

Open Targets: Identifying Drug Targets in a Pre- competitive Framework

Ian Dunham

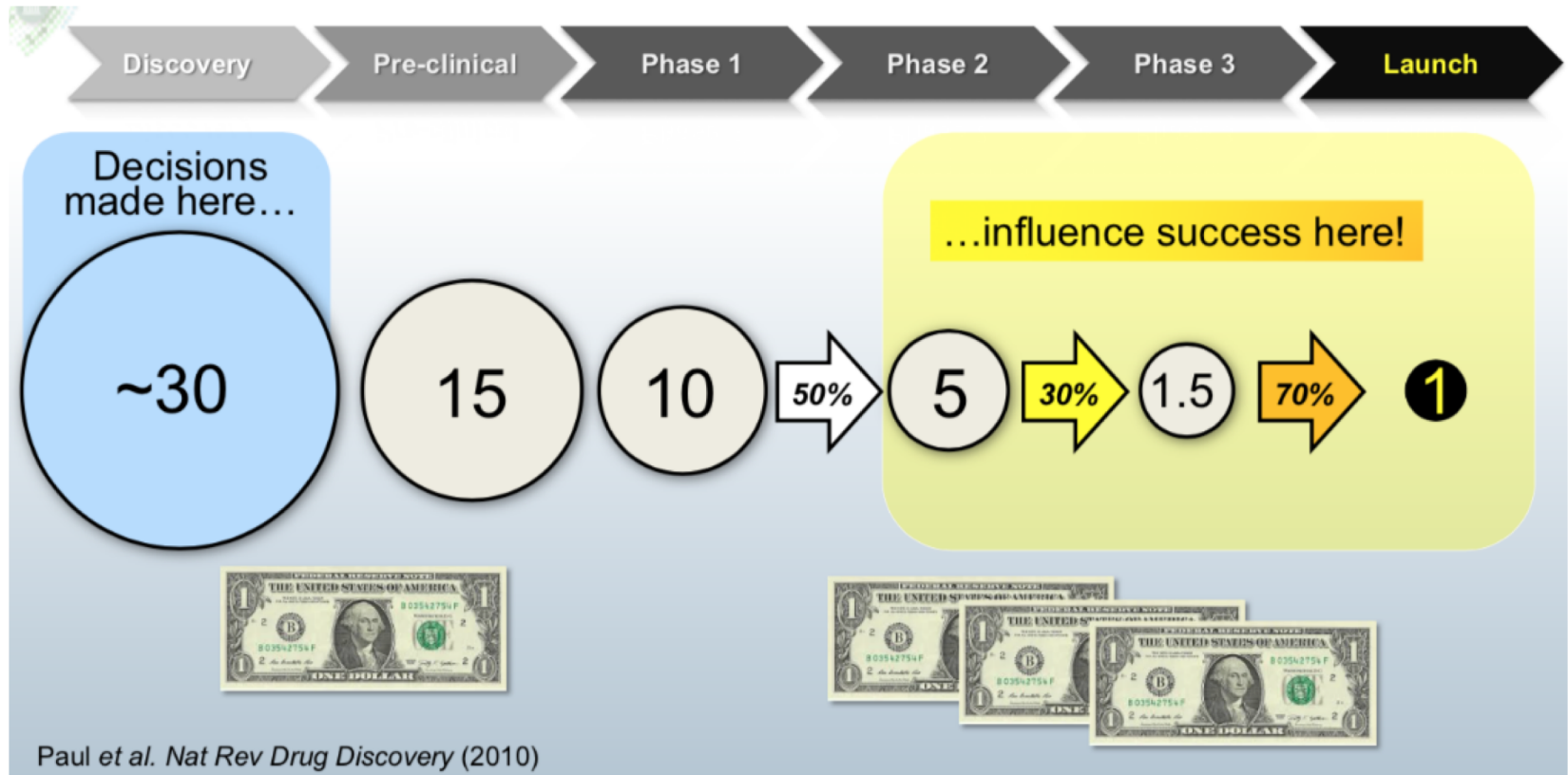
Director, Open Targets

www.opentargets.org



Open Targets

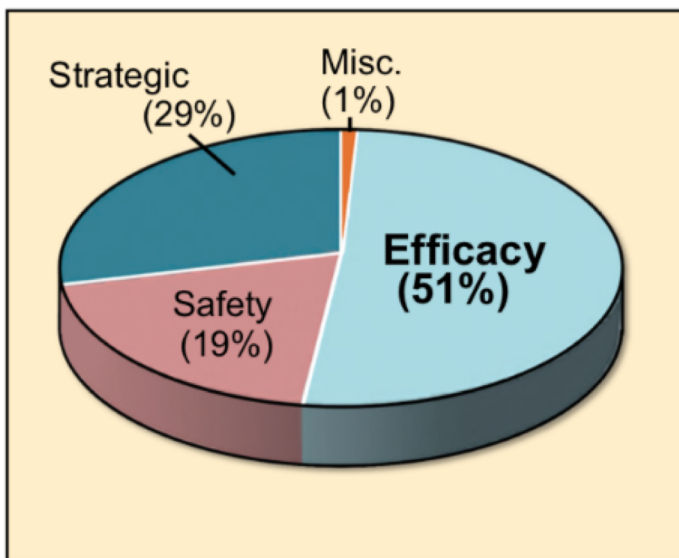
Drug Discovery has High Attrition and Long Lead Times



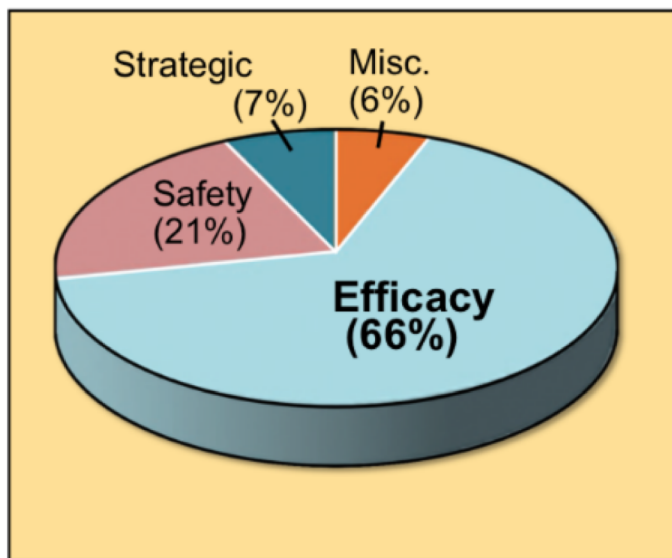
Credit: Robert Plenge, Celgene

Most Clinical Trial Failures are due to Lack of Efficacy

**Phase II failures
(2008-2010)**

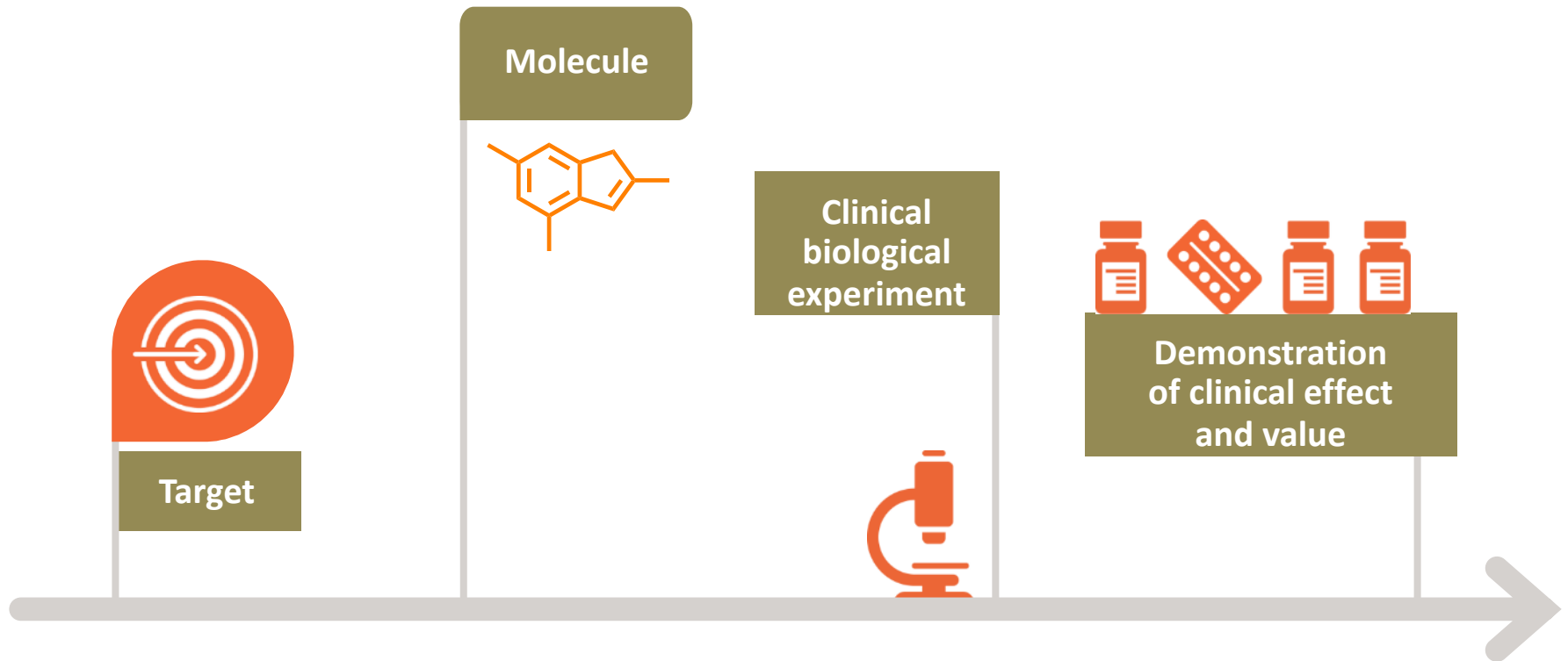


**Phase III failures
(2007-2010)**



Arrowsmith Nature Reviews Drug Discovery (2011)

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.



Open Targets

Transforming drug discovery through the systematic identification and prioritisation of targets



Open Targets

Pioneering Public Private Partnership



Unique location: Cambridge Cluster & Wellcome Genome Campus, UK

Europe's leading cluster in
pharma and biotech



Genomics
England

BioData
Innovation
Centre
(Incubator)

Wellcome Sanger Institute
World leading in human
functional genomics

European Bioinformatics
Institute (EMBL-EBI)
World leading in biomedical data
provision and computational biology

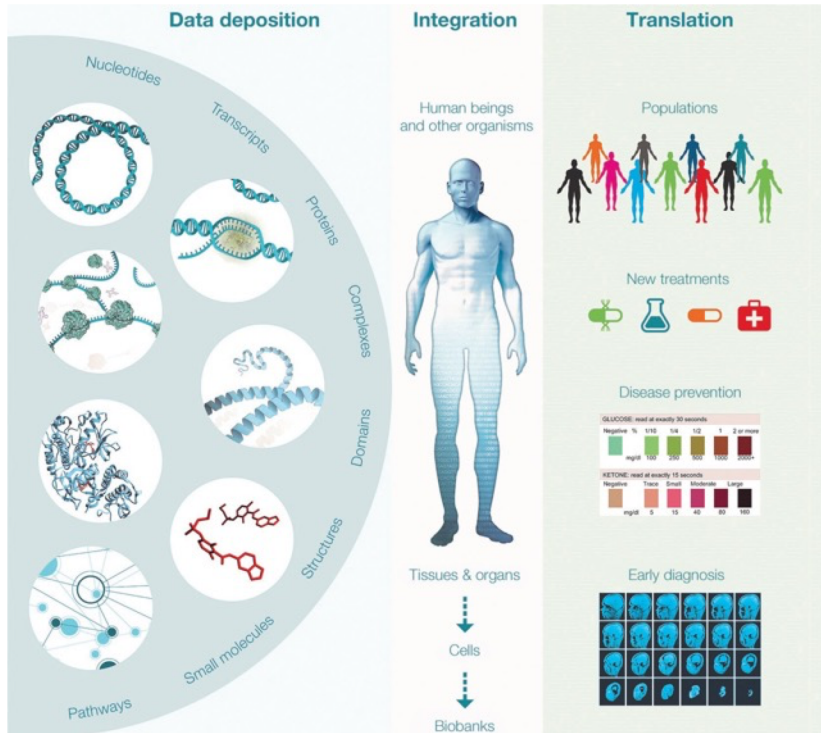
The Wellcome Sanger Institute



- Human Genetics
- Cancer, Ageing & Somatic Mutation
- Pathogens & Microbes
- Cellular Genetics
- Tree of Life



Open Targets



Credit: Spencer Phillips, EMBL-EBI

The home for big data in biology

A trusted data provider for the life sciences

Contributes to the advancement of biology through investigator-driven research

Part of the European Molecular Biology Laboratory, an intergovernmental research organisation

International: 650 members of staff from 66 nations

Open Targets Vision and Mission

Improve success rates and be the world-leading centre for human target identification and prioritisation

Identify, pinpoint, understand the processes in the human body that have a demonstrable effect on disease

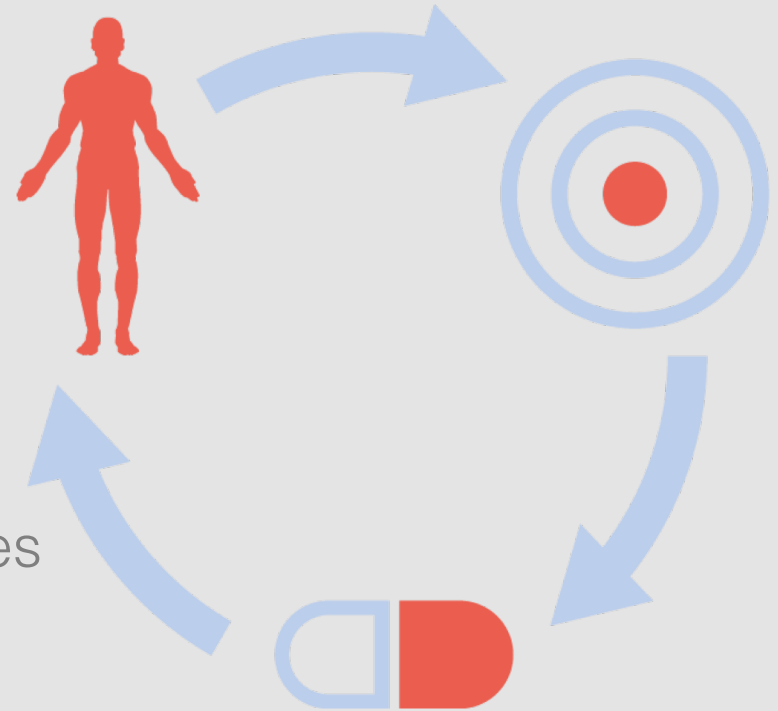
Combine ground-breaking experimental and computational approaches



Credit: Spencer Phillips, EMBL-EBI

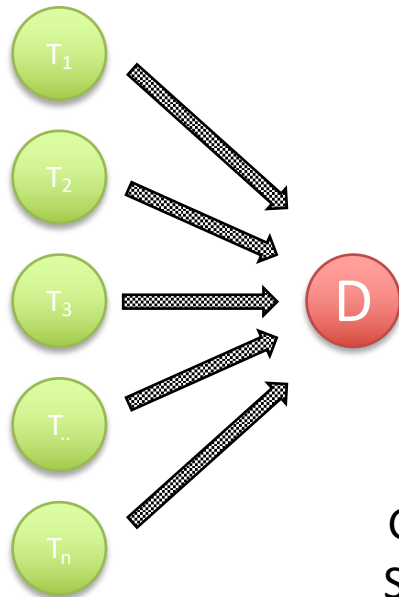
Open Targets Key Technologies

- WSI cell line collections
- Gene editing (CRISPR)
- iPS cell differentiation and phenotyping
- Single cell methods
- Organoid and tissue culture
- Large scale genomics and epigenomics
- Genome wide association studies
- Next-generation sequencing
- Bioinformatics
- High performance computing



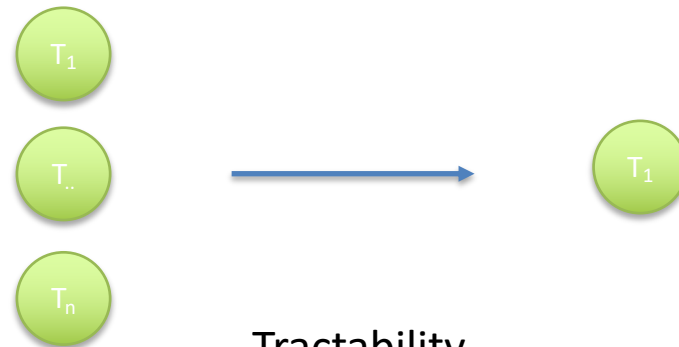
Systematic Identification and Prioritisation

Identification



Data Integration
GWAS & Genetics
Synthetic genetics

Prioritisation



Tractability
Safety
Expression
Biomarkers

How We Build Projects: Smart Project Sourcing

Collect
Ideas

Connect
Minds

Commit
Projects



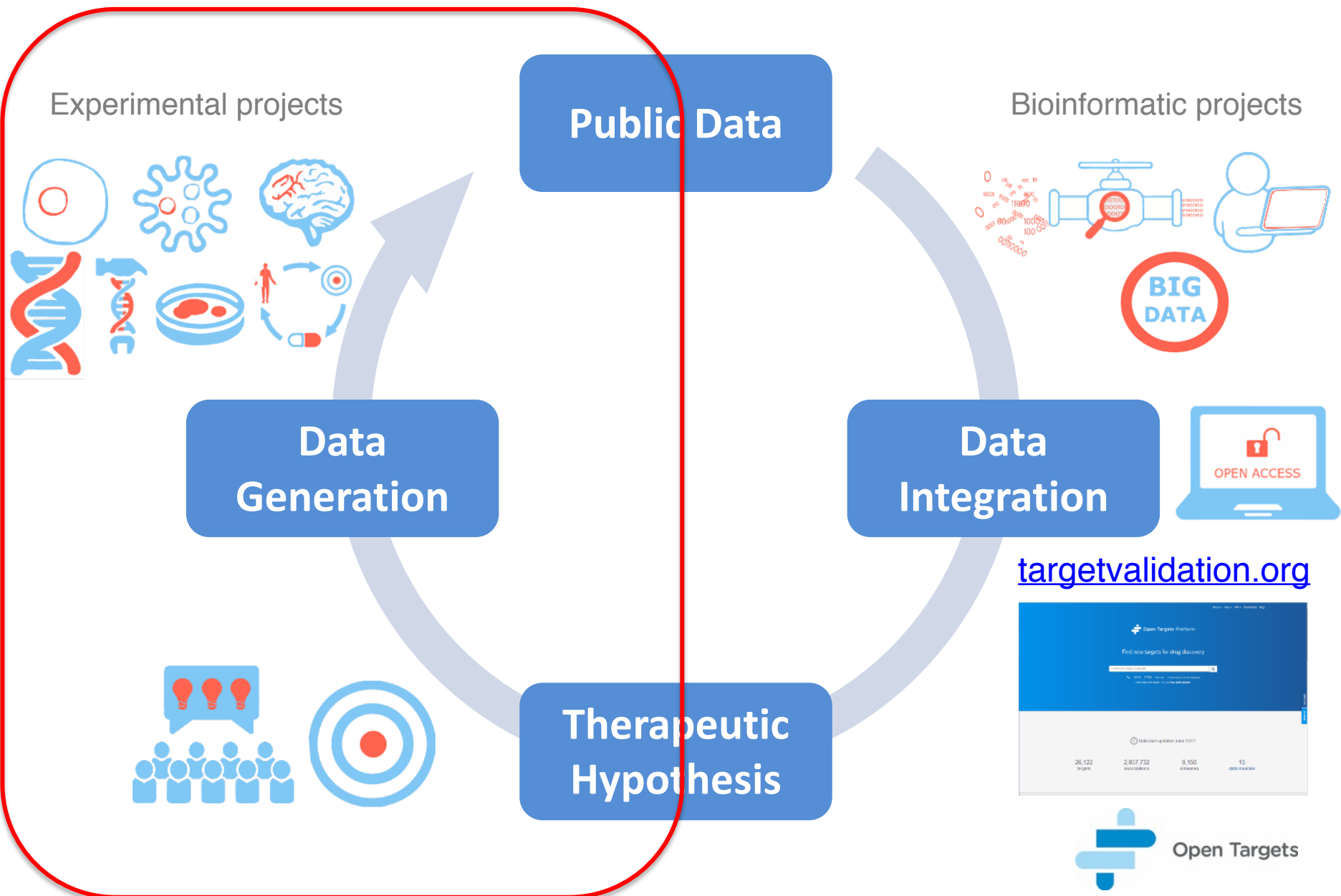
50+

Calls for proposals
Expressions of interest

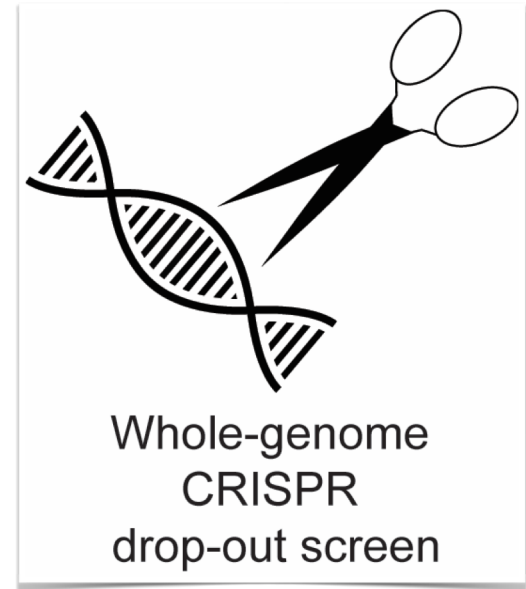
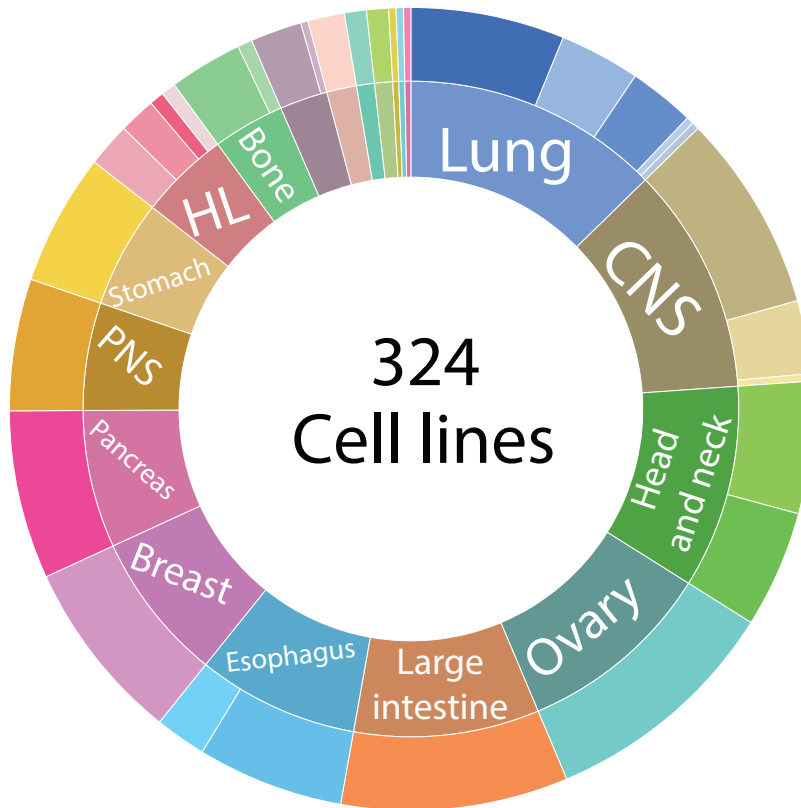
Workshops
Proposals

Review and feedback
Governance Board Approval

Efficacy Data through Cellular Models

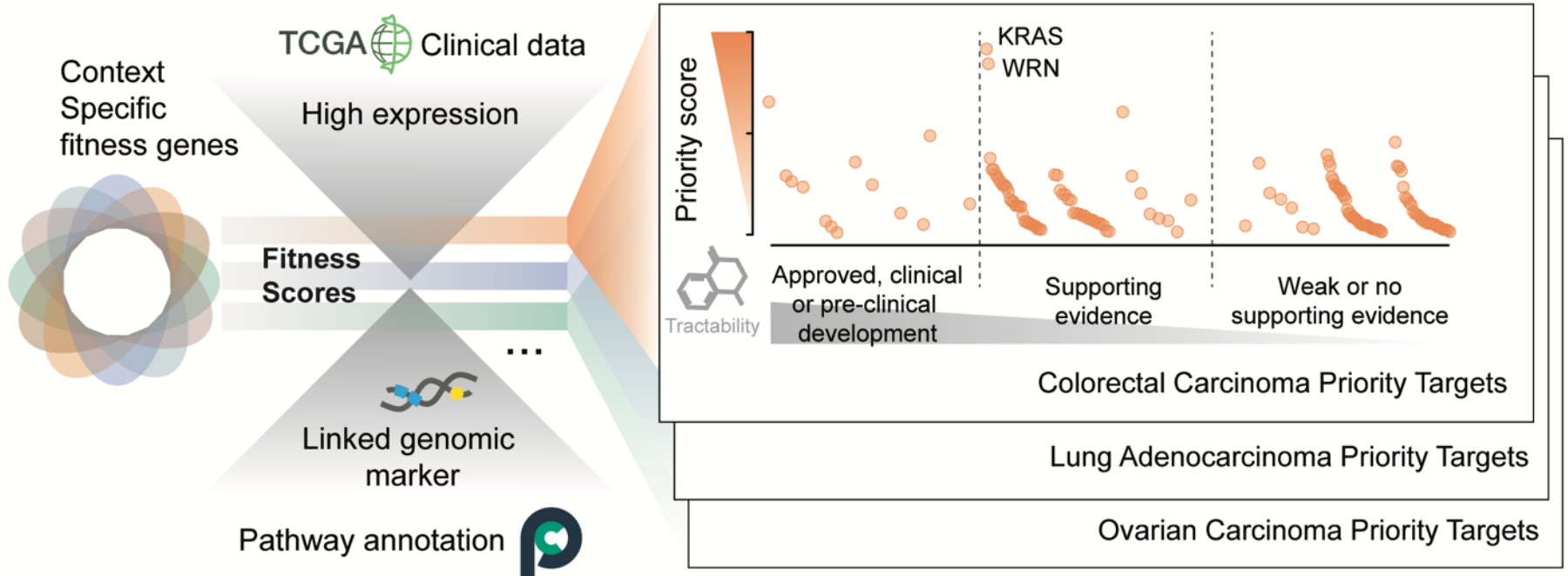


project score



Behan et al Nature **568**, 511–516 (2019)

Target Prioritisation & Tractability Assessment



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2019-04-13 15:57:57

genomeweb

Start your journey to become a genome engineer.

Using CRISPR to identify a new cancer drug target

Apr 10, 2019 1:00pm

BBC NEWS

Home UK World Business Politics Tech Science Health Family & Education

Printed on April 10, 2019

NEWS MEDICAL LIFE SCIENCES

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Hundreds of new anti-cancer drug targets identified

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By Kate [Profile]

Review

ENGLMED Health News

Worldwide health and medical news - Provider of tailored news services

已经WRN确定为针对MSI肿瘤的有

ENGLMED Health News

Cancer's genetic vulnerabilities revealed

Thursday April 11th, 2019

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FierceBiotech

BIOTECH RESEARCH CRO MEDTECH

Scientists use editing tool to identify low vulnerability cancer drug targets

Apr 10, 2019 1:00pm

BBC NEWS

Home UK World Business Politics Tech Science Health Family & Education

ARTICLE

'Dismantling cancer' reveals weak spots

By James Gallagher
Health and science correspondent, BBC News

10 April 2019 1:20

Functional genomics approaches can overcome limitations – such as the lack of identification of robust targets and poor clinical efficacy – that hamper cancer drug development. Here we performed genome-scale CRISPR-Cas9 screens in 324 human cancer cell lines from 30 cancer types and developed a data-driven framework to prioritize candidates for cancer therapeutics. We integrated cell fitness effects with genomic biomarkers and target tractability for drug development to systematically prioritize new targets in defined tissues and genotypes. We verified one of our most promising dependencies, the Wnt3n syndrome ATP-dependent helicase, as a synthetic lethal target in tumours from multiple cancer types with microsatellite instability. Our analysis provides a resource of cancer dependencies, generates a framework to prioritize cancer drug targets and suggests specific new targets. The principles described in this study can inform the initial stages of drug development by contributing to a new, diverse and more effective portfolio of cancer drug targets.

重磅! CRISPR助力发现抗癌药物新靶点! WRN

来自雪球 发布于04-12 07:36

ENGLMED Health News

Worldwide health and medical news - Provider of tailored news services

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nature

NEWS AND VIEWS 10 APRIL 2019

Lethal clues to cancer-cell vulnerability

Cancer cells often have mutations in anticancer genes that make their survival dependent on other genes. The gene-editing approach CRISPR-Cas9 offers a way to identify such vulnerabilities.

Philipp Faust & Luke A. Gilbert

ARTICLE

Prioritization of cancer therapeutic targets using CRISPR-Cas9 screens

Fiona M. Behan^{1,2,3,4}, Francesco Iorio^{1,2,3,4,5}, Gabriele Piccinini^{1,2,3,4}, Emmanuel Gougeon^{1,2,3,4}, Charlotte M. Bowler^{1,2,3,4}, Giorgia Migliorini^{1,2,3,4}, Ilina Romashina^{1,2,3,4}, Francesco Scalet^{1,2,3,4}, Martina Pavesi^{1,2,3,4}, Giovanni A. M. S. Lima^{1,2,3,4}, Sarah Harper^{1,2,3,4}, David Adam Jackson^{1,2,3,4}, Rebecca McLean^{1,2,3,4}, Rachel Peckley^{1,2,3,4}, Peter W. Hitchcock^{1,2,3,4}, Dorothea von der Muehl^{1,2,3,4}, Carol Dow^{1,2,3,4}, Carolyn Isaac^{1,2,3,4}, Douglas G. Klapper^{1,2,3,4}, Andrea Iorio^{1,2,3,4}, Ulrike Traub^{1,2,3,4}, Diana A. Sommerich^{1,2,3,4}, Julie Szae^{1,2,3,4}, Rodrigo Lopez^{1,2,3,4}, Susana Yano^{1,2,3,4} & Matthew J. Goss^{1,2,3,4}

Functional genomics approaches can overcome limitations – such as the lack of identification of robust targets and poor clinical efficacy – that hamper cancer drug development. Here we performed genome-scale CRISPR-Cas9 screens in 324 human cancer cell lines from 30 cancer types and developed a data-driven framework to prioritize candidates for cancer therapeutics. We integrated cell fitness effects with genomic biomarkers and target tractability for drug development to systematically prioritize new targets in defined tissues and genotypes. We verified one of our most promising dependencies, the Wnt3n syndrome ATP-dependent helicase, as a synthetic lethal target in tumours from multiple cancer types with microsatellite instability. Our analysis provides a resource of cancer dependencies, generates a framework to prioritize cancer drug targets and suggests specific new targets. The principles described in this study can inform the initial stages of drug development by contributing to a new, diverse and more effective portfolio of cancer drug targets.

ists use DNA-editing tool CRISPR to catalogue c

关注

New cancer drug targets accelerate path to precision medicine

APRIL 10, 2019

By Melissa Tsou/Sanger Institute

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7 May

BUSINESSWEEKLY

A WORLDWIDE WINDOW TO CAMBRIDGE BUSINESS, INNOVATION & TECHNOLOGY

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HOME NEWS ACADEMY & RESEARCH CAMBRIDGE-LED STUDY CLEARS WAY TO PRECISION CANCER MEDICINES

The space to invent.

10 April, 2019 - 19:04 By Tony Quested

Cambridge-led study clears way to precision cancer medicines

Sanger Institute - Making a difference: Fiona Behan, cancer researcher

0:39 / 0:51

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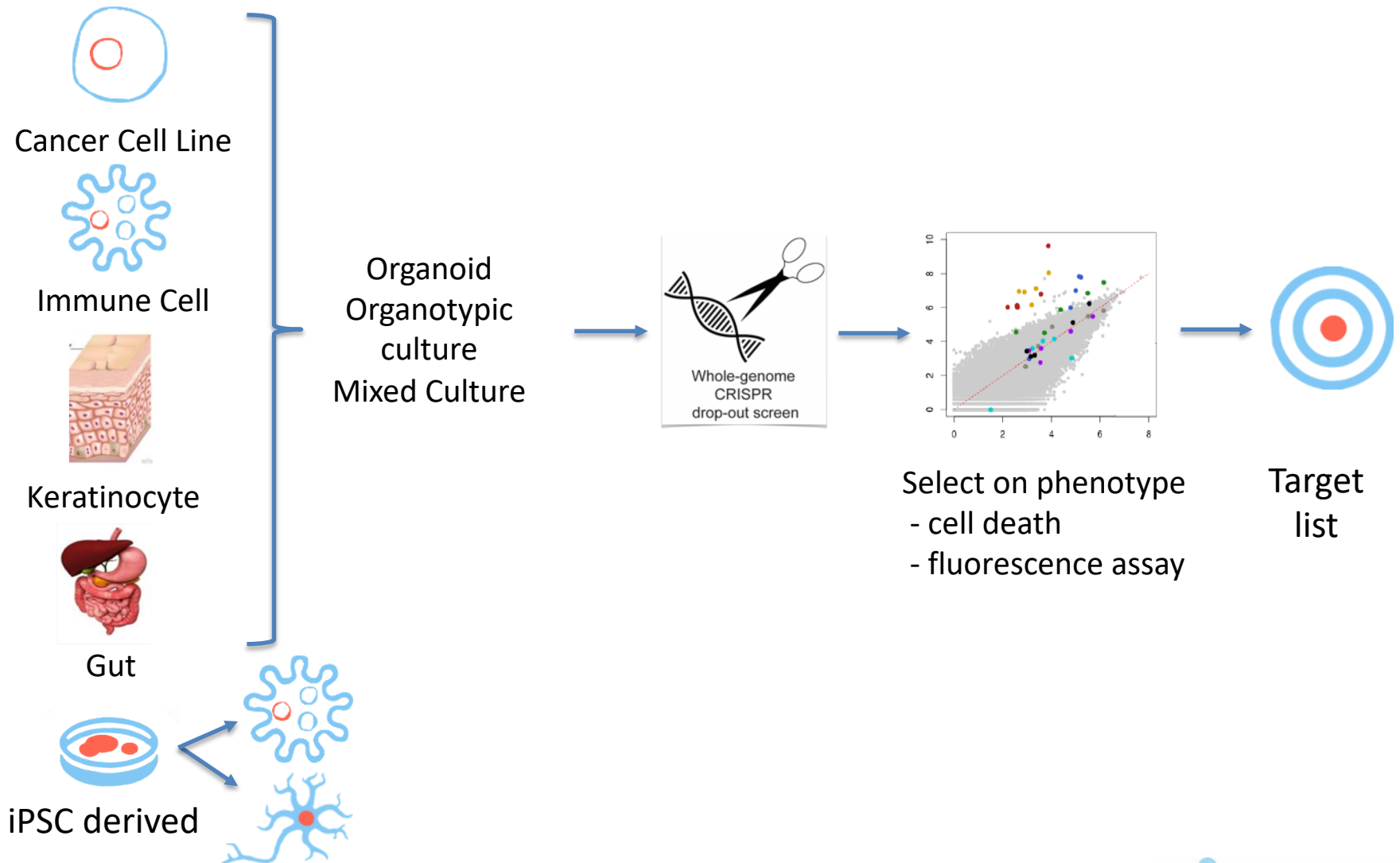
WATCH: Mother's cancer diagnosis inspired Kildare woman Dr Fiona Behan's groundbreaking research

TEAM LED BY CASTLEDERMOT'S DR FIONA BEHAN CONDUCTING CUTTING-EDGE RESEARCH IN CANCER GENETICS

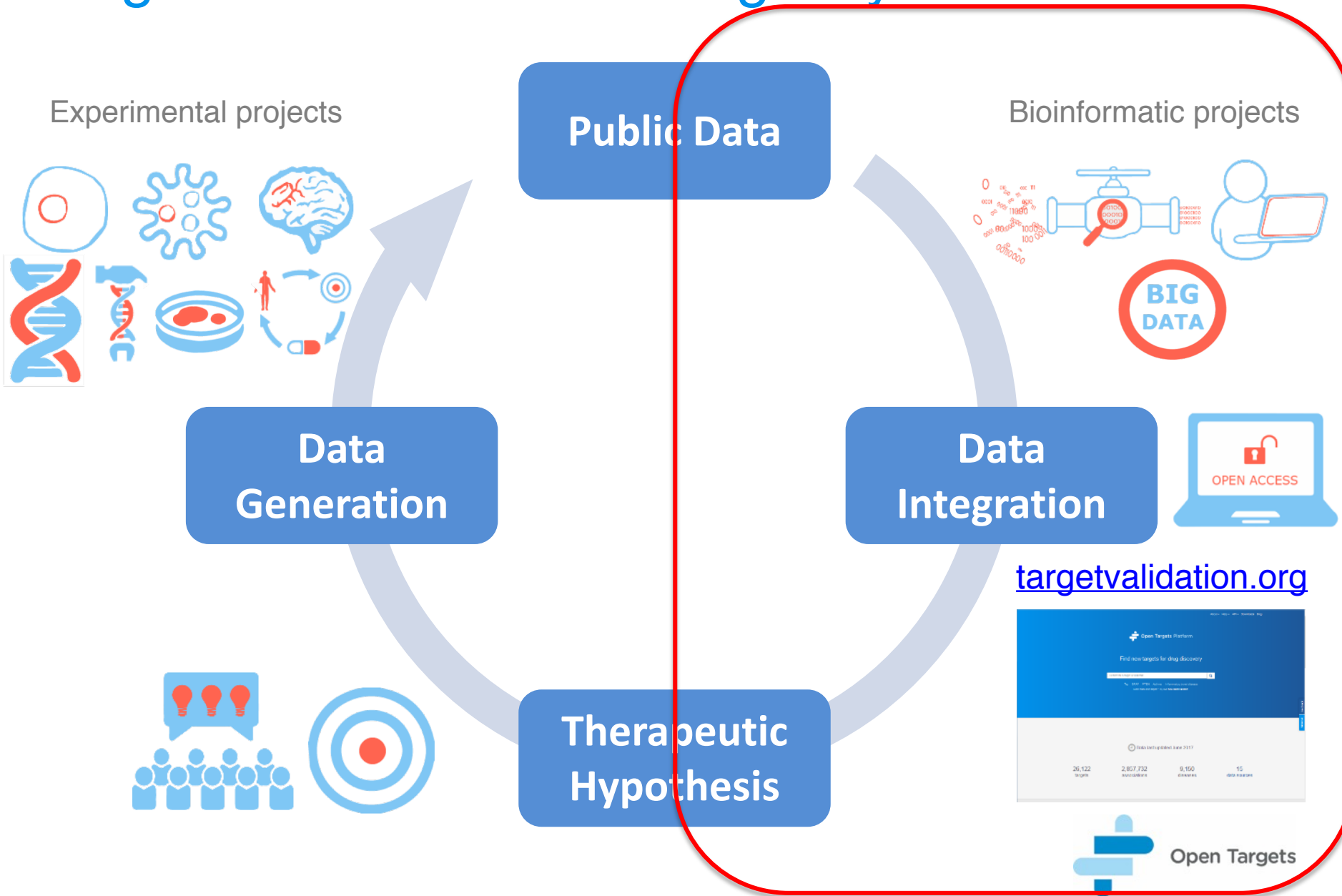
By Laura Coates 23 Apr 2019

Open Targets

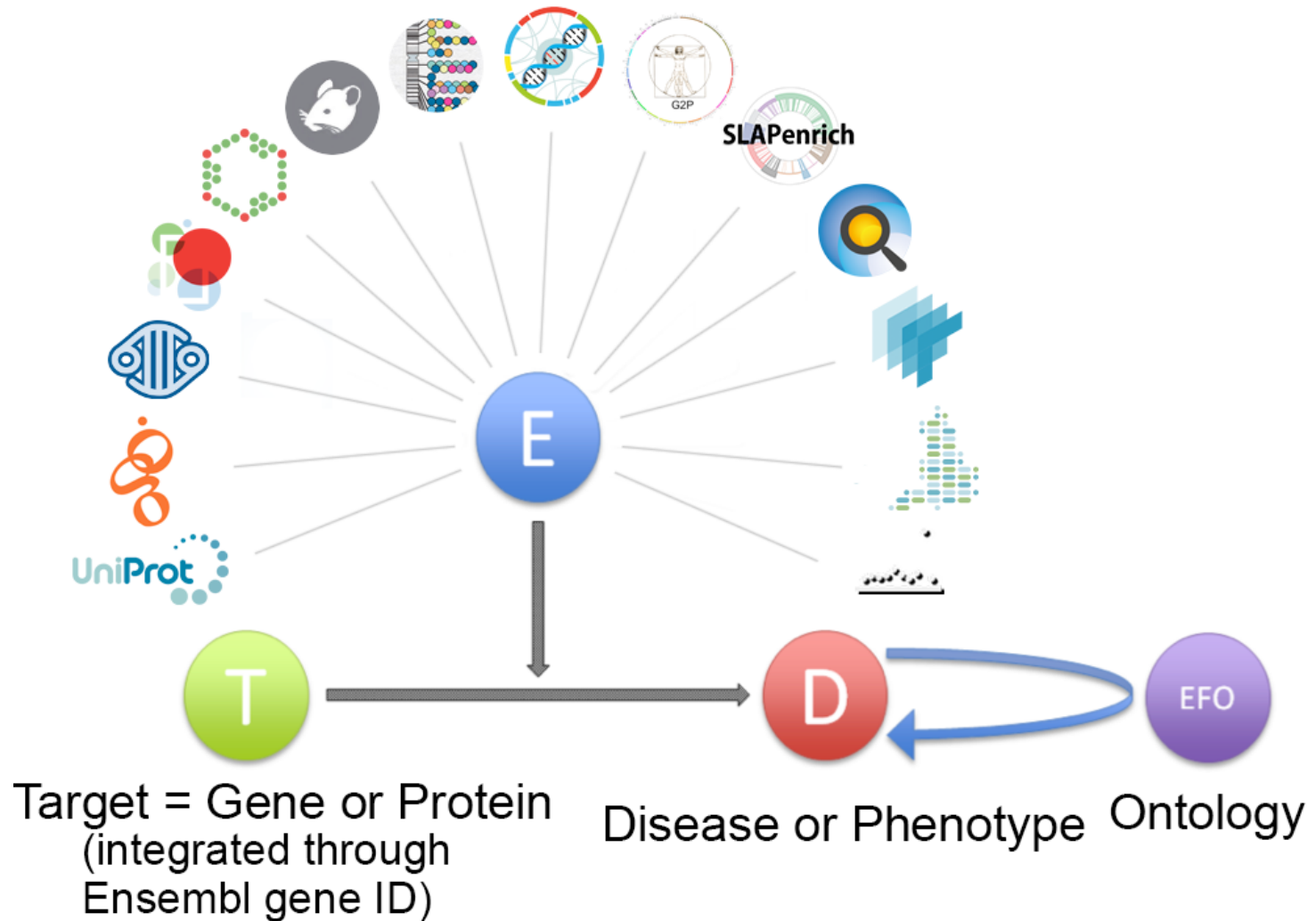
CRISPR Modulation to Identify Targets



Target Validation Knowledge Cycle



Data Integration for Target ID and Prioritisation



Informatic Products: The Open Targets Platform

Open Targets Platform

Find new targets for drug discovery

Search for a target or disease

Try: IL2RA ADORA3 Multiple sclerosis Dementia

More than one target? Try our [batch search](#)

Data last updated February 2019

28,426 targets	3,147,934 associations	10,183 diseases	19 data sources
-------------------	---------------------------	--------------------	--------------------

targetvalidation.org

Nucleic Acids Research, **2017**, 45, D985–D994

Nucleic Acids Research, **2019**, 47, D1056–D1065

Which targets are associated with breast carcinoma?

10545 targets associated with breast carcinoma

[View disease profile](#)

Filter by

Data type

Clear all ✕ Select all ✓

- Genetic associations (790)
- Somatic mutations (750)
- Drugs (462)
- Affected pathways (4k)
- RNA expression (5k)
- Text mining (7k)
- Animal models (0)

Pathway types

Target class

RNA tissue specificity ⓘ

Your target list

[Choose File](#) No file chosen

Showing 1 to 50 of 10,545 targets

Search:

[Download .csv](#)

Target symbol	Overall association score	Genetic associations	Somatic mutations	Drugs	Affected pathways	RNA expression	Text mining	Animal models	Target name
BRCA2	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	BRCA2, DNA repair associated
BRCA1	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	BRCA1, DNA repair associated
PIK3CA	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	phosphatidylinositol-4,5-bisph...
CHEK2	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	checkpoint kinase 2
PALB2	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	partner and localizer of BRCA2
RAD51C	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	RAD51 paralog C
TP53	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	tumor protein p53
AKT1	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	AKT serine/threonine kinase 1
RAD51D	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	RAD51 paralog D
ATM	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	ATM serine/threonine kinase
BRIP1	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	BRCA1 interacting protein C-t...
ESR1	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	estrogen receptor 1
FGFR2	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	fibroblast growth factor recept...
KDR	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	kinase insert domain receptor
CCND1	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	cyclin D1
ERBB2	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	erb-b2 receptor tyrosine kinas...
PIK3R1	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	phosphoinositide-3-kinase reg...
EGFR	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	epidermal growth factor receptor
PTEN	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	phosphatase and tensin homo...
STK11	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	serine/threonine kinase 11
FGFR4	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Dark Blue	Light Blue	Light Blue	Light Blue	fibroblast growth factor recept...
RAD51B	Dark Blue	Dark Blue	Dark Blue	Light Blue	Dark Blue	Light Blue	Light Blue	Light Blue	RAD51 paralog B

Order by evidence type and evidence strength

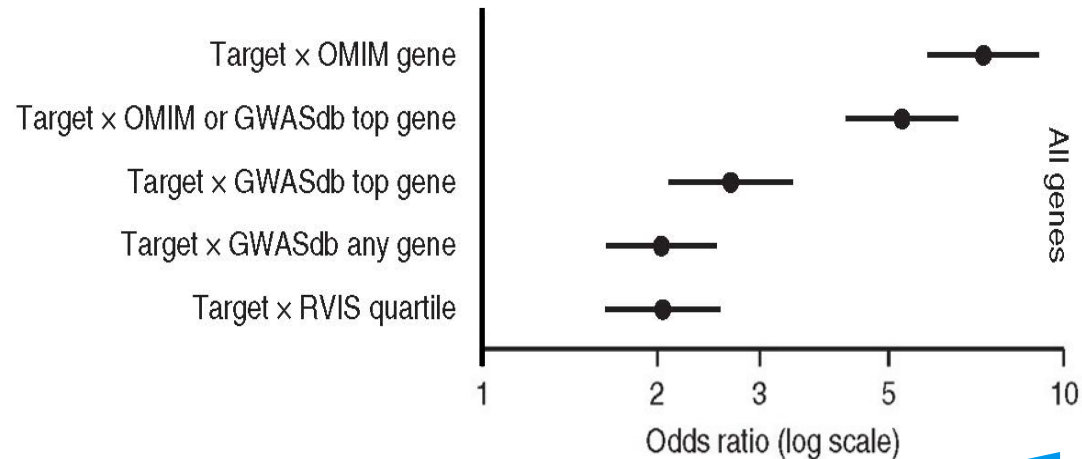
Filter by evidence type: e.g. 750 targets are supported by somatic mutations

Filter by pathway type and particular pathways

Improved Efficacy through Genetics

Nelson *et al.*, *Nature Genetics*, 2013

Genetic link



Drugs with genetic link between target and disease

Chance of clinical success



Systematic Identification : Genetics and GWAS



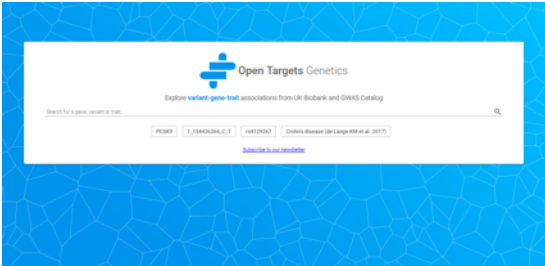
GWAS Catalog
Summary Stats



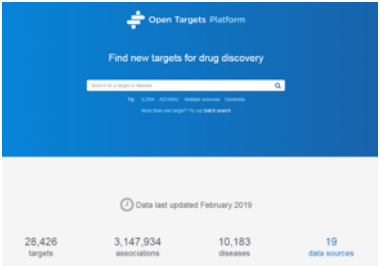
eQTL Catalogue



Regulation data

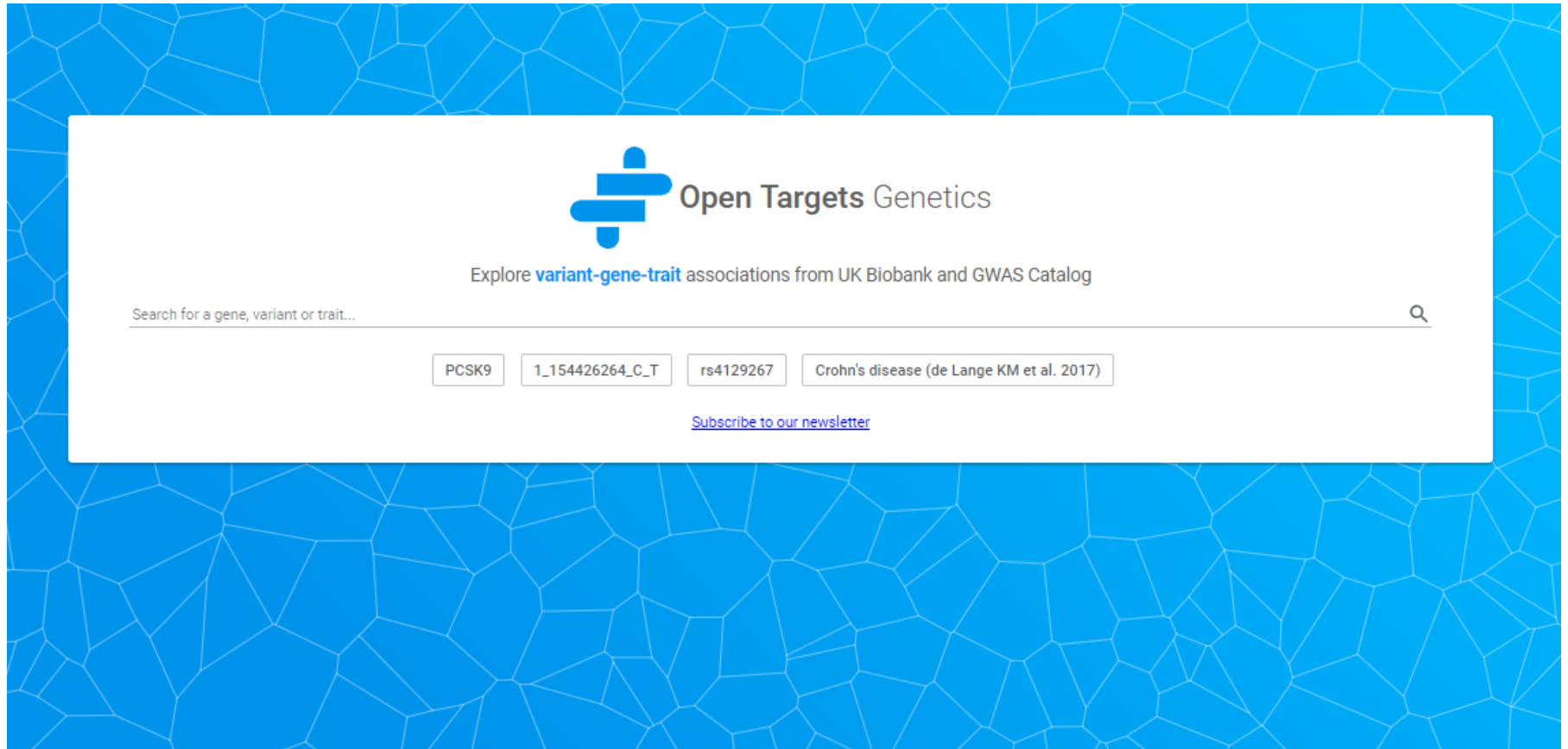


OT Genetics



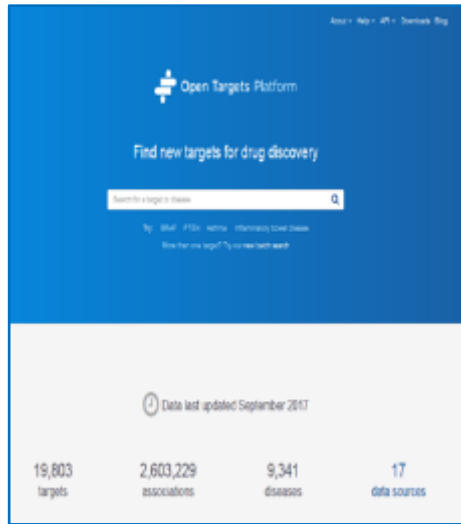
OT Platform

Informatic Products: The Genetics Portal



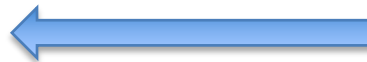
The screenshot shows the Open Targets Genetics portal interface. At the top center is the logo, which consists of three horizontal bars of varying lengths and a small circle above the longest bar. To the right of the logo is the text "Open Targets Genetics". Below this is a subtitle: "Explore variant-gene-trait associations from UK Biobank and GWAS Catalog". A search bar is positioned below the subtitle, containing the placeholder text "Search for a gene, variant or trait...". To the right of the search bar is a magnifying glass icon. Below the search bar are four filter buttons: "PCSK9", "1_154426264_C_T", "rs4129267", and "Crohn's disease (de Lange KM et al. 2017)". At the bottom center of the interface is a link that says "Subscribe to our newsletter".

Open Targets Informatics

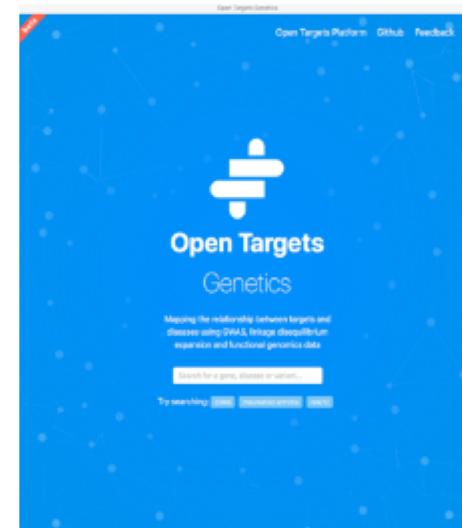


targetvalidation.org

Aggregate genetics evidence for target



Link out to investigate details of the evidence



genetics.opentargets.org

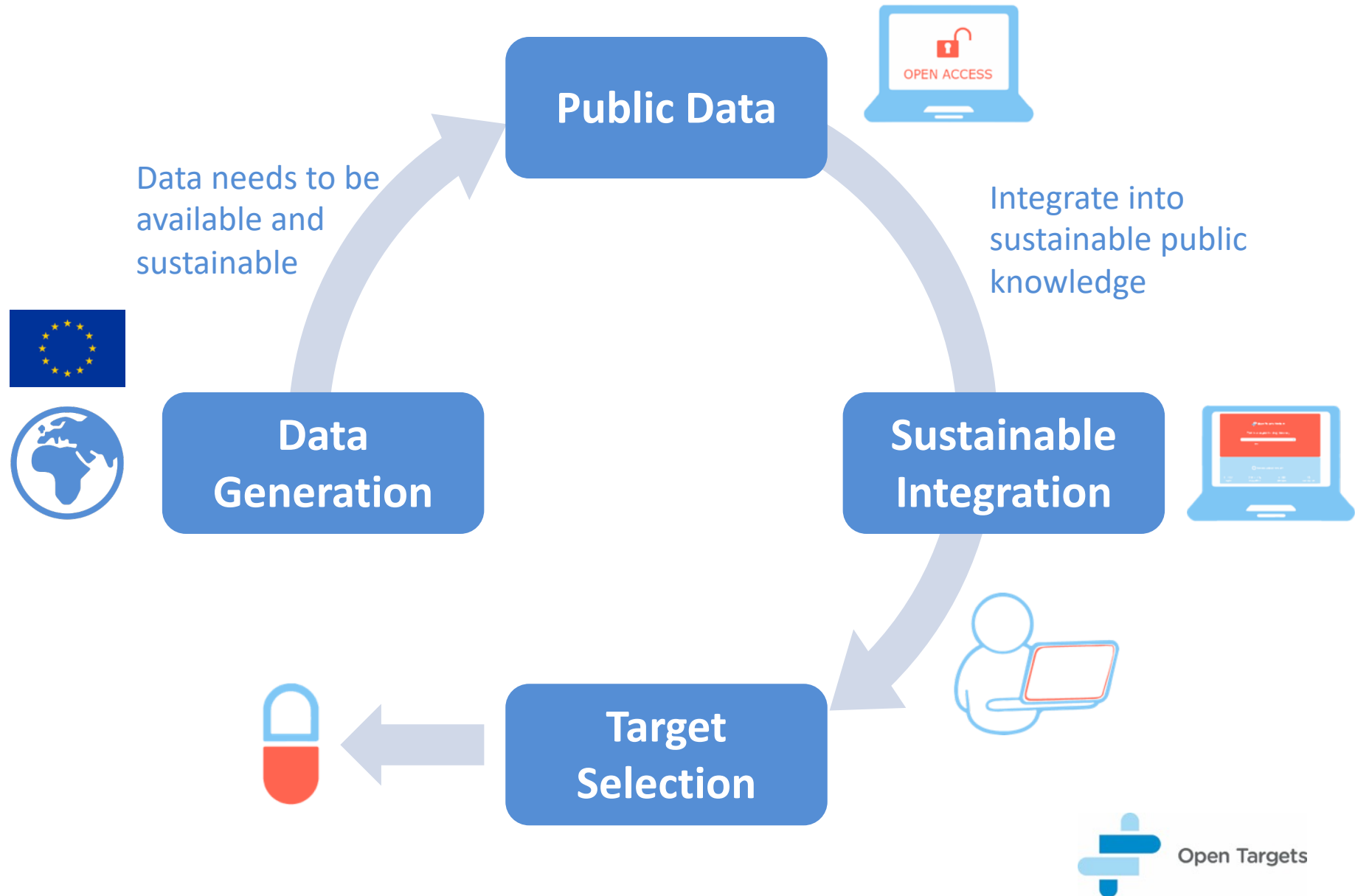
Detailed investigation of genetics evidence including bespoke tools

<https://www.opentargets.org/resources/>

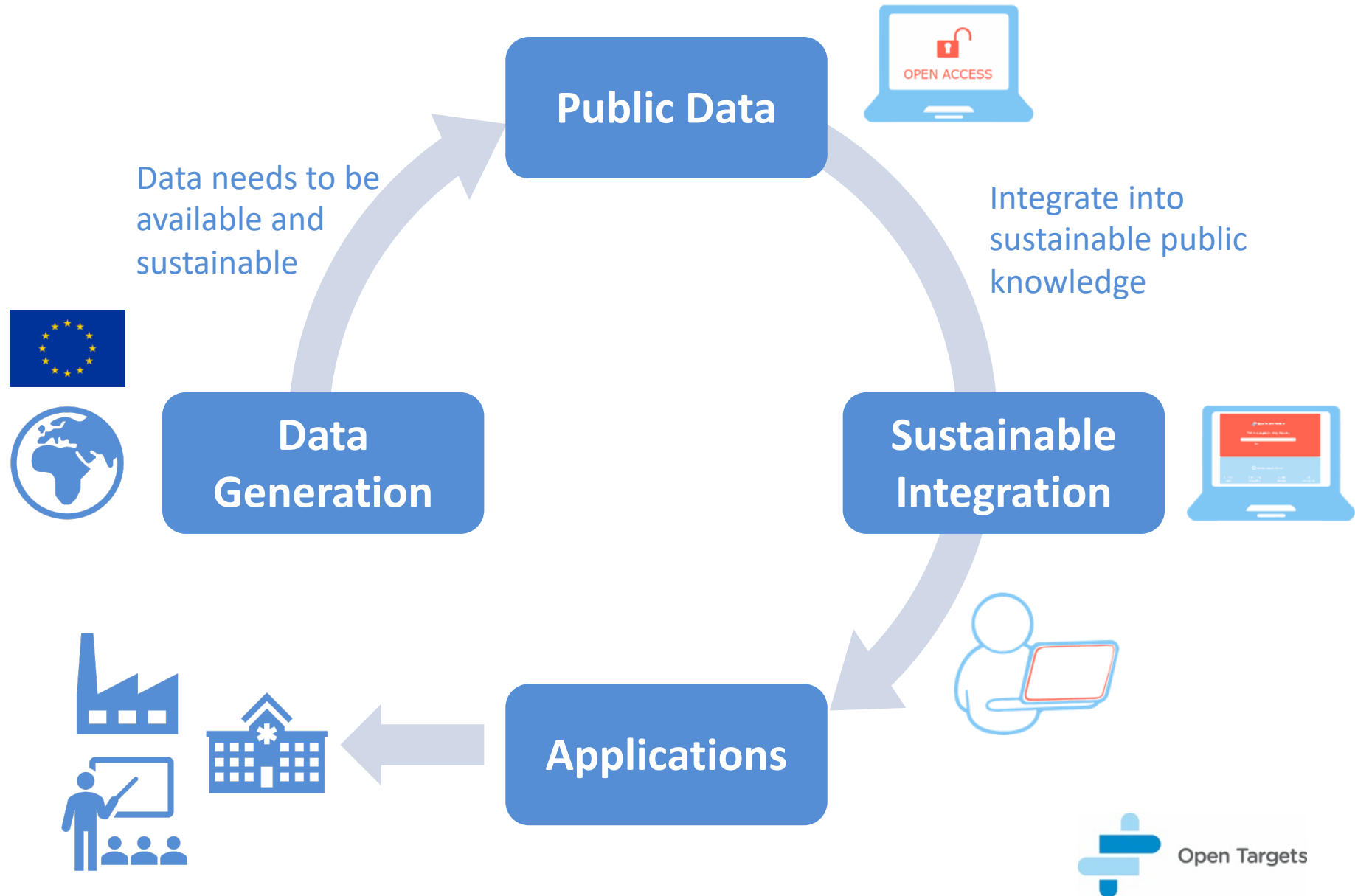
Membership Benefits for Partners

- Direct Open Targets research direction, therapeutic area focus and strategy
- Access to data, methods and technologies to support internal research programmes
- Enhance in-house R&D capability and capacity, de-risk emerging areas
- Work with world-leading teams in genetics, bioinformatics and cell modelling
- Engagement with community transforming therapeutic target selection
- Lean structure, low bureaucratic burden, swift decision-making
- Clear, rapid IP process
- Industry standard project management
- Support for private instance of the bioinformatics platform
- Reputational benefits through partnership and open innovation

Policy Implications – Open Targets



Policy Implications - General



Acknowledgements



Open Targets Governance

Governance Board

Scientific Advisory Board

Scientific Director

Director

Operations Director

Executive Team

Scientific Leads



Open Targets

Open Targets Governance

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Open Targets Governance

Strategy
Project Approval

Governance
Board

Scientific
Advisory Board

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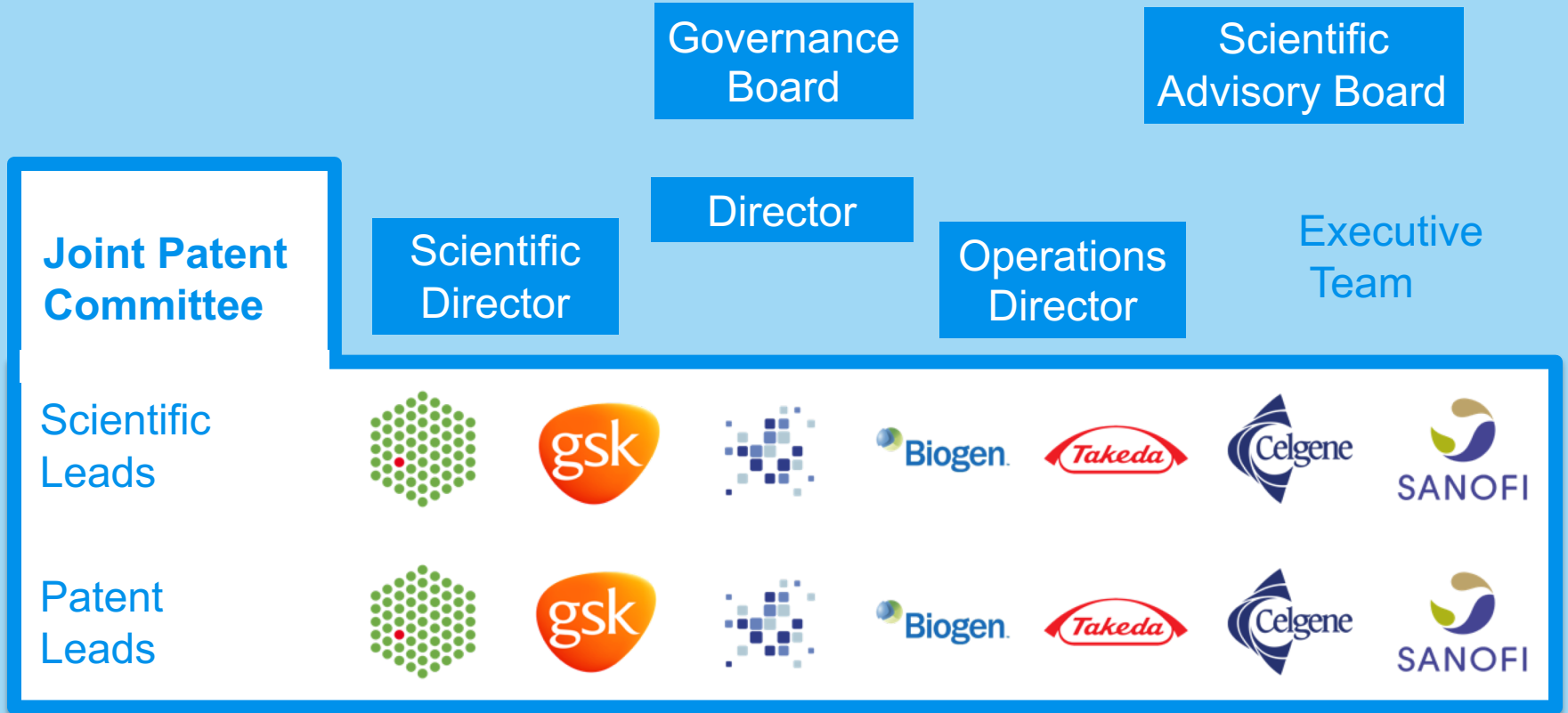


Project Review



Open Targets

Open Targets Governance



How can genetics be used to guide therapeutic target identification and Prioritisation?

targetvalidation.org

- Rare and complex diseases
- Search for **target** or **disease**
- Germline and somatic mutations, drugs, pathways, expression, text mining, animal models
- Released 2015

genetics.opentargets.org

- Complex diseases, common genetic variation
- Search for **variant**, **target**, or **disease**
- Variant-to-gene scoring
- Functional genomics, QTLs
- Released 2018