Next up:

Lecture 5 Target tractability and drug associations

ISMB/ECCB 2025

20 July 2025
Liverpool, UK

PDBe Protein Data Bank in Europe
Open Targets
wellcome sanger institute
UniProt
e!Ensembl
EMBL-EBI

Outline

Introduction to Open Targets

Overview of the Open Targets Platform

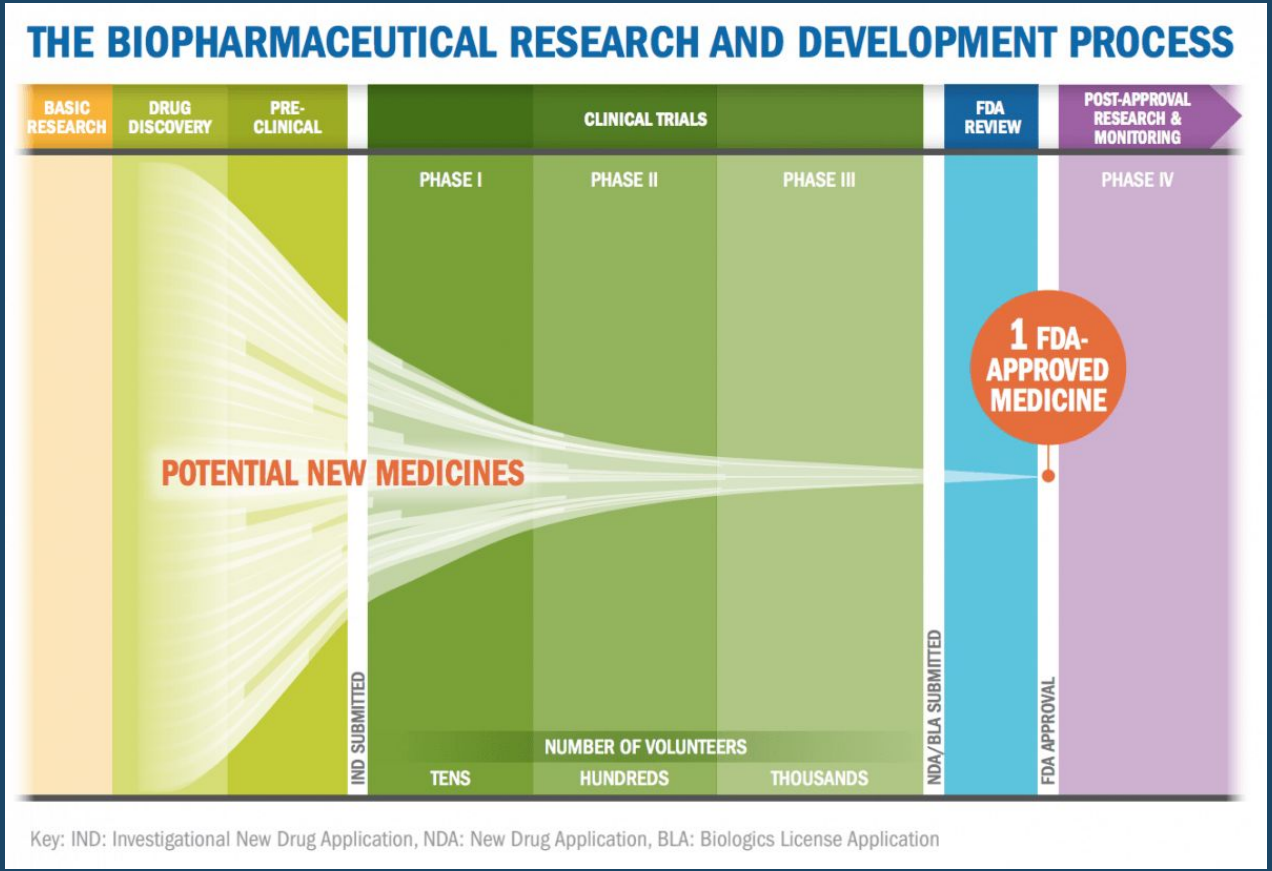
Target-disease associations

Target prioritisation

Case Studies

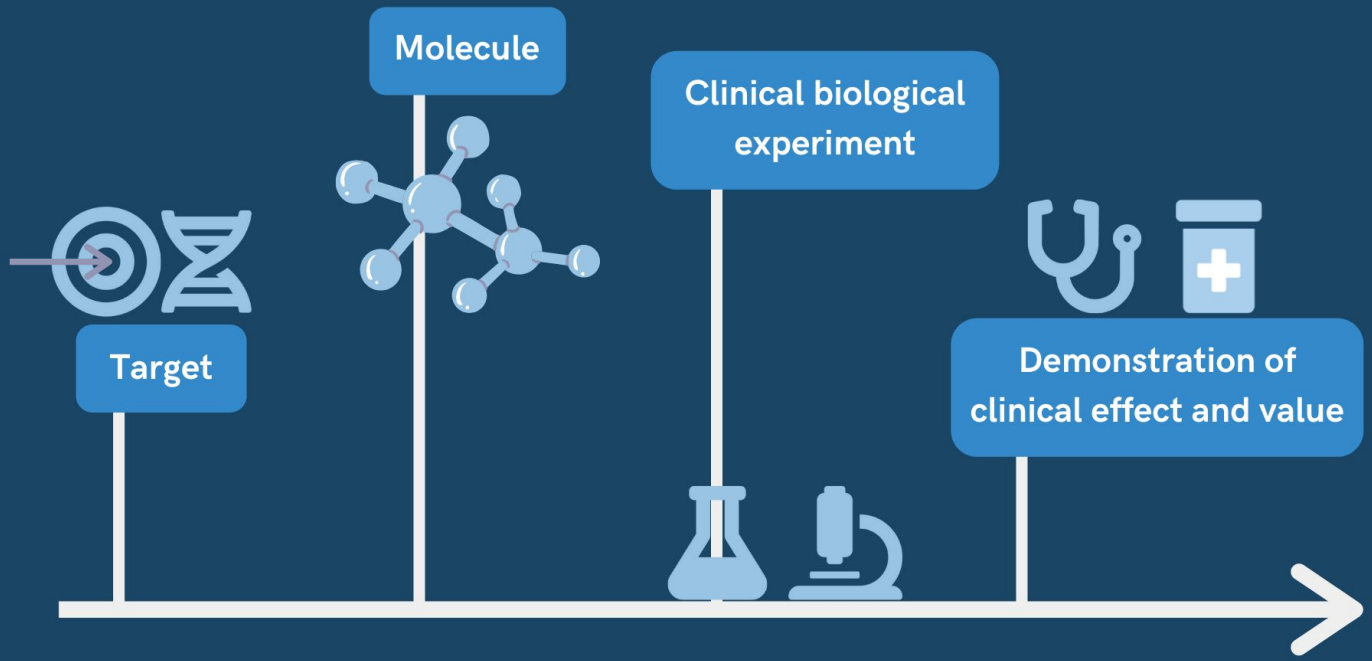
PART 1

Introduction to Open Targets



Biopharmaceutical Research & Development, PhRMA, 2015 (PDF)

Target identification is the first step



The importance of genetic evidence for drug success

A drug is:

8x more likely to succeed if target identified in **Mendelian genetic evidence**

2x more likely to succeed if target supported by **GWAS evidence**

📜 **Nelson et al. (2015)** | Nat Genet

📜 **King et al. (2019)** | PLoS Genet.

⅔ of **2021 FDA-approved drugs** supported by human genetics evidence

63% of **new drugs approved in the past decade** supported by human genetics evidence

📜 **Ochoa et al. (2022)** | Nat Rev Drug Discov.

📜 **Rusina et al. (2023)** | Nat Rev Drug Discov.

2.6 **Drug mechanisms with genetic support** have 2.6 greater probability of success

"These results indicate we are **far from reaching peak genetic insights** to aid the discovery of targets for more effective drugs."

📜 **Minikel et al. (2024)** | Nature

10 YEAR ANNIVERSARY

Open Targets

2014-2024

Open Targets is an innovative, large-scale, multi-year, **pre-competitive industry-academia partnership**

Open Targets

A partnership to transform drug discovery through the systematic identification and prioritisation of targets

EMBL-EBI

wellcome sanger institute

Genentech
A Member of the Roche Group

GSK

MSD

Pfizer

sanofi

Academic Institutes

Industry Partners

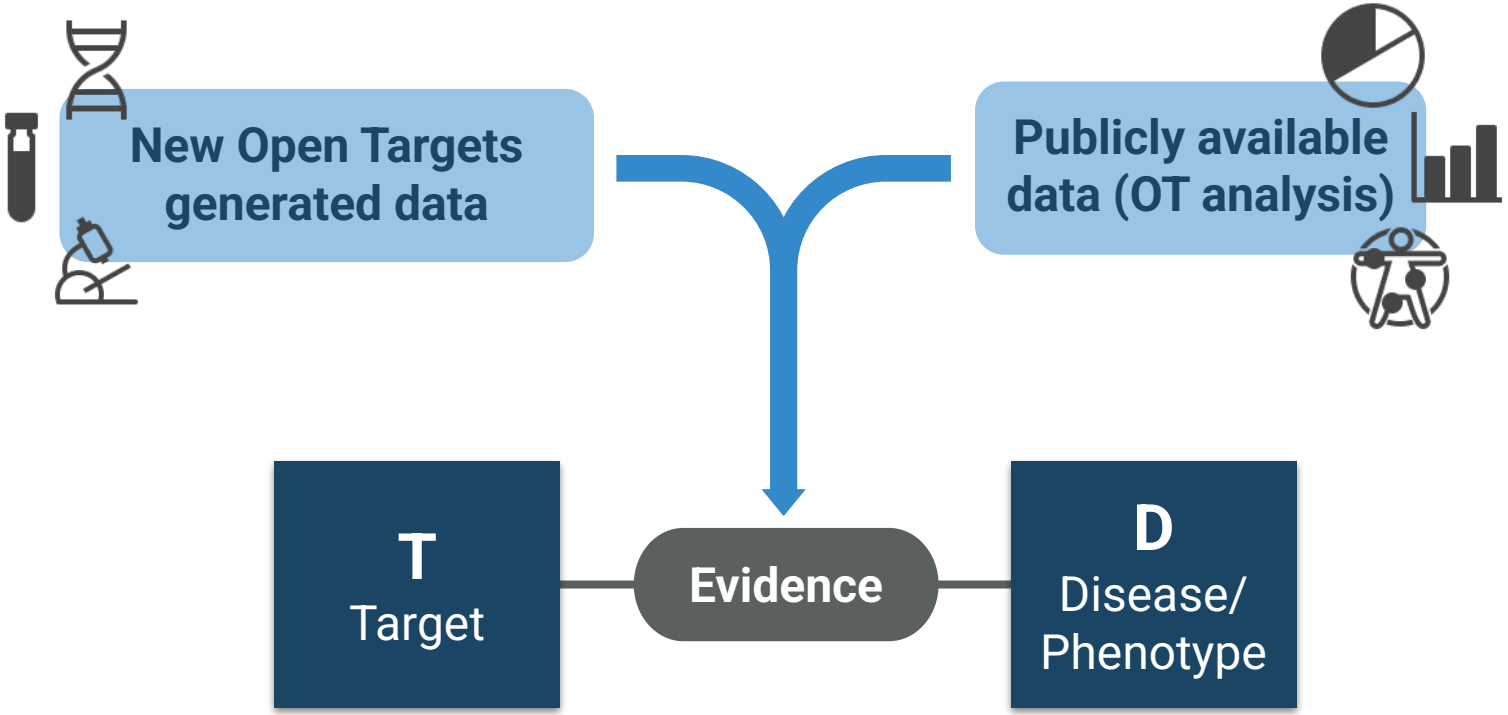
10 YEAR ANNIVERSARY

Open Targets

2014-2024

We use human genetics and genomics data for **systematic drug target identification and prioritisation**

We systematically use **evidence** to build therapeutic hypotheses between **targets** and **disease**



New Open Targets generated data

Oncology

Immunology & Inflammation

Neurodegeneration

Genetics

eQTLs

CRISPR

scRNA-seq

Cell models

T
Target

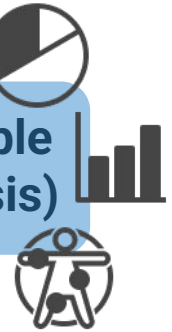
Evidence

D
Disease/
Phenotype

Open Targets Platform

\+ Open Targets projects

Publicly available data (OT analysis)



T
Target

Evidence

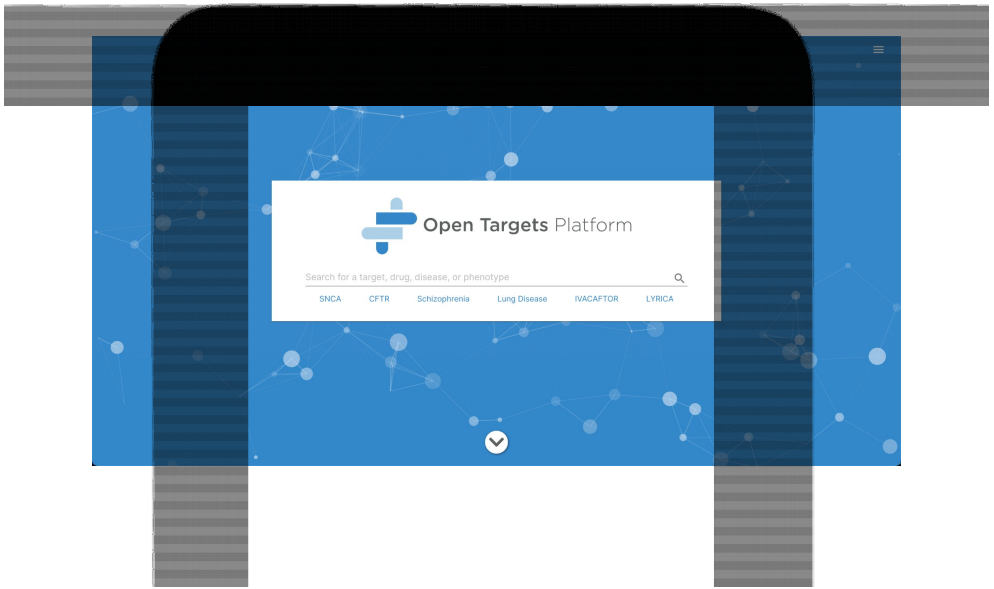
D
Disease/
Phenotype

Intro to Open Targets — Summary

- Target-disease associations supported by **genetic evidence** are more likely to result in successful drugs
- Open Targets is an **industry-academia partnership**
- We create and apply **evidence** to build therapeutic hypotheses

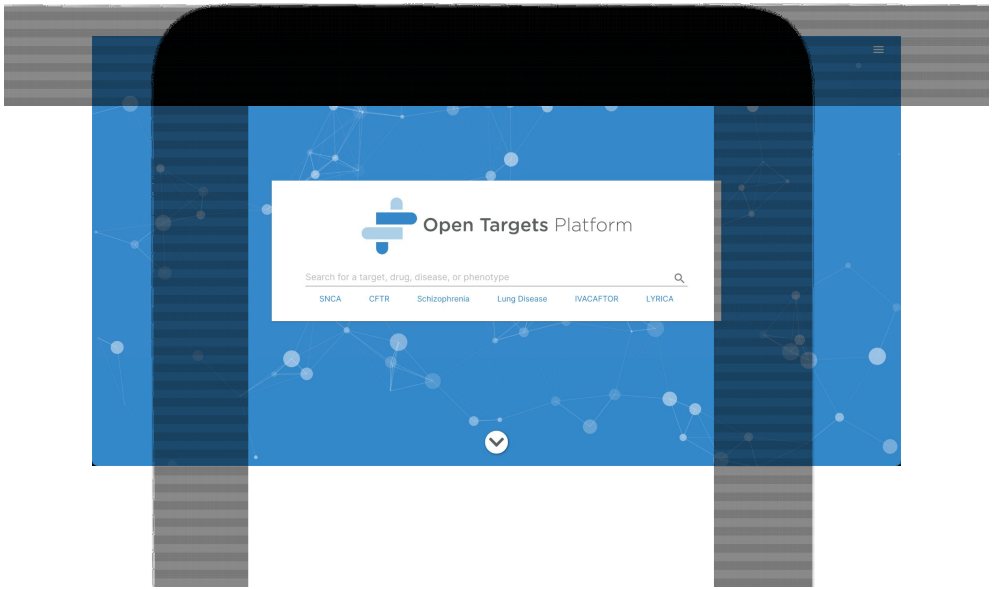
PART 2

Overview of the Open Targets Platform



platform.opentargets.org

- Data integration and analysis tool for systematic drug target identification and prioritisation
- Integrates 20+ data sources to build up and score evidence for **target- disease associations**

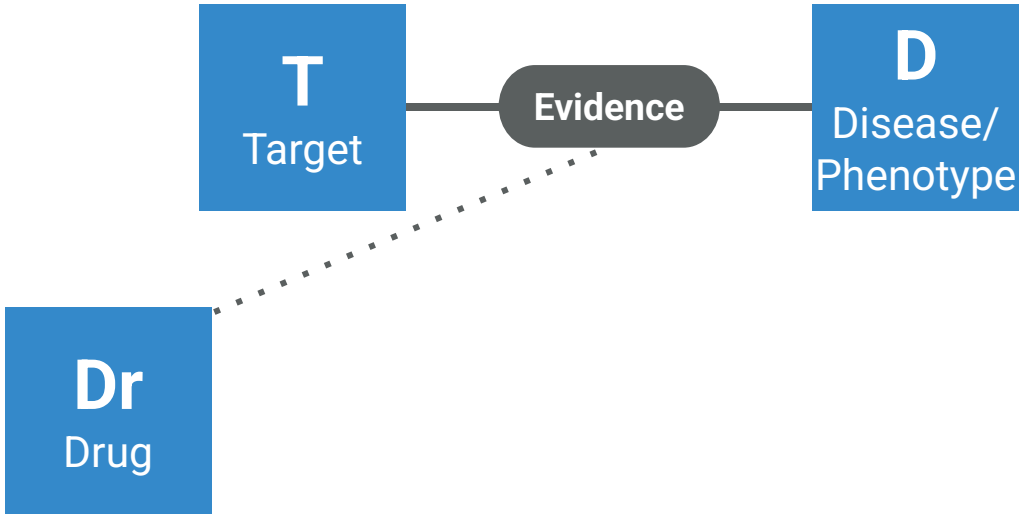


platform.opentargets.org

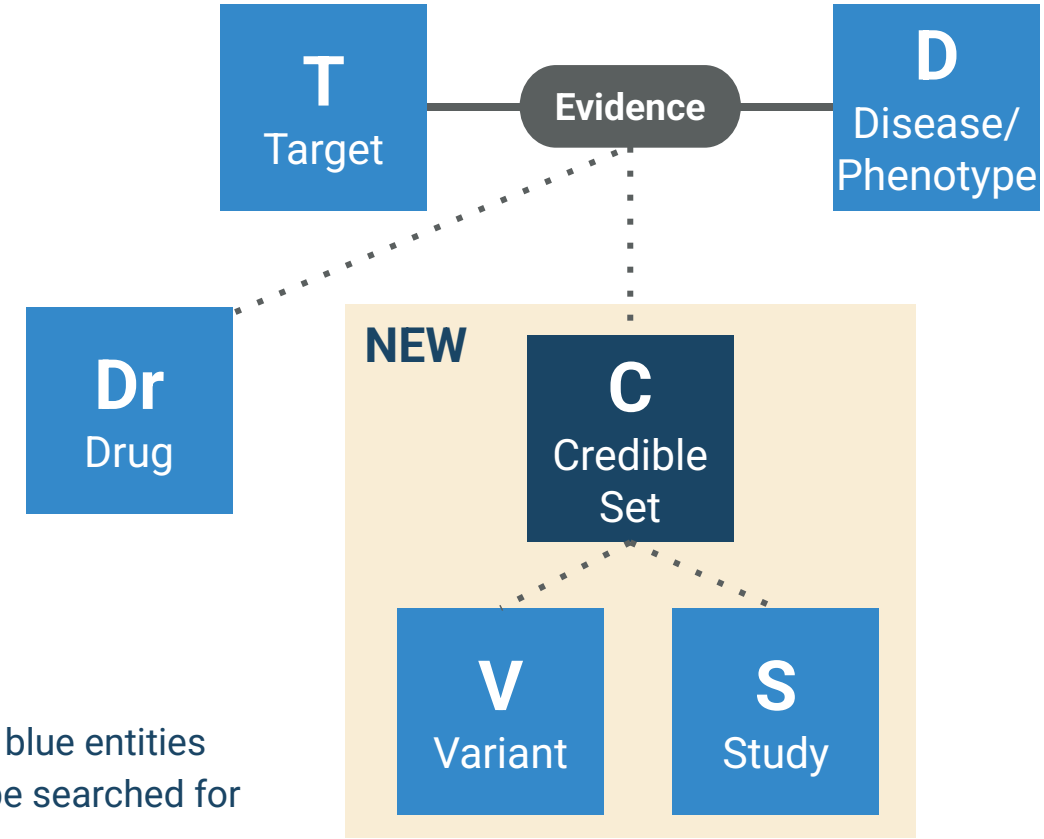
- Web interface supports search by:
  - Variant
  - Study
  - Target
  - Disease/phenotype
  - Drug
- Open source; data available via GraphQL API, Google BigQuery, or data downloads
- Quarterly updated

Our data model

Our data model

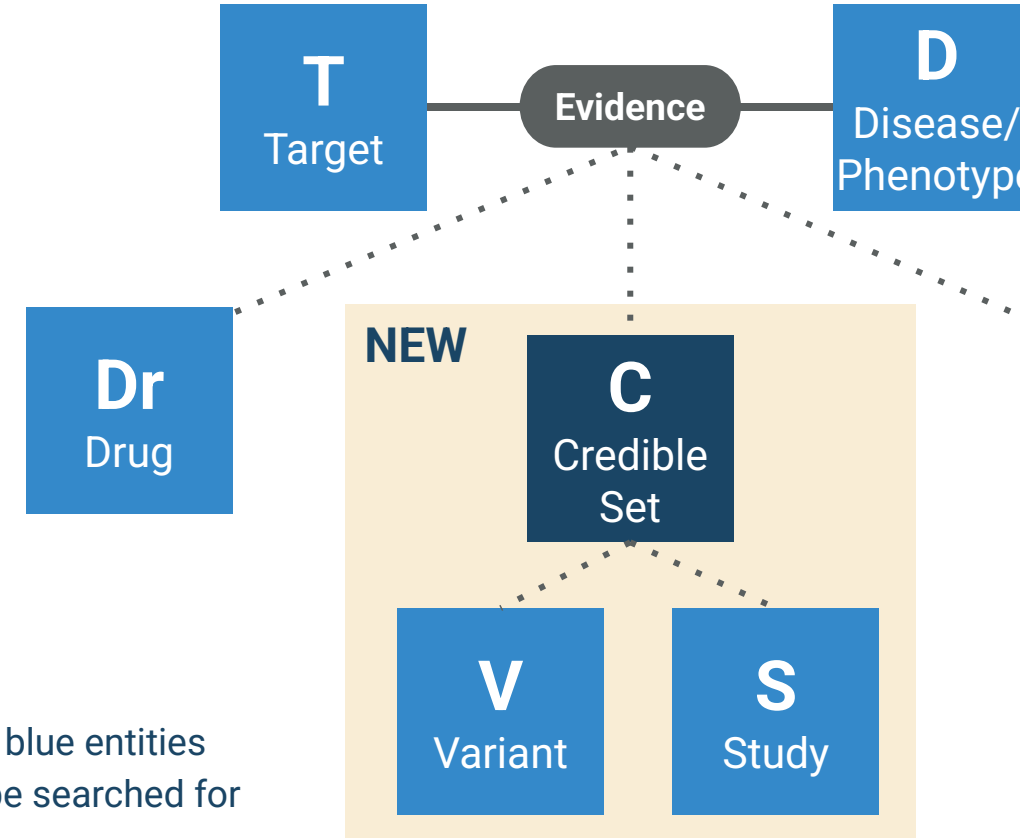


Our data model



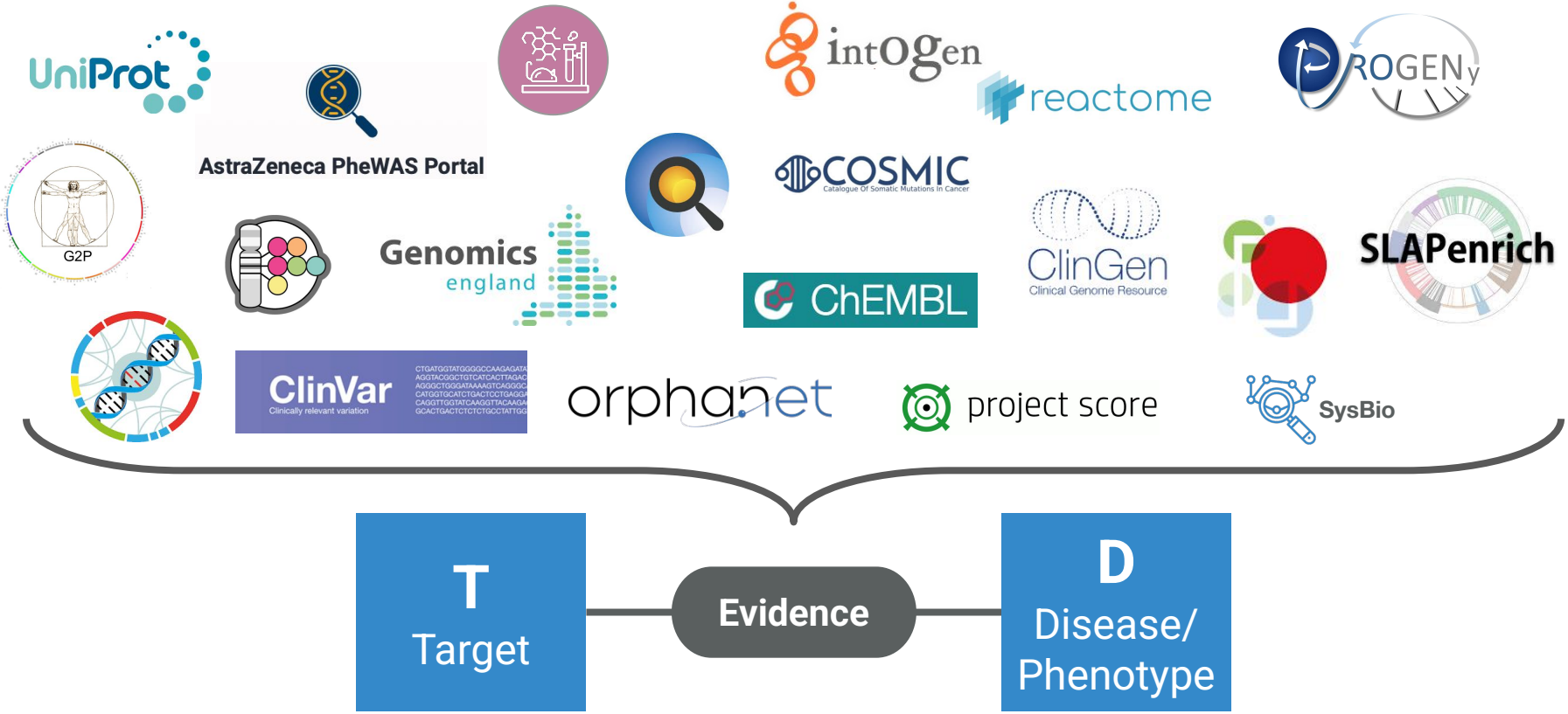
Light blue entities
can be searched for

Our data model



Other sources of evidence
(rare variation, somatic mutations, pathways, literature, animal models, …)

Light blue entities can be searched for

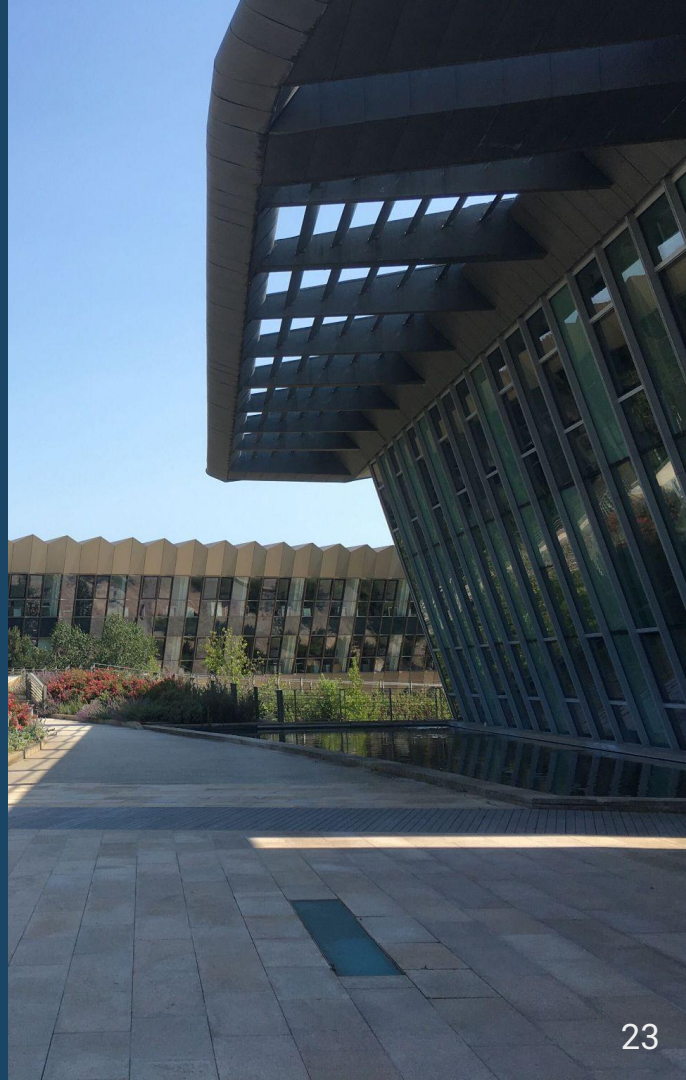

UniProt
AstraZeneca PheWAS Portal
intOgen
reactome
PROGENy
G2P
COSMIC
Catalogue Of Somatic Mutations In Cancer
Genomics england
ChEMBL
ClinGen
Clinical Genome Resource
SLAPenrich
ClinVar
Clinically relevant variation
orphanet
project score
SysBio
T
Target
Evidence
D
Disease/
Phenotype

Genetics updates in Open Targets Platform 25.03

- **Quality control and validation** of GWAS studies and credible sets
- New **ancestry-specific fine-mapping**
- Much **greater coverage** of GWAS, diseases and molQTLs. More than 4x more molQTLs and more than 3x more GWAS credible sets.
- All GWAS vs all GWAS and all GWAS vs all molQTLs colocalisation
- **Larger training set** for our Locus-to-Gene model (L2G), less biased towards nearest gene. **Improved L2G model performance** results by all measures.
- **Feature interpretation** of L2G using Shapley values

Open Targets Platform — Summary

- The Platform data model is built on six entities: **targets, diseases, drugs, variants, studies,** and **credible sets**
- The Platform integrates data to:
  - support associations between targets and diseases
  - provide annotation information for the six entities
  - analyse evidence from common disease genetics



PART 3

Case Studies

KRAS: the “undruggable” target

Challenges:

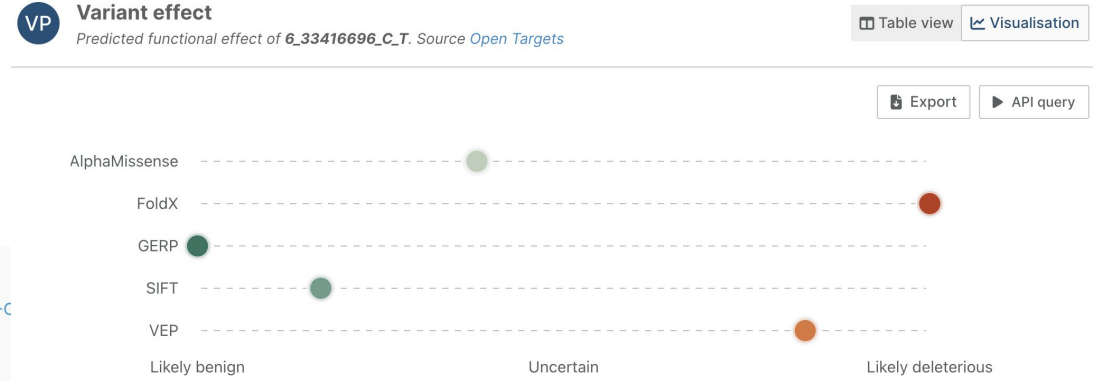
- Lack of allosteric binding sites
- Intracellular location requiring membrane penetration
- Extremely high affinity for GTP/GDP

Clinical validation:

- Selective small molecule binding thanks to a binding pocket adjacent to the G12C mutation
- Structure-based drug design accelerated development

Hypertension: what does evidence suggest?

6_33416696_C_T: from variant to credible set



6_33416696_C_T

Ensembl: rs41267649 | ProtVar: 6_33416696_C_T | gnomAD: 6-33416696-C

Profile

Description
Missense variant overlapping with CUTA, causing amio-acid change: R165H with moderate impact.

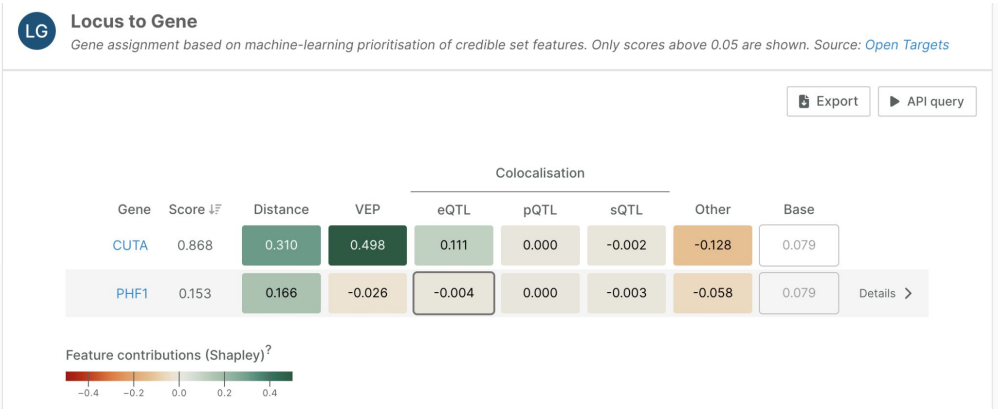
Location
GRCh38: 6:33416696
Reference allele: C
Alternative allele (effect allele): T

Variant Effect Predictor (VEP)
Most severe consequence: missense variant

Population Allele Frequencies *Source: gnomAD*

African/African-American	0.00312
American Admixed/Latino	0.00202
Amish	0.00110
Ashkenazi Jewish	0.00054
East Asian	0
Finnish	0.03537
Middle Eastern	0.00017
Non-Finnish European	0.02568
South Asian	0.00022
Other	0.01759

6_33416696_C_T: from variant to credible set



Credible set

Lead variant: 6_33416696_C_T | Study ID: GCST90132222

Profile

Lead Variant

P-value: 1.266×10^{-62}

Beta[?]: 0.0271

Posterior probability[?]: 1.00

Fine-mapping

Locus: 6:33409447-34909447

Method: SuSiE-inf

Confidence[?]: ★★★☆

Minimum R^{2}[?]: 1.00

QC warnings

GWAS Study

Reported trait: Rheumatoid arthritis

Disease or phenotype: rheumatoid arthritis

Publication: Ishigaki K *et al.* Nat Genet (2022)

PubMed: 36333501

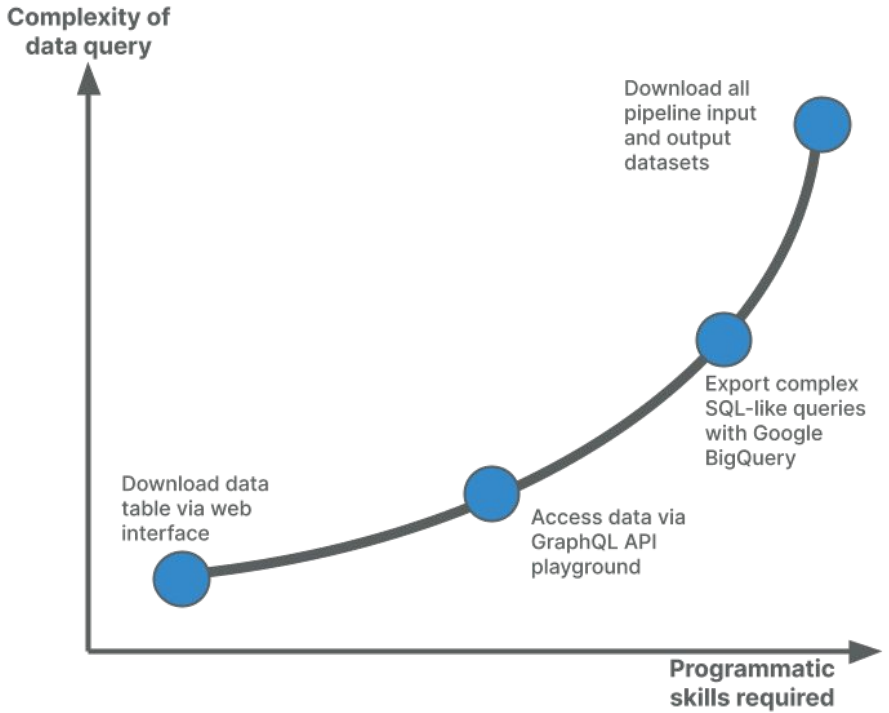
Summary statistics: **Available**

Sample size: 276,020 (cohorts: CLEAR, BBJ, IORRA, EIRA, NARAC, NHS, Vanderbilt, WTCCC, other)[?]

EAS 64% | NFE 35% | AFR 1%

Questions?

Ways to access our data



- Web interface
- API (GraphQL)
- Google BigQuery, Microsoft Azure (public datasets)
- Data downloads

platform-docs.opentargets.org/data-access

Thank you!

Social media

@OpenTargets

Open Targets

Key links

platform.opentargets.org

blog.opentargets.org

community.opentargets.org

platform-docs.opentargets.org