Open Targets: A public-private partnership to enable systematic drug target identification and prioritisation

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Selecting the target is a key decision when making medicines...and it costs over $1bn and more than a decade to find out if you chose well.
However, Drug development rarely succeeds…

A partnership to transform drug discovery through the systematic identification and prioritisation of targets
Based on the Wellcome Genome Campus

- The Campus - one of the world’s largest genomic research centres (home to over 2000 genomic scientists; hosts of major international conferences; situated within one of the world’s top innovation districts (Cambridge, UK)

- Location enables close collaboration and leverages existing campus expertise and synergies - integrating scientists specialising in genomics, drug discovery and bioinformatics in one centre to focus on major challenges in target validation.
Our Goals

1. Systematically find the best targets for safe & effective medicines
2. Help others find good targets
3. Get those targets adopted into drug discovery pipelines

Our Methods

- High throughput human genetics
- Advanced data analysis
- Open source software, rapid data release, open publication
- Make target decisions together
Target Validation Knowledge Cycle

- Data Generation
- Public Data
- Data Integration
- Therapeutic Hypothesis

Experimental Projects

Bioinformatic Projects

targetvalidation.org

Open Targets
Our Principles

- We are focused on pre-competitive research that will enable the systematic identification and prioritisation of targets
- We are committed to rapid publication and making data, methods and results publically available as soon as possible
- We believe in non-exclusive partnerships that foster the free exchange of ideas and expertise

We welcome partnership with organisations with similar philosophies and scientific interests

Contact us

Contact@OpenTargets.org

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Experimental Programme
Experimental Projects

- Oncology
- Neurodegeneration
- Human Cellular experiments
- Genetics as a tool
- Enabling resources
- Immunology

- Target information is the key outcome
- Genome-scale where possible
- Physiological relevance to disease
Industrial Scale Data Production

Capacity for 150 - 200 genome-wide CRISPR screens per year

3 – 12 x 5-layer flasks per replicate
Immunology Integration for Target ID

- NK cell receptors
- Macrophages & Dendritic cells
- Cytoimmunogenomics
  - Genetics
  - Cell Models
  - Cell Profiling

Additional labels:
- IBD GWAS
- IBD Organoids
- Keratinocytes
- TargetID Asthma Bronchiectasis

Keywords:
- Keratinocytes
- Macrophages
- Dendritic cells
- IBD GWAS
- IBD Organoids
- TargetID Asthma Bronchiectasis
Oncology Integration for Target ID

1000 Cancer Cell Lines

RNA-seq for gene fusions

Mutations
Amplifications & deletions
Promoter methylation
Drug sensitivity

TF Networks

1000 Cancer Cell Lines

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Oncology targets & in silico drug prescriptions

Genetics of clinical trial samples

Screen for T cell immune oncology modifiers

Open Targets
Neurodegeneration & Neurodevelopment Integration for Target ID

GWAS

Introduce mutations by CRISPR-Cas9

Familial PD
LOAD
PSEN, APP
Developmental mutations

iPSCs

Neural Progenitors

Bulk & sc RNA-seq, ATAC, eQTLs, caQTLs (AD)

Neurons (AD)
Dopaminergic (PD)
Neurons/microglia
Glut/Gaba/microglia
Enteric Neurons iNeurons

Stress Response (orthogonal assays)

Oxidative Stress (PD)

Tau uptake (AD)

RNA-seq, ATAC, 4C

Chromatin modifier drugs & CRISPR

Open Targets
Informatics Programme
Informatics Ecosystem

Informatics strategically important for Open Targets.

To maximise alignment and impact proposing consolidation to form a connected programme of projects.

Supporting an ecosystem of Open Targets products.
Informatics Projects

Open Targets Platform: What do the users want?

• Easy access to all relevant evidence for associations between potential drug targets and disease
  – i.e. get relevant data in one place.

• Capabilities for the user to identify and prioritise targets
  – i.e. scores and lists

• Requires
  – modelling of complex research approaches,
  – an intuitive interface that allows the right tasks to be accomplished,
  – timely, relevant and integrated content (data),
  – sustainable infrastructure.
Using a User Experience Approach
Facilitating decision-making

A) Which targets are associated with a disease?

B) What evidence supports this target-disease association?

C) Are there drugs for this association in clinical trials?

D) For a given target, are there other diseases associated with it?

E) Can I find the association focusing on two (or more) different therapeutic areas?

F) What else can I find out about my drug target?

G) What else can I find out about my disease?

H) Can I look at multiple targets at a time?
Technologies

- Cloud based development and production installations
- Open Source software repositories e.g. https://github.com/opentargets/rest_api
- Use Elastic Search, Python, Docker, AngularJS, D3, etc.
- Working towards continuous integration and deployment systems
Which targets are associated with breast carcinoma?

- Filter by evidence type: e.g. 237 targets are supported by somatic mutations
- Filter by pathway type and particular pathways
- Order by evidence type and evidence strength
Target Profile Page

PDE4D
phosphodiesterase 4D | View associated diseases

Hydrolyzes the second messenger cAMP, which is a key regulator of many important physiological processes.

(information provided by UniProt)

Synonyms: DPDE3, PDE43, 3.1.4.53, phosphodiesterase E3 dunce homolog (Drosophila), CAMP specific 3,5-cyclic phosphodiesterase 4D

Drugs
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
Open targets: a platform for therapeutic target identification and validation, NAR Database 2017, Pages D985–D994

ABSTRACT

We have designed and developed a data integration and visualization platform that provides evidence about the association of known and potential drug targets with diseases. The platform is designed to support identification and prioritization of biological targets for follow-up. Each drug target is linked to a disease using integrated genome-wide data from a broad range of data sources. The platform provides either a target-centric workflow to identify diseases that are associated with a specific target, or a disease-centric workflow to identify targets that may be associated with a specific disease. Users can easily transition between these target- and disease-centric workflows. The Open Targets Validation Platform is accessible at https://www.targetvalidation.org.

INTRODUCTION

The fundamental tenet of pharmacology is that a drug (small molecule or biological) can be identified that specifically interacts with a target molecule (usually a protein) to modulate a physiological process and thus alter the course of a disease (1,2). The pharmaceutical industry has developed powerful approaches to discover and optimize drug molecules that affect the function of a target. There are also complex strategies in practice to deal with drug efficacy, drug-drug safety issues that accompany getting a drug into humans and finally to market. However, analysis of progress through development pipelines has highlighted that lack of efficacy is a major cause of failure, particularly in the later, more expensive, clinical stages (3,4). The implications of this...
Help and documentation

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https://www.targetvalidation.org/about

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