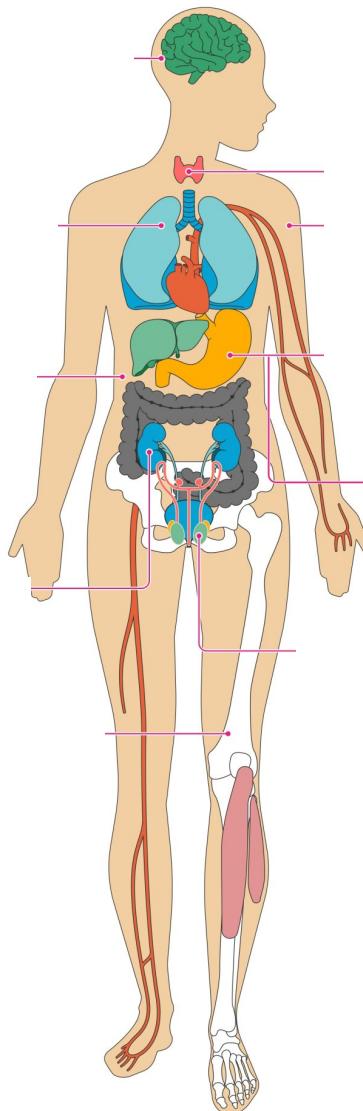
Predicted tractable - medium to low confidence

UniProt location - low or unknown confidence

UniProt predicted signal peptide or transmembrane region

GO cell component - medium confidence

Is my target safe to be modulated?



⚠ Target safety New

The following effects have been observed and noted in one or more publications on drug target safety assessment.

Showing 1 to 2 of 2 entries

Search:

[Download .csv](#)

Main organs & systems affected	Agonism or activation effects	Antagonism or inhibition effects	Publications
• Endocrine	General <ul style="list-style-type: none">Increased prostate carcinomaOedemaAndrogenicity femalesIncreased muscle massIncreased hostilitySleep apnoeaLiver complications	General <ul style="list-style-type: none">Decreased spermatogenesisImpotenceGynecomastiaMastodyniaIncreased breast carcinoma	Bowes et al. (2012)

193 proteins with safety information

- Drowsiness
- Increased heart rate
- Hepatotoxicity

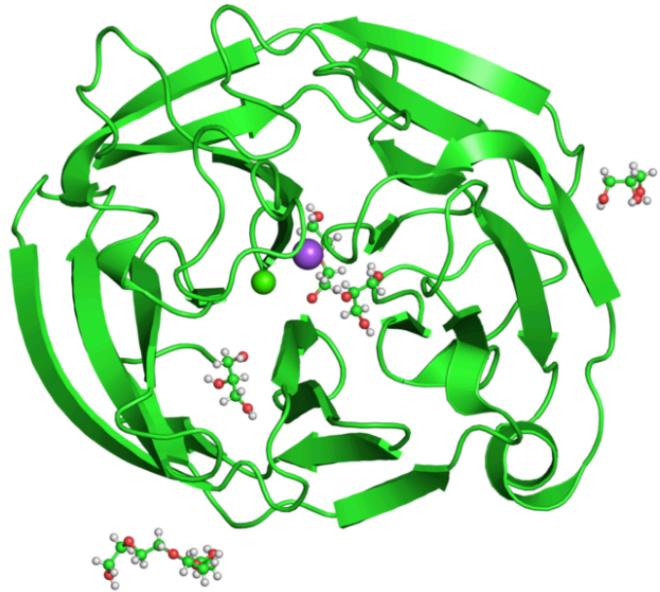
Target prioritisation

	Target safety	New
Drugs		
Target tractability		New
Protein information		
Pathways		
Similar targets (based on diseases in common)		
Variants, isoforms and genomic context		
Protein interactions		
RNA and protein baseline expression		
Mouse phenotypes		
Protein structure		
Gene ontology		
Gene tree		
Bibliography		
Cancer hallmarks		
Cancer biomarkers		

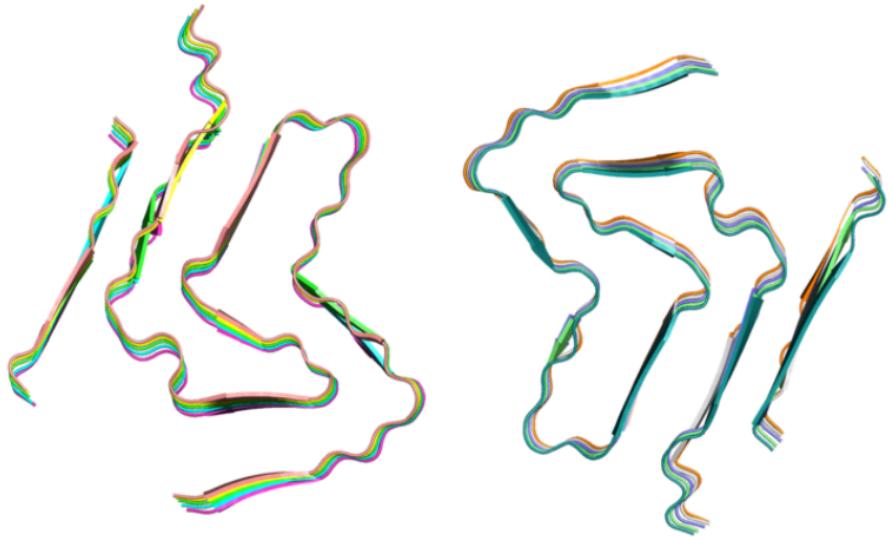


Target profile

What is the protein function in health?



MYOC - glaucoma
(PDB ID 4wx5)

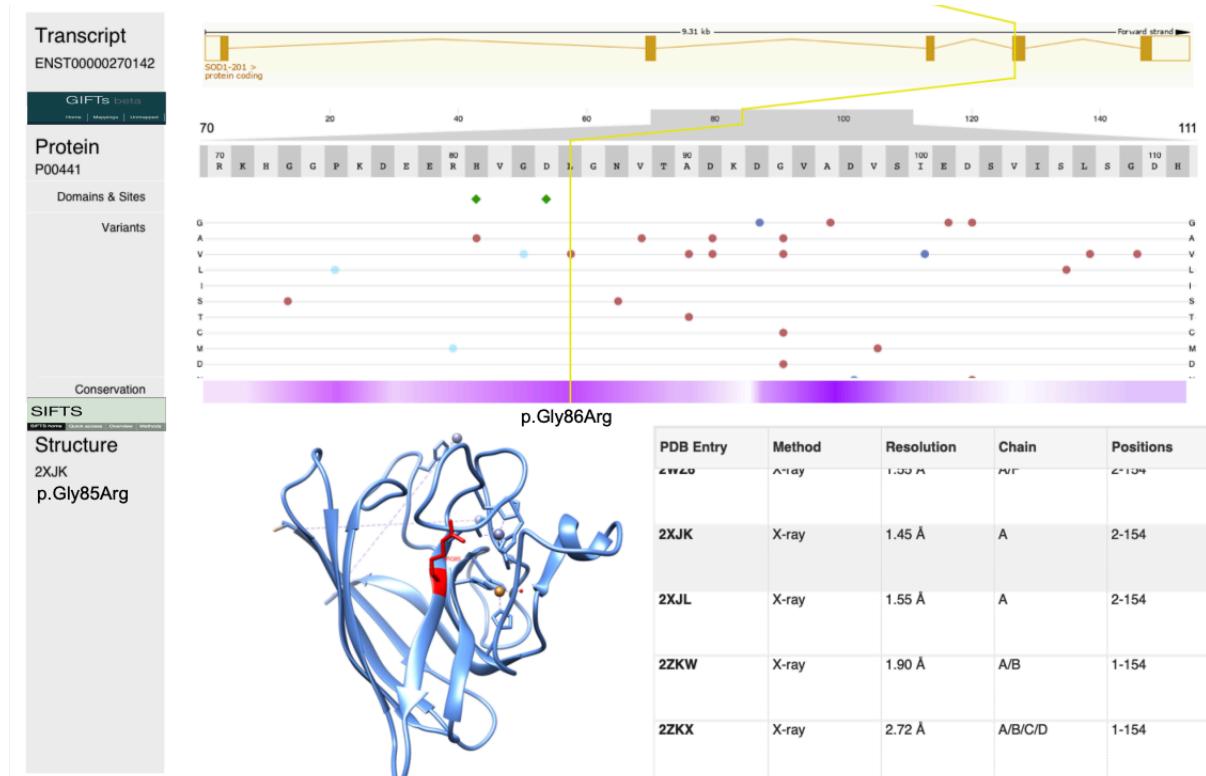


SNCA - Parkinson's
(PDB ID 6rt0)

**UNDER
DEVELOPMENT**

PepVEP

- Integrated framework to deliver functional information per AA
- Mapping to clinical and disease associations



 **PDBe**
Protein Data Bank in Europe

 **UniProt**

 **e!Ensembl**

Open Targets Platform

- Resource of integrated multiomics data
- Target identification and prioritisation
- Graphical web interface: easy to use
- REST-API for larger, more flexible queries

27K
targets

10K
diseases

3.3 M
associations

7.2 M
evidence

June 2019 release, 19.06

Where to find out more?

Nucleic Acids Research

Issues Section browse ▾ Advance articles Submit ▾ Purchase About ▾



Nucleic Acids Research, 2018 **1**
doi: 10.1093/nar/gky1133

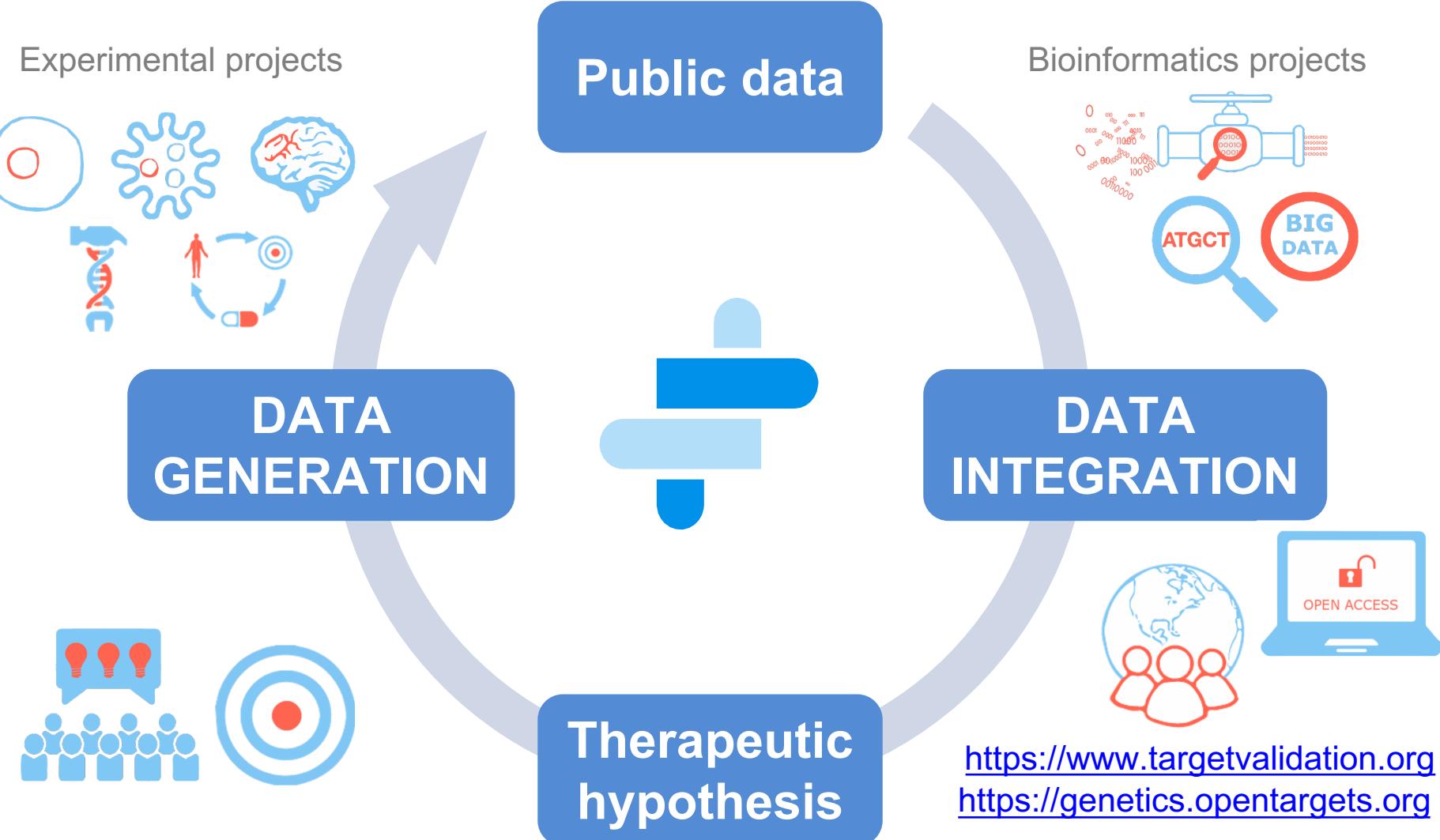
Open Targets Platform: new developments and updates two years on

Denise Carvalho-Silva^{1,2,*}, Andrea Pierleoni^{1,2}, Miguel Pignatelli^{1,2}, ChuangKee Ong^{1,2}, Luca Fumis^{1,2}, Nikiforos Karamanis^{1,2}, Miguel Carmona^{1,2}, Adam Faulconbridge^{1,2}, Andrew Hercules^{1,2}, Elaine McAuley^{1,2}, Alfredo Miranda^{1,2}, Gareth Peat^{1,2}, Michaela Spitzer^{1,2}, Jeffrey Barrett^{2,3}, David G. Hulcoop^{2,4}, Eliseo Papa^{2,5}, Gautier Koscielny^{2,4} and Ian Dunham^{1,2,*}

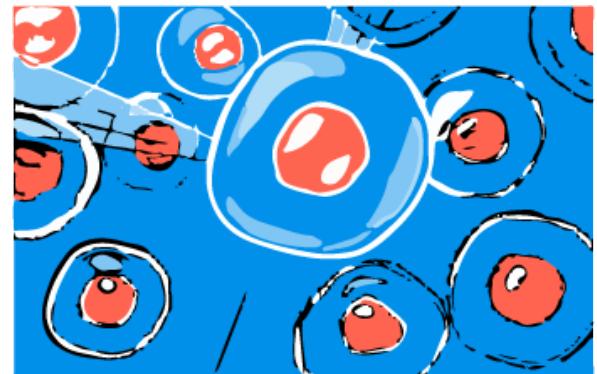
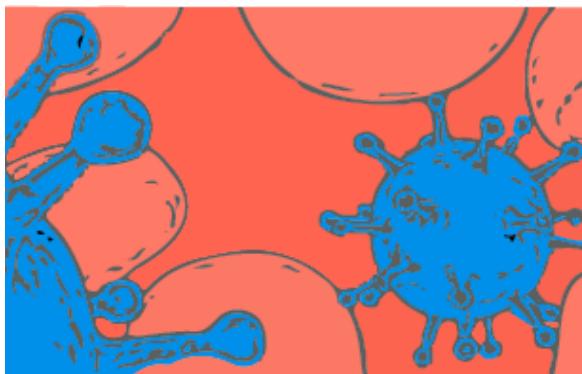
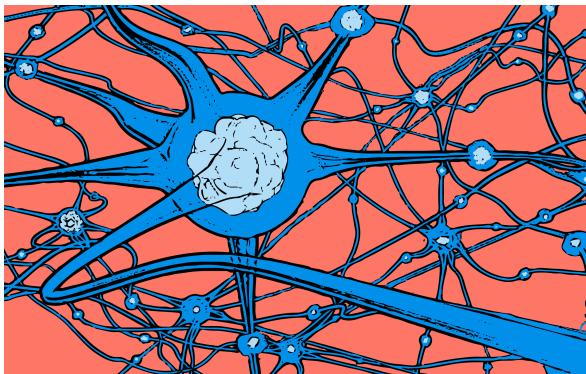
¹European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton, Cambridgeshire CB10 1SD, UK, ²Open Targets, Wellcome Genome Campus, Hinxton, Cambridgeshire CB10 1SD, UK, ³Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge CB10 1SA, UK, ⁴GSK, Medicines Research Center, Gunnels Wood Road, Stevenage, SG1 2NY, UK and ⁵Biogen, Cambridge, MA 02142, USA

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Knowledge cycle



Data generation: therapeutic areas



9 ongoing projects

2 complete projects

3 manuscripts on bioRxiv

7 ongoing projects

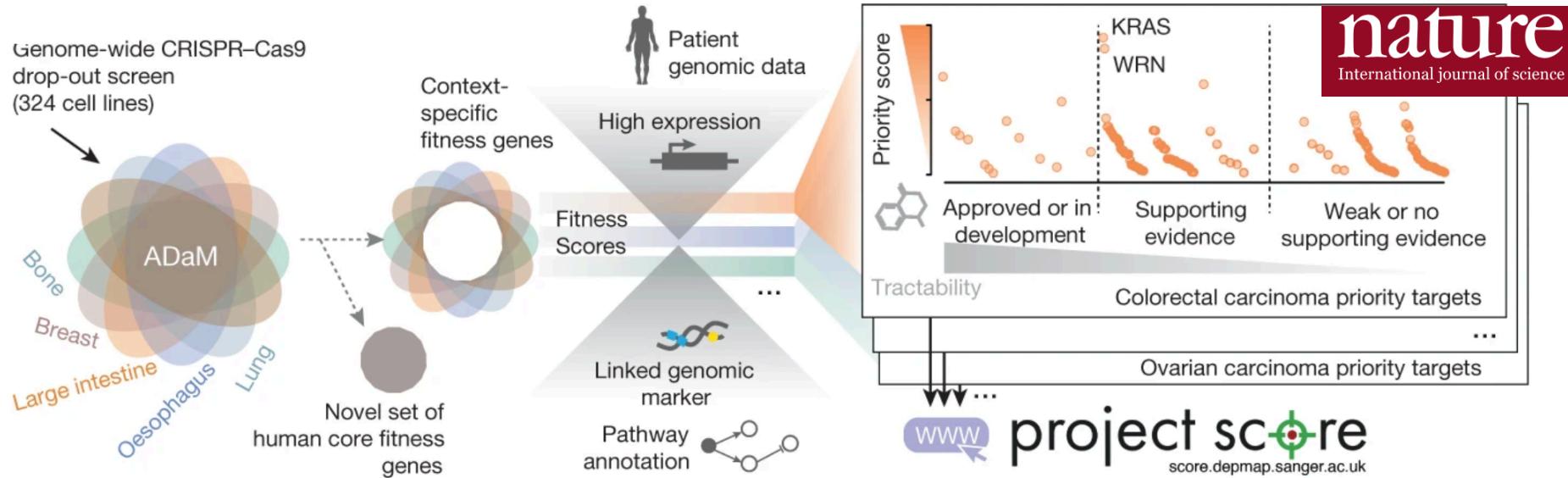
1 publication (2019)

3 complete projects

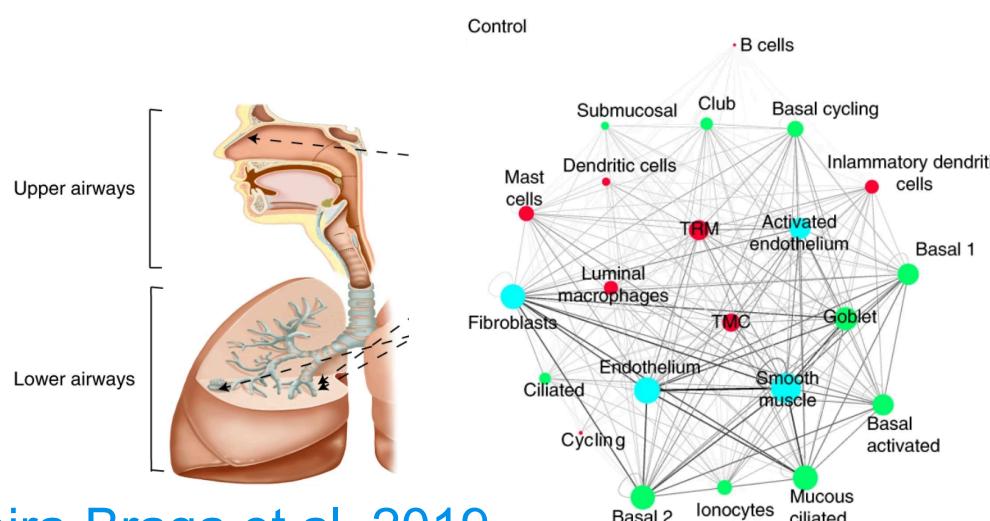
5 ongoing projects

1 publication (2019)

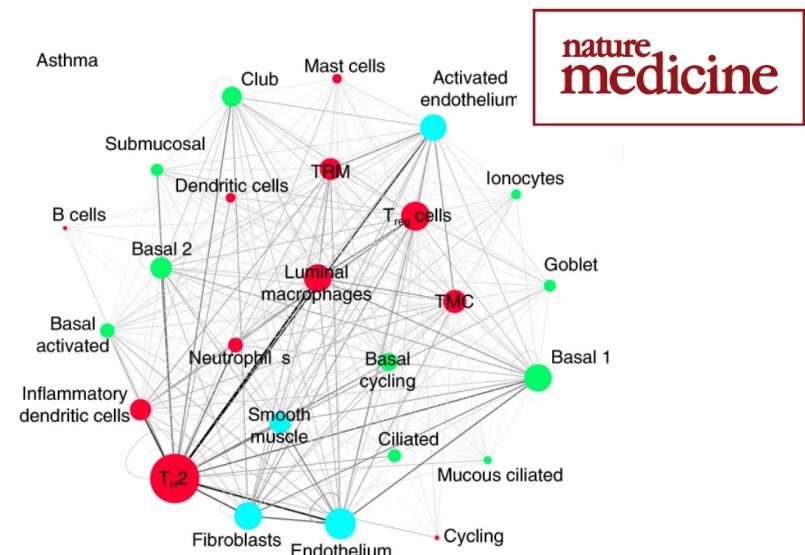
Prioritising targets and pathways



Behan et al. 2019



Vieira-Braga et al. 2019



Open Targets community



@targetvalidate



blog.opentargets.org/



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



<https://tinyurl.com/opentargets-youtube>

Thank you!