



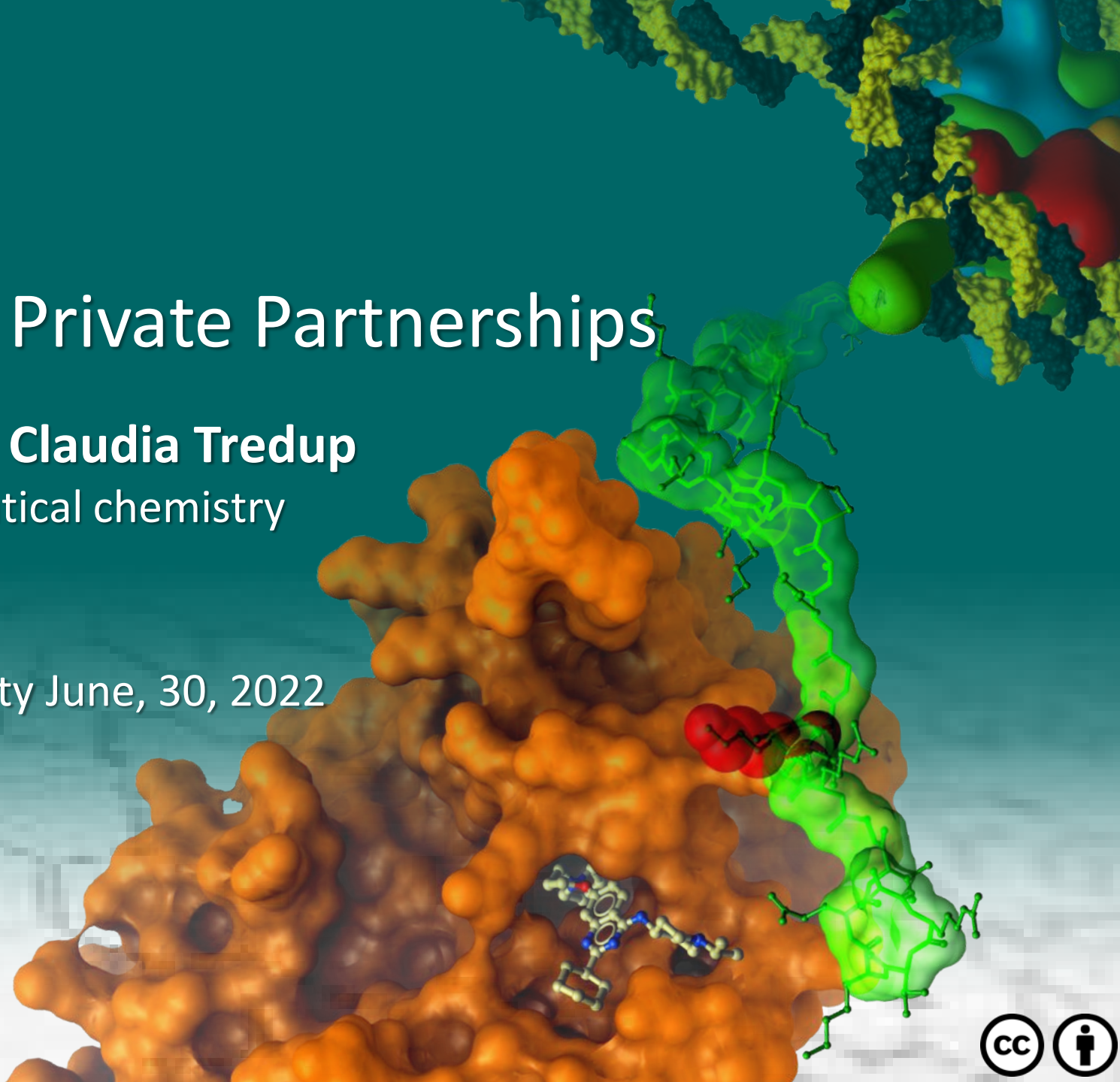
SGC

Open Science in Public Private Partnerships

Dr. Susanne Müller-Knapp & Dr. Claudia Tredup

SGC Frankfurt, Institut für pharmaceutical chemistry
Goethe University Frankfurt

Open Science Forum, Goethe University June, 30, 2022



THE STRUCTURAL GENOMICS CONSORTIUM (SGC) IS A GLOBAL PUBLIC PRIVATE PARTNERSHIP DEDICATED TO OPEN SCIENCE



- International public-private partnership (PPP) with a mission to accelerate the discovery of new medicines through precompetitive, open science.
- SGC supports a network of scientists in 6 universities in 5 countries plus a network of 300+ collaborators.
- Global network of partners, funders over 18 years, including pharmaceutical companies, charities, and government agencies.
- SGC co-authors ~25 peer-reviewed papers each year with industry.
- SGC is a charity incorporated in the UK, SGC Head Office is in Canada.

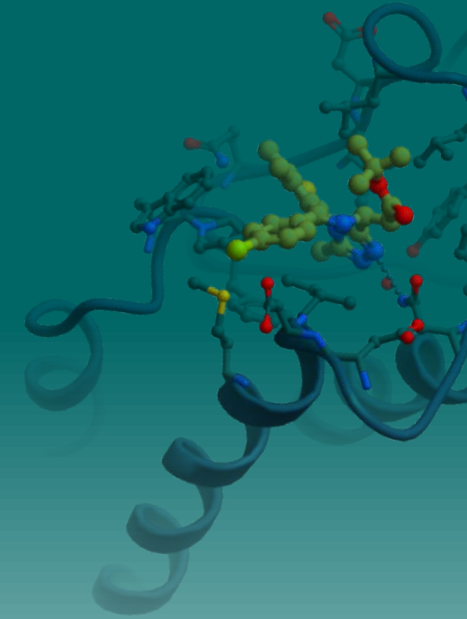


SGC at a glance



Main outputs:

- High Throughput Structural Biology (>4000 structures deposited)
- Renewable Antibodies/Binders
- Patient-Cell Derived Assays
- Chemical Probes (~190) and Chemogenomics Libraries
- Data driven research (ML)



GenomeCanada



Ontario



Innovative Medicines Initiative

BILL & MELINDA
GATES foundation

THE ESHELMAN FOUNDATION
WILMINGTON • NORTH CAROLINA



Boehringer
Ingelheim

Genentech

Janssen



Bristol Myers Squibb™



Pfizer

Takeda

MERCK

Our Ethos: Open Access

Promptly placing results,
reagents and know-how
in the public domain



We agree **not** to file for
patent protection on any of
our research outputs
(and encourage our collaborators to do the same)



OPEN  ACCESS

www.thesgc.org

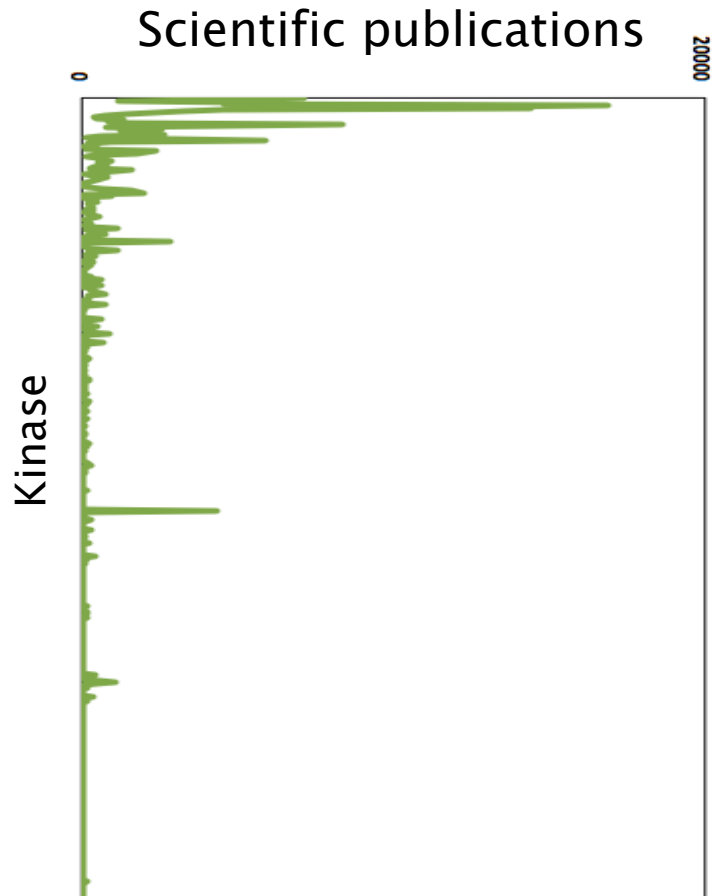
- > \$250B a year invested in biomedical research
 - No new medicines for schizophrenia since 1950's
 - No new treatment for Alzheimer's since early 80's

Medicines are not affordable for most people in the world

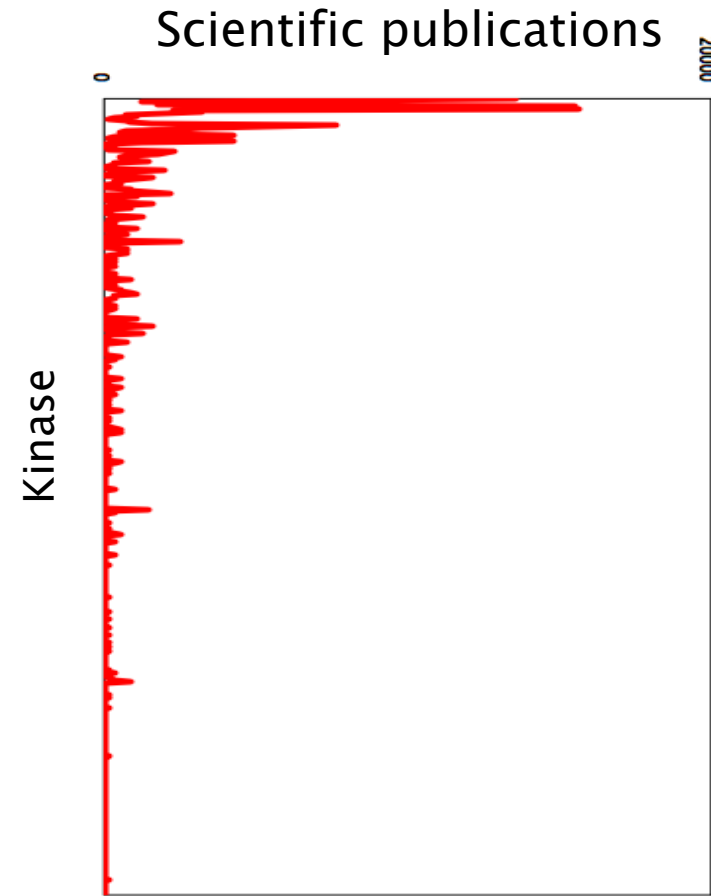


MOST SCIENCE IS REDUNDANT

Global Effort (2019)



German Effort (2019)



COMMENT

ANTHROPOLOGY Call for unity in the science of human beings [p.168](#) | **GENETICS** Reviewed: two primers on personal genomics [p.169](#) | **POLICY** Sanitation, not vaccination, is most important in Haiti [p.175](#) | **OBITUARY** Jack Oñiver, key player in proof of plate tectonics, remembered [p.176](#)



Too many roads not taken

Most protein research focuses on those known before the human genome was mapped. Work on the slew discovered since, urge **Aled M. Edwards** and his colleagues.

When a draft of the human genome was announced in 2000, funders, governments, industry and researchers made grand promises about how genome-based discoveries would revolutionize science. They promised that it would transform our understanding of human biology and disease, and provide new targets for drug discovery. Yet more than 75% of protein research still focuses on the 10% of proteins that were known before the genome was mapped — even though many more have been genetically linked to disease.

We performed a bibliometric analysis to assess how research activity has altered over time for three protein families that are central to disease and drug discovery: kinases, ion channels and nuclear receptors. For all three, we found very little change in the pattern of research activity — which proteins are associated with the highest number of publications — over the past 20 years*. Even those proteins that have been directly associated with disease remain 'hidden in plain sight', with scientists proving very reluctant to study them.

Where there has been a shift in research activity, it was often spurred by the emergence of tools to study a particular protein, not by a change in the protein's perceived importance. We believe that ensuring high-quality tools are developed for all the proteins discovered may be all that is needed to drive research into the unstudied parts of the human genome — even within funding and peer-review systems that are inherently conservative.

We searched for mention of every human

*NATURE.COM Protein mapping gains a human focus: go.nature.com/vbqeff

10 FEBRUARY 2011 | VOL 470 | NATURE | 163

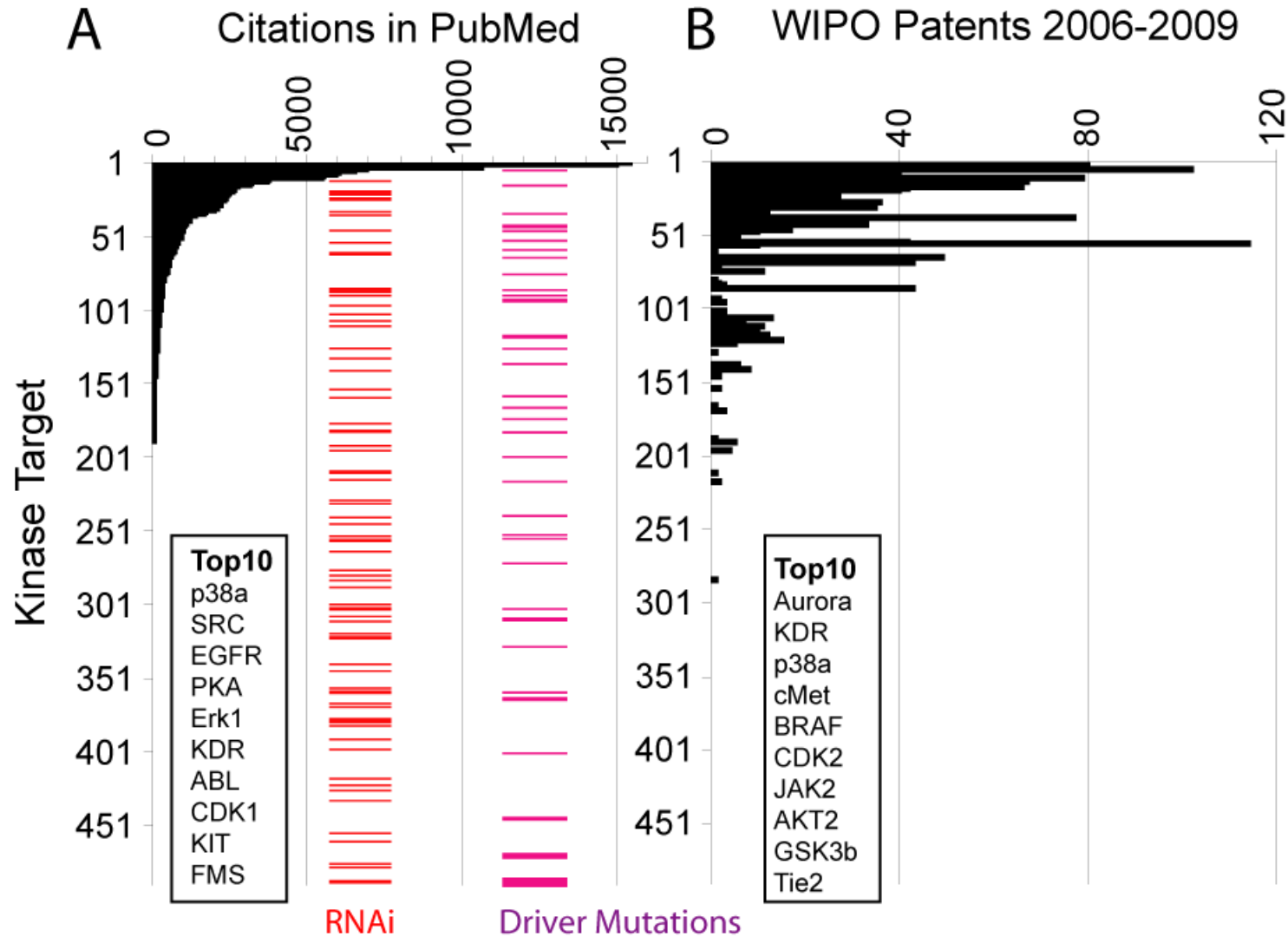
THE SYSTEM IS THE PROBLEM



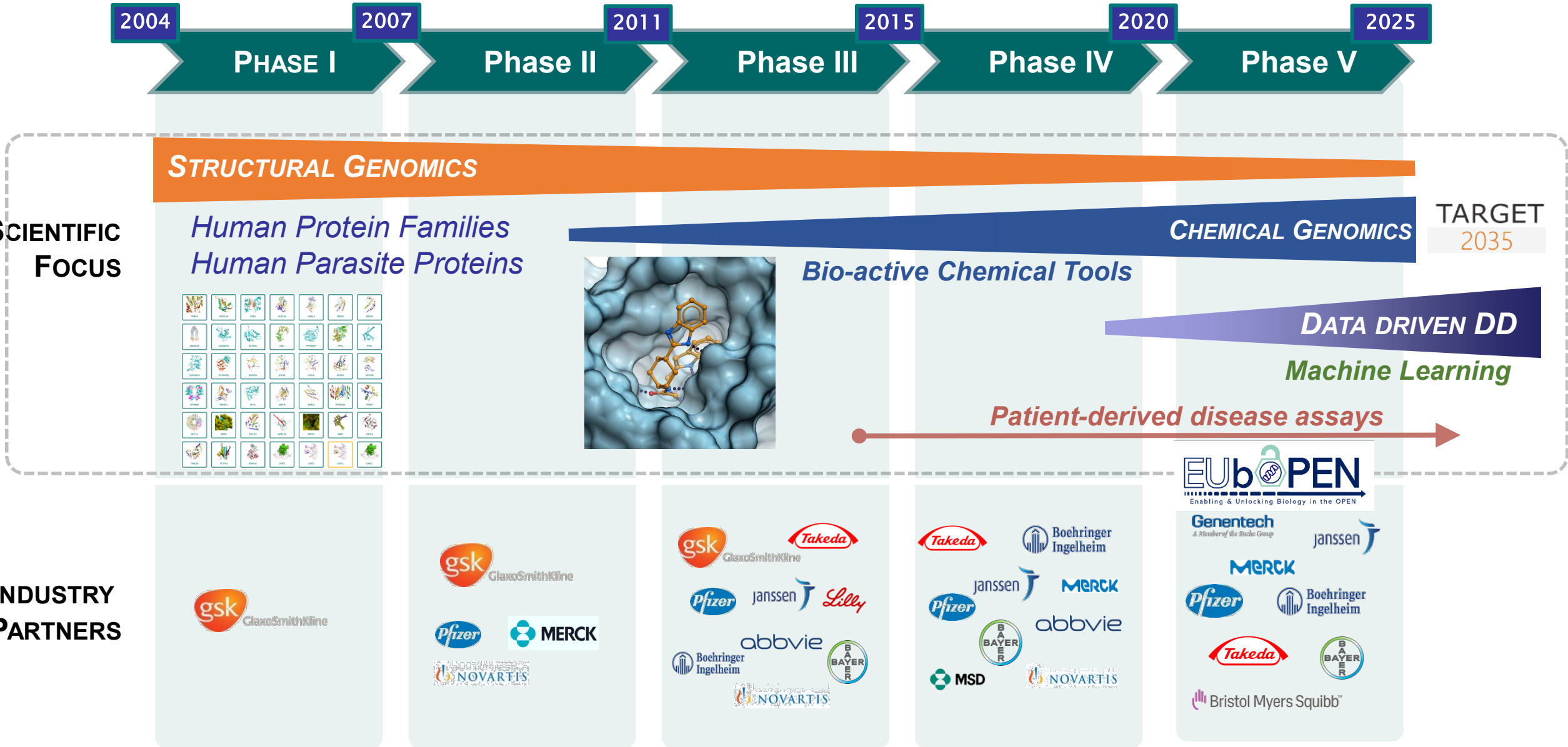
- Funding based on published results
- Lack of funding for truly innovative ideas
- Small increments
- Agreements/IP – time consuming

charitably, mixed. [A recent Bloomberg report](#) shows how quickly university patent incomes plunge once we look beyond the megastars. In 2014, just 15 US universities earned 70% of all patent royalties. British science policy researchers [Paul Nightingale and Alex Coad](#) conclude that 'Roughly 9/10 US universities lose money on their technology transfer offices... MIT makes more money from selling T-shirts than it does from licensing'. [A report from the Brookings institute](#)

WHERE ACADEMIA SHINES LIGHT, INDUSTRY SEARCHES




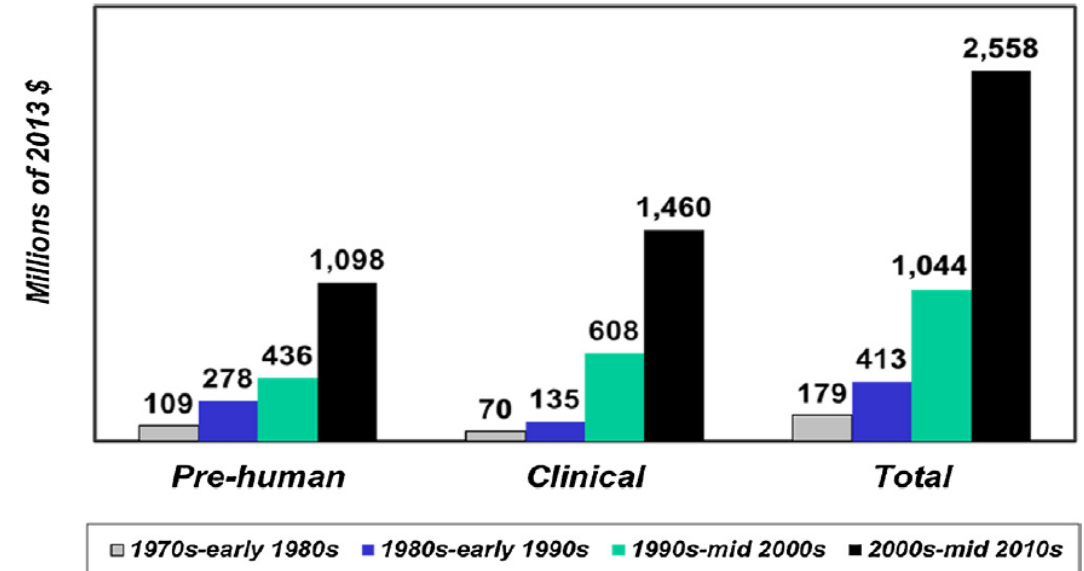
Evolving science and partners to address pressing global SGC



WHAT DOES INDUSTRY GAIN?

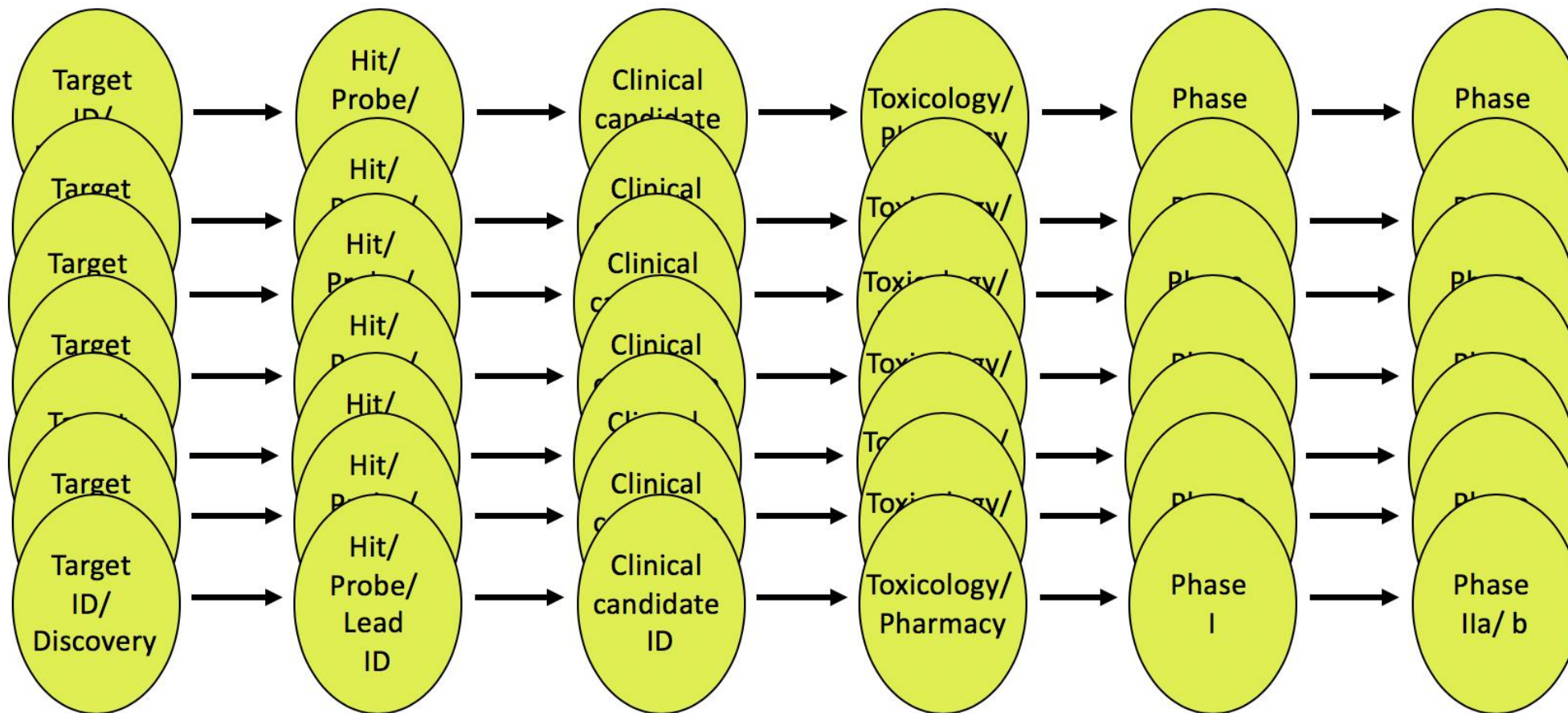


- New medicines are exorbitantly expensive
- >\$2.5B in private sector R&D costs per approved new drug
- # new drugs approved per \$1B halved every 9 years since 1950s
- clinical attrition rates 



- Launches at \$100,000's per patient per year the new normal
 - Kalydeco® (Ivacaftor); Orkambi® (Lumacaftor/Ivacaftor) for genetic subsets of CF -> \$300K/year
 - Rare disease drugs now launching at almost \$1M/year in some cases
 - Targeted cancer therapies - mAbs, kinase inhibitors \$\$\$
 - Glybera example (gene therapy for lipoprotein lipase disorder developed at UBC) - \$1M for one dose
- Trends exacerbating pricing:
 - Increasing development costs, costs of failure, and clinical attrition - YES
 - BUT ALSO: patient population sizes getting smaller with better genetic characterization
- Sustainability for public and private payers?

SILOED PROPRIETARY DEVELOPMENT LEADS TO REDUNDANCY



Examples of failed parallel late-stage clinical programs: NK1 receptor antagonists for analgesia; matrix metalloproteases and farnesyltransferase inhibitors for cancer; cholesterol ester transfer protein for CVD; beta-amyloid for AD; aurora kinase inhibitors for breast cancer

Precompetitive Research – from lab to patients?



GSK collaboration starts

Oxford and Harvard start collaboration BET /NMC



GSK carries out first in man study (open)

Co-publication of JQ1 probe (SGC; cancer) and I-BET probe (GSK; inflammation)

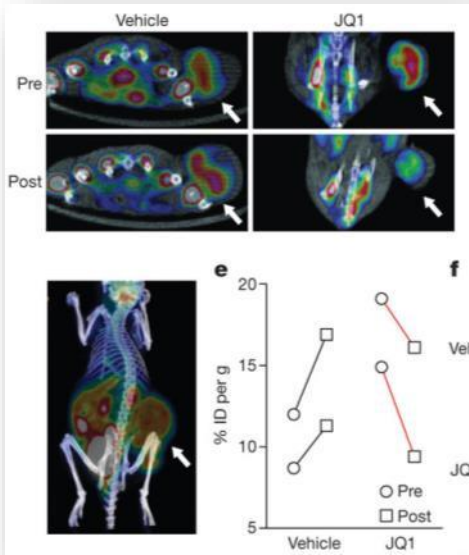
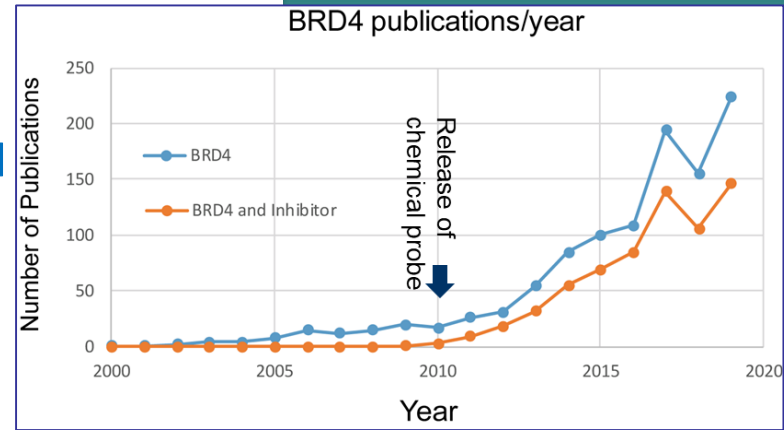
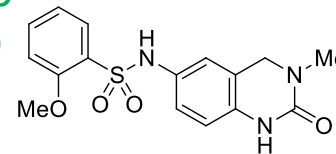
JQ1 distributed to 100+ labs



Booming interest in Academia and Industry

Pfizer BET probe announced

Brd4 linked to AML (Nature) MM (Cell)



Currently >30 clinical trials

Creative commons

Proprietary

Public Private Partnership



Public Domain

Private Sector

Chemical Probes

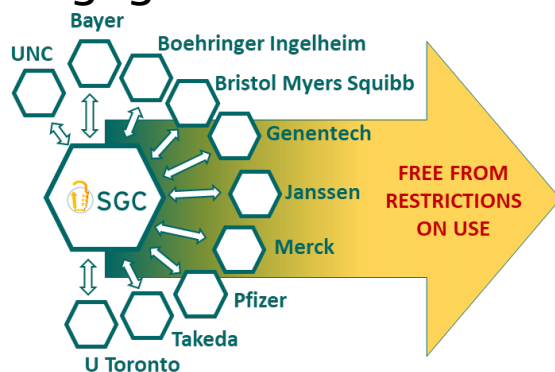
Target Validation

Drug Discovery Development

Proteins,
Assays/Screening
3D Protein Structure
Medicinal Chemistry
Target Engagement in cells

Disease studies
No restrictions
Publication
Tools for all

Lead optimization
Pharmacology
DMPK
Toxicology
Chemical development
Clinical development



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Edwards et al, Nature Chem Biol, 2009

PUSHING THE OPEN SCIENCE BOUNDARIES



RSC Medicinal Chemistry

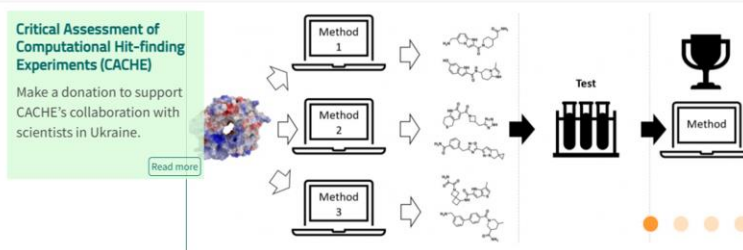
OPINION

Check for updates

Target 2035 – update on the quest for a probe for every protein

Cite this: *RSC Med Chem*, 2022, 15, 15

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The Chemical Probes Portal

chemical Probes.org

- Open online resource designed to change the way scientists find and use high quality use small-molecule reagents called chemical probes in biomedical research and drug discovery
- Aimed to makes it easy for non-experts to select the right chemical probe before they initiate a study – and also to help use probes to achieve a more informative experiment
- Established in 2015 alongside the Arrowsmith et al Nat Chem Biol article – 579 citations on Google Scholar
- Based on expert recommendations and commentary on selected probes
- Provides an alternative to reliance on citation rates, Google, Wikipedia or vendor catalogues
- Expert review mechanism complements more quantitative, large scale resources such as Probe Miner and Drugs & Probes
- Also provides a range of useful information



... crowd-sourced evaluation of research tools

Agora Open Science Trust (Charity)

Latest Blog Posts

[18F]DG-PET

Childhood brain tumours: From tissue samples to new treatment options

M4K Team publishes in the Journal of Medicinal Chemistry

Sept 2020 M4K Pharma Open Scientific Update Meeting – Recording

Partners



BioImage Archive

High-Content Live-Cell Multiplex Screen for Chemo-genomic Compound Annotation; EUBOPEN wave 1

Aranya Tapan S, Susanna-Pöhlmann, J. Stefan Knapp?

Accession: S-884245

Description: This submission holds the raw data and processed images for a high-content live-cell multiplex screen. The screen is used for chemo-genomic compound annotation, i.e. the evaluation of e.g. synthetic effects. This submission is about a set of 1500 chemo-genomic candidate compounds, tested in a pre-screen and a primary screen. Further information about the EUBOPEN project, from which this set and equipment originated can be found in the links section.

Study Type: compound library screen

Organism: Homo sapiens (Human)

Study Protocol: N/A

Model: N/A

Type: treatment/probe

Description: see description in accompanying publication

Study Component: see description in accompanying publication

... deposition of metadata

Open Lab Notebooks

Extreme Open Science Initiative: SGC scientists around the world are starting to post their lab notebook online in real time.

University of Toronto, Canada

Heng Zhang, Jolene Ho, Megha Abbey, Rachel Harding

University of Oxford, U.K

Jong Fu Wong, Roslin Adamson, Elizabeth Brown

University of North Carolina, U.S.A.

Alfredo Picado, Carla Alamillo, Nirav Kapadia

... University of British Columbia, Emory University, Sick Kids Hospital...

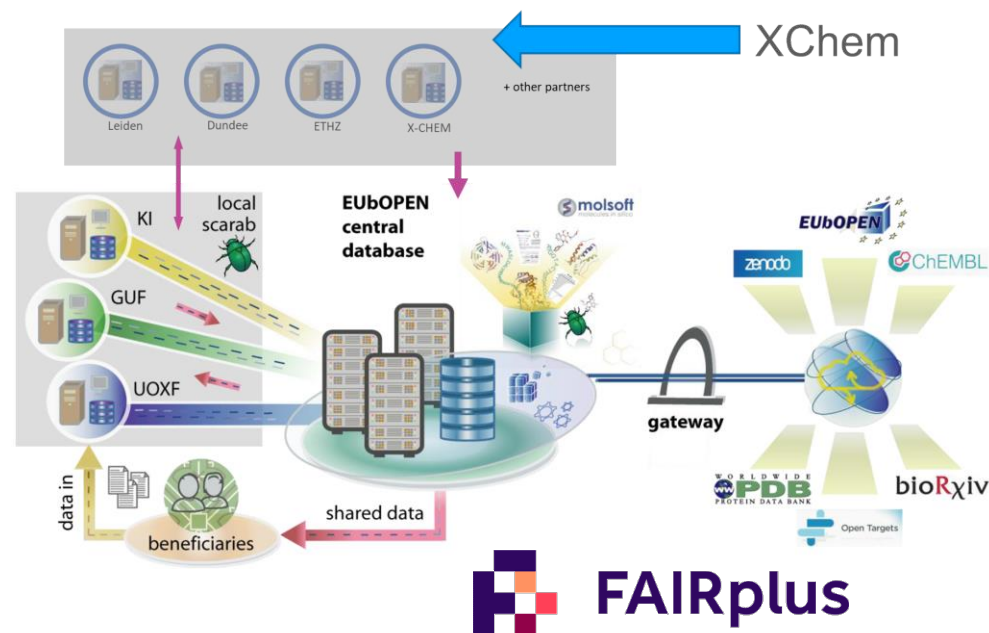
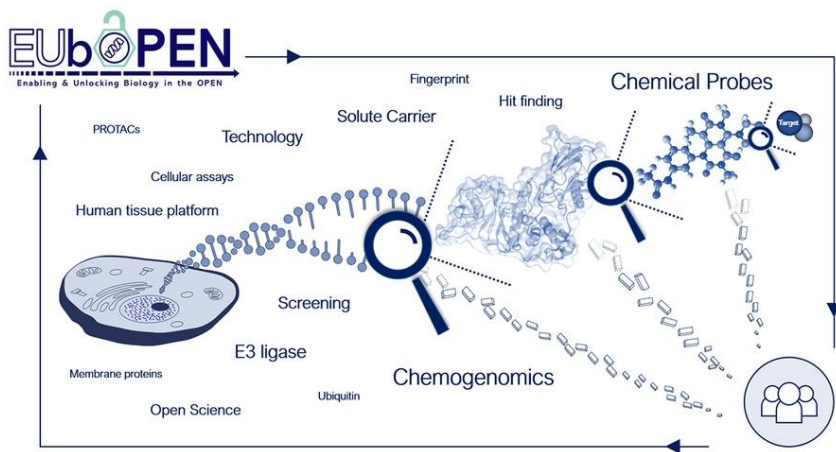
SGC in Numbers



- Publication of more than 2 manuscripts per week (many in high impact factor journals)
- More than 4000 protein structures deposited in the PDB contributing 12% of all known structural information for human proteins
- 2 Spin-out companies
- > 190 chemical probes
- Common development of assay platforms with biotech companies (e.g. Eurofin, Promega, DiscoverX, Sigma)
- Worldwide network of collaborators



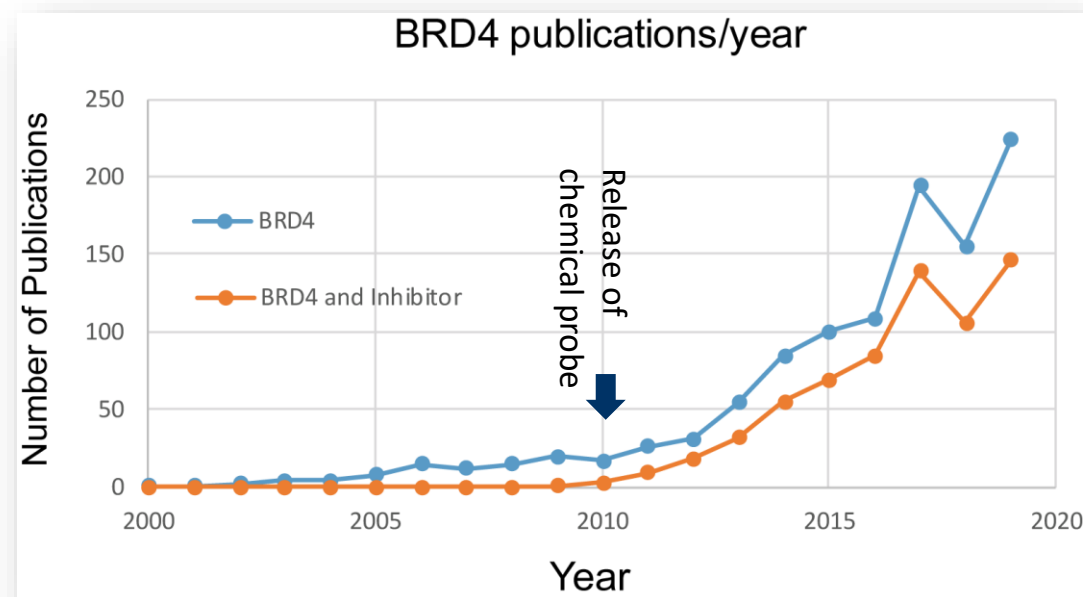
EUBOPEN



- The EUBOPEN consortium is an Innovative Medicines Initiative (IMI) funded project to enable and unlock biology in the open.
- 22 partners from academia and industry
- five years (2020–2025)
- Total budget of 65.8 million euros covered by a grant from the IMI and cash and in-kind contributions from the EFPIA companies, IMI Associated Partners and non-EU partners.
- Coordinated by GUF
- Open Science Policy

- Open access requirement for all EUBOPEN and SGC publications
- Depositing publications in repositories
- Subject-based/thematic repository (e.g., [arXiv](#), [Europe PMC](#)), OR
- [Zenodo](#) the OpenAIRE repository hosted by CERN
- [FAIR Guiding Principles](#)
Findable, Accessible, Interoperable, Reusable

- Encourage innovation
- Engage industry
- Accelerate science
- Increase reproducibility
- Reduce redundancy
- Engage patients
- Mobilize funding
- Develop new technologies through crowd sourcing



- 20 years after deciphering the human genome, our understanding of human disease is still far from complete
- Lack of tools, which help understand biology and disease-relevant processes
- In a bibliometric analysis, we found that chemical probes were the most impactful tools to enable researchers to work on new genomics targets
- Freely available probes to human proteins will enable discovery of new medicines

Chemical probe = a drug-like small molecule that selectively modulates the activity of a specific protein in cells



DISCOVERED

190+

Chemical probes discovered by SGC or with pharma or academics



DISTRIBUTED

42,662+

Samples of chemical probes distributed globally by SGC and trusted vendors



CITATIONS

7,285+

SGC chemical probes used by scientists around the world



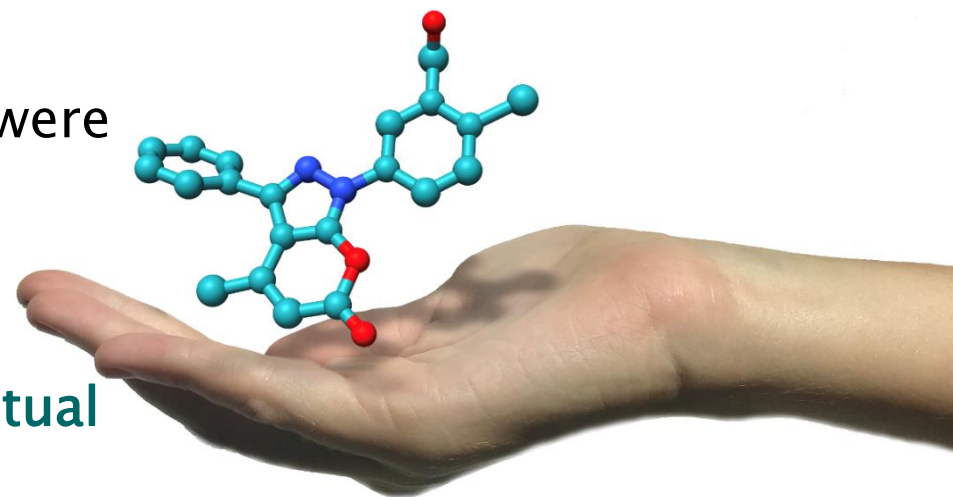
CLINICAL TRIALS

25+

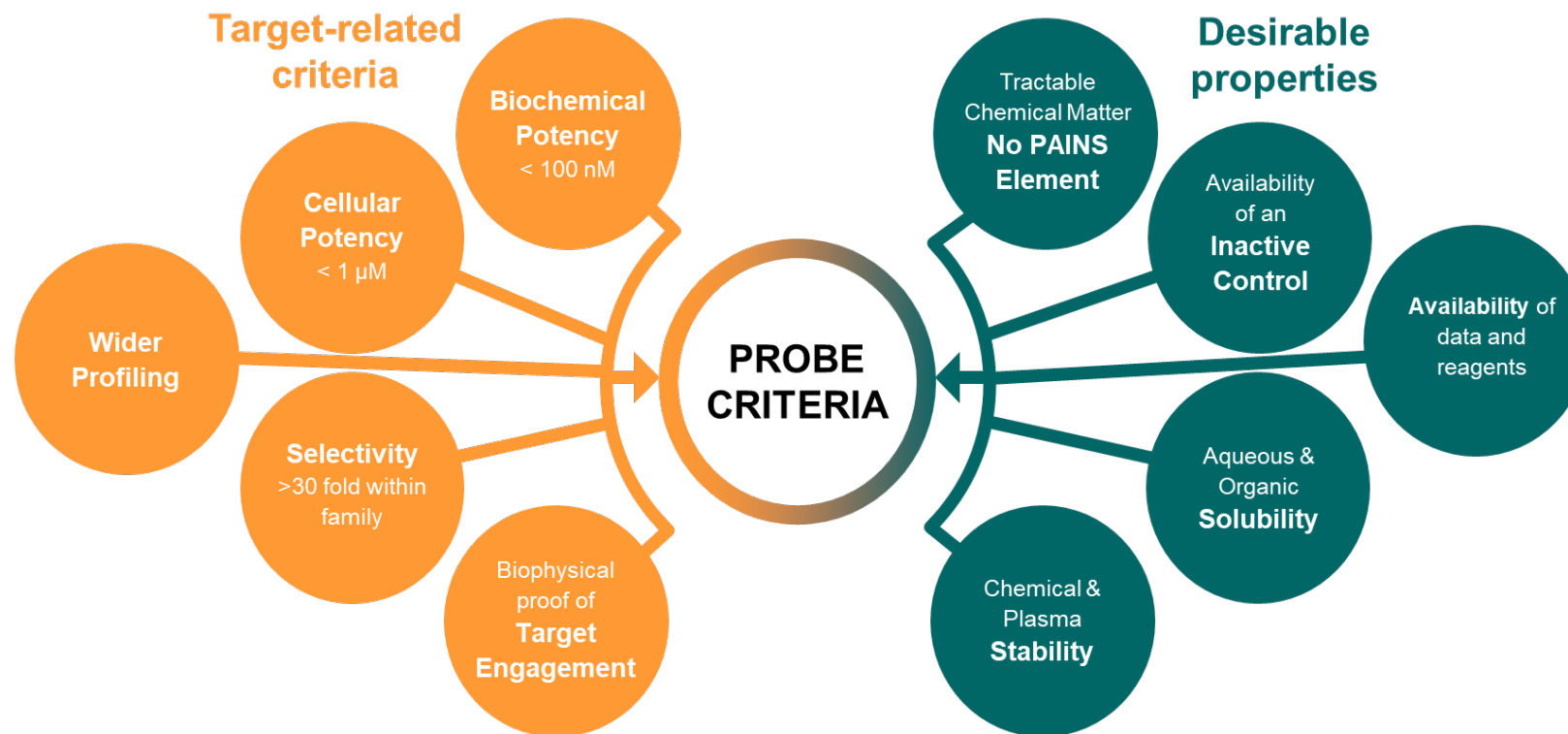
Clinical trials and late-stage preclinical programs based on therapeutic hypotheses generated with SGC chemical probes

HUNDREDS OF PAPERS USING SGC PROBES RESULTING IN THERAPEUTIC HYPOTHESES

- **Initiated 2017** by SGC pharma partners (AbbVie, Bayer, Boehringer Ingelheim, Janssen, MSD, Pfizer, and Takeda) and **led by SGC Frankfurt**
- A collection provided by the pharmaceutical industry to the global scientific community
- Make openly available chemical probes, many of which were previously **not in public domain**
- Initially donations from pharma, later academics joined
- Available to all researchers **without complicated contractual** restrictions
- Make available through **chemical vendors**



REVIEW AND DISSEMINATION PROCESS



Probe proposal

Review and approval by independent committees

Database

Distribution by SGC and vendors

ALL DATA IN A PUBLICLY AVAILABLE DATABASE

- Overview
- Usage
- Order
- Properties
- Structures
- Profiling assays
- Data download

Overview for BAY-3827 an inhibitor of PRKAA1, RPS6KA1

Target information: [PRKAA1](#) [RPS6KA1](#)

Probe criteria	
Inhibitor/agonist potency: goal is < 100 nM (IC50, Kd>/sub>)	Surpasses criterion: High potency in biochemical PRKAA1 assay with IC50 = 1.4 nM @ 10 µM ATP; 15 nM @ 2 mM ATP (Bayer in house); IC50 = 7 nM (Eurofins @ 1 µM) RPS6KA1(h); IC50 = 9.1 nM (Eurofins @ 1 µM)
Selectivity within target family: > 30-fold	Surpasses criterion: Selectivity > 500 fold against 322 out of 329 off-kinases tested; Most potent off-kinases @ 1µM: RPS6KA3 (IC50 = 52 nM (Eurofins)), RPS6KA2 (IC50 = 24 nM (Eurofins)), RPS6KA6 (IC50 = 36 ± 8 nM (n=6, Bayer in house)), FLT3 (IC50 = 124 ± 140 nM (n=6, Bayer in house)), RPS6KA5 (IC50 = ...)
Selectivity outside target family	Shows off-target activity in the GPCR scan: the closest hits are GABA/PBR (Ki = 222.4 nM) and DRD1 (Ki = 634.31 nM)
On target cell activity for cell-based targets: goal is < 1 µM IC50/EC50	Surpasses criterion: Active in cellular mechanistic assay (150 nM) demonstrating cellular target engagement Additional proof for on target activity: ATP-competitive binding mode demonstrated (X-ray available)
Control compound (100 times less potent than the probe)	Surpasses criterion: BAY-974 inactive (IC50 > 30 µM); Shows off-target activity in the GPCR scan for GABA/PBR (Ki = 20.99 nM) and TMEM27 (Ki=4470.95 nM)

View detailed potency data
View GPCR scan data
View KINOMEScan data

Additional information

PLEASE press the button to get more information for the probe!

Get more probe information

Evaluated by: [PrObes.org](https://www.chemical-profiling-services.org)

DOI: [10.6019/CHEMBL4507319](https://doi.org/10.6019/CHEMBL4507319)

References and patents

Compound IDs

Detailed potency data from criteria table for probe BAY-3827 and control BAY-974

Download data file | Back to probe overview

Biochemical assays							
Target name	Target information	Species	Assay description	Compound conc.	Probe result (SE)	Control result (SE)	Publication of assay conditions
PRKAA1		Homo sapiens	Biochemical PRKAA1 assay with 10 µM ATP (Bayer in house)		IC50 1.4 nM	IC50 >200 µM	
PRKAA1		Homo sapiens	Biochemical PRKAA1 assay with 2 mM ATP (Bayer in house)		IC50 15 nM	IC50 >200 µM	
PRKAA1		Homo sapiens	Eurofins kinase panel (PRKAA1)	1 µM	IC50 7 nM		
RPS6KA1		Homo sapiens	Eurofins kinase panel (RPS6KA1)	1 µM	IC50 9.1 nM		

Cellular assays							
Target name	Target information	Species	Assay description	Compound conc.	Probe result (SE)	Control result (SE)	Publication of assay conditions
PRKAA1		Homo sapiens	Cellular mechanistic pACC assay using MCF-32 neuroblastoma cells		IC50 150 nM	IC50 >30.0 µM	
PRKAA1		Homo sapiens	Cellular mechanistic pACC assay using Colo-320 cells		IC50 390 nM	IC50 >30.0 µM	

For compounds showing more than 50% inhibition in the primary screening assay, a Ki will be determined.

View assay details

Download data file | Back to probe overview

GPCR scan data for probe BAY-3827 an inhibitor of PRKAA1, RPS6KA1

Compound concentration: 10 µM

Receptor	HSNC target name	Primary experimental value (% inhibition)
GABA/PBR		85.63
D1	DRD1	67.39
Sigma 2	TMEM27	78.28
5-HT2B	HT2B	32.47
MOR	OPRM1	30.5
Sigma 1	SIGIRR1	30.47
M1	CHRM1	32.25
DDR	DRD1	20.48
5-HT2C	HT2C	20.02
5-HT5A	HT5A	19.9
M5	CHRM5	17.88
MOR	OPRM1	16.12
5-HT2A	HT2A	14.85
5-HT7A	HT7A	13.86
H2	HTR2A	12.65
Alpha2B	ADRB2B	10.59
D3	DRD3	10.41
BtkA3	ADRB1	10.32
Alpha2C	ADRB2C	10.0
5-HT1B	HT1B	9.48
5-HT6	HT6	9.23
D5	DRD5	8.47
M4	CHRM4	8.27

KINOMEScan data for probe BAY-3827 an inhibitor of PRKAA1, RPS6KA1

HSNC target name	Dissolved Gene Symbol of Kinase	% Control
RPS6KA1	AMPA-alpha2	0.0
FLT3	FLT3(BB41)	0.0
RPS6KA2	RSK39n.Dom.1-N-terminal	0.0
RPS6KA3	RSK29n.Dom.1-N-terminal	0.3
RPS6KA5	RPS6A99n.Dom.1-N-terminal	1.0
RPS6KA6	RSK19n.Dom.1-N-terminal	1.8
RPS6KA4	FLT3(DK31)	2.3
RPS6KA7	RPS6A99n.Dom.1-N-terminal	2.8
FLT3	FLT3(DK31)	3.2
MET	MET	2.3
RPS6KA1	AMPA-alpha1	7.5
RPS6KA4	RPS6A99n.Dom.1-N-terminal	8.9
FLT3	FLT3(TD)	11.0
FLT3	FLT3(TD-F99L)	11.0
FLT3	RET(WSN4)	11.0
FLT3	FLT3(TD-DK31)	12.0
FLT3	FLT3(WA3Q)	13.0
PRKCG	PRKCG	15.0
FLT3	FLT3	16.0
FLT3	FLT3(DK31H)	16.0
FLT3	RET(WSN4)	16.0

their target protein(s). This website provides a unique collection of probes with their associated data, control compounds and recommendations on their use as well as a way to order the molecules.

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DCP DATA IS FINDABLE, ACCESSABLE, INTEROPERABLE AND RE-USABLE



FINDABLE

- specific URL for each probe, DOI number

ACCESSABLE

- DCP database website is open and free
- Data accessible through ChEMBL

INTEROPERABLE

- use a formal, accessible, shared, and broadly applicable language for knowledge representation
- link to other sources of knowledge / open repositories such as ChEMBL, PubCHEM, OpnMe, chemicalprobe.org

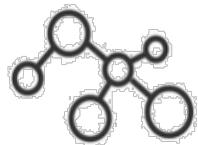
RE-USABLE

- Data update history
- CC-BY
- Metadata publication, modification and versioning not possible

REAGENTS AND UPTAKE FROM RESEARCH COMMUNITY



DCP probes in numbers



105

DCP PROBES



92

INDUSTRY
PROBES



13

ACADEMIC
PROBES



12500

COMPOUNDS
SHARED



28

COUNTRIES

Contributors



TECHNISCHE
UNIVERSITÄT
DARMSTADT

WHAT IS TARGET 2035?

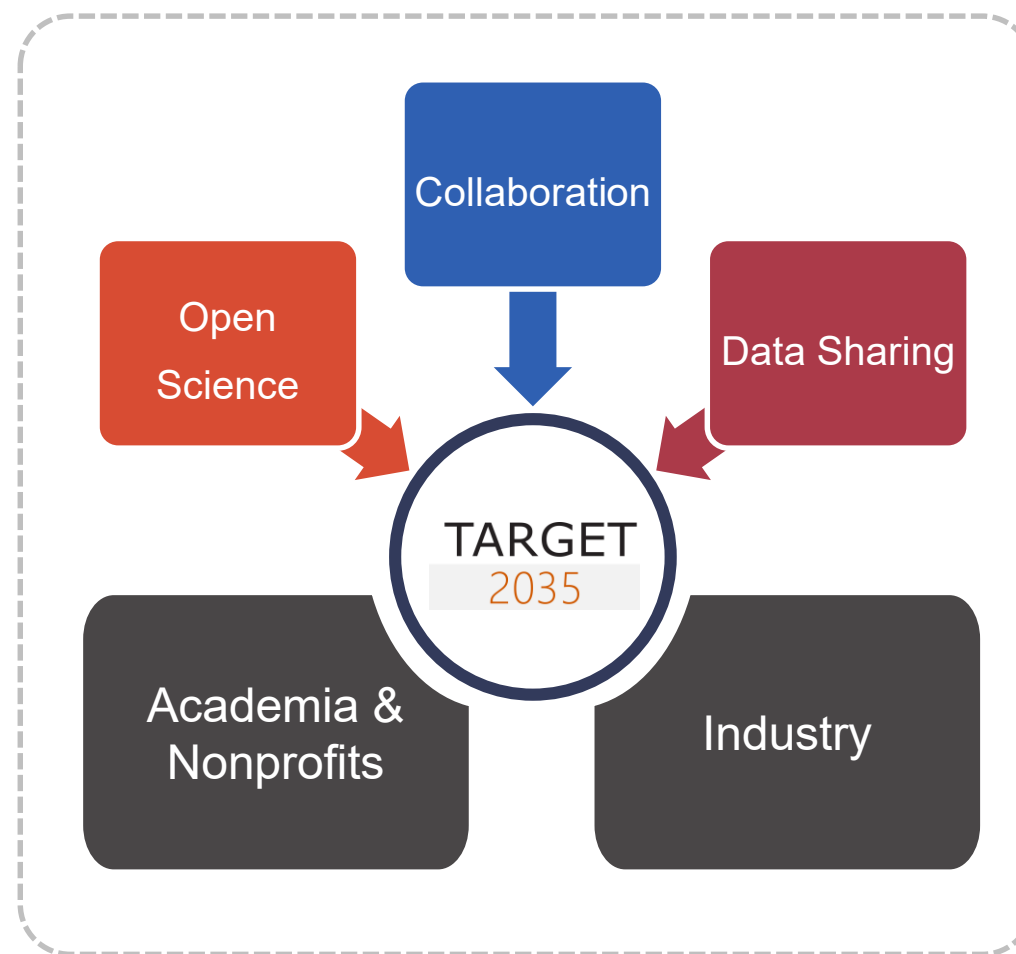
Open science global movement, focusing on the creation of chemical and biological tools to study human proteins and inform drug discovery.

OUR MISSION

Development of a pharmacological modulator for every human protein by 2035.

OUR VISION

Global collaborative effort to create open access tools to study each human protein and gene.



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innovative
medicines
initiative



www.thesgc.org

FUNDING PARTNERS

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