Setting up partnerships to discover drug targets

Structural Genomics Consortium

SGC Toronto

SGC Oxford

SGC Stockholm

1. Choose an important problem

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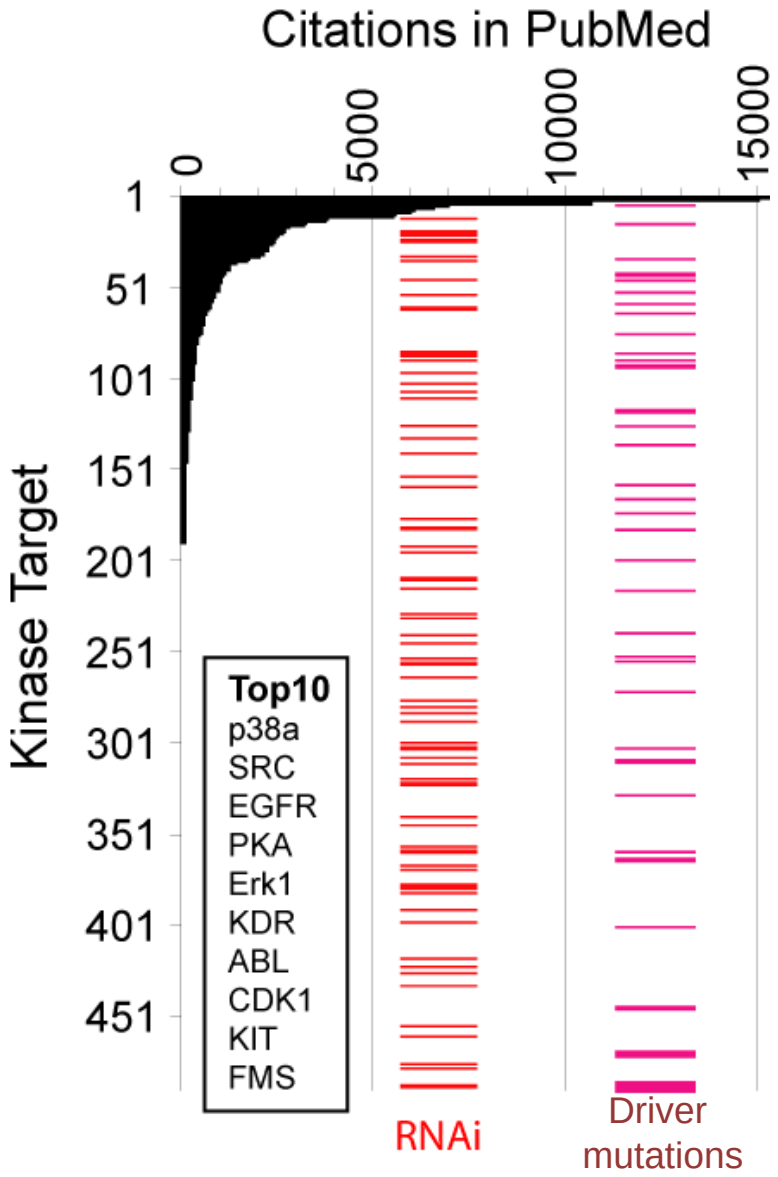
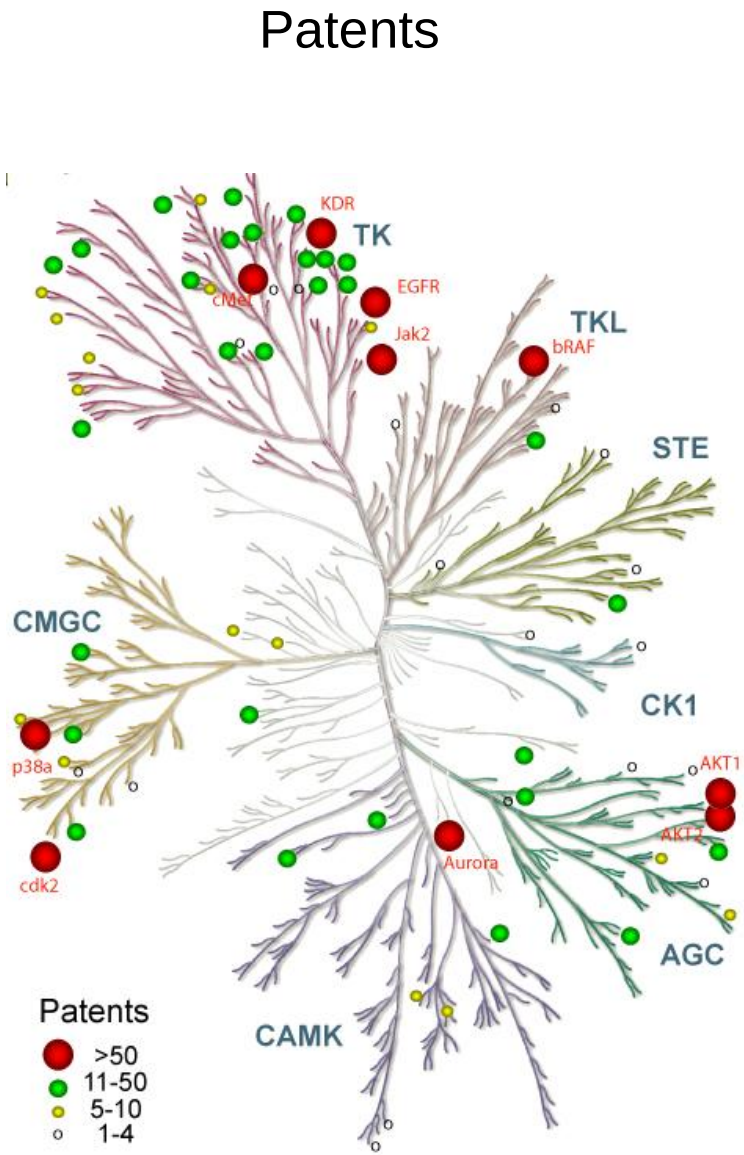
10 years post-genome: The proteome remains underexplored

Protein kinase citation patterns (the "Harlow-Knapp Effect")





2. Agree on clear mandate and use top-down decision making

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Clear mandate

- 1000 3D structures of therapeutically relevant human targets (selected by funders)

- 100 3D structures of parasite drug targets

Simple top-down organization

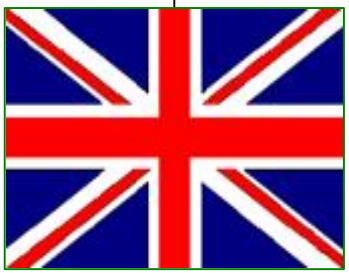
CIHR, Genome Canada, GSK, Merck, Novartis,, Ontario, Sweden, Wellcome Trust

Board of Directors — Wayne Hendrickson, Columbia, Chair

Funder nominated →

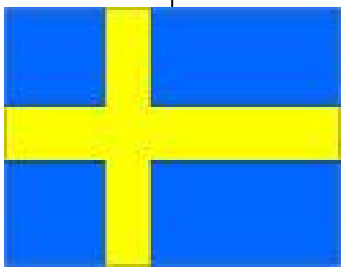
Scientific Committee — Kirk Clark, Novartis, Chair

Chief Executive
Aled Edwards



SGC-Oxford, ~90 staff
Chief Scientist
Chas Bountra

SGC-Toronto, ~95 staff
Chief Scientist
Cheryl Arrowsmith



SGC-Stockholm, ~30 staff
Chief Scientist
Johan Weigelt

3. Generate clear rules for IP

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SGC does not take out IP

- Collaborate quickly with any scientist, lab or institution
- Work closely with multiple private organisations, on same project
- Generate data quickly
- Place data in public domain quickly

Has it worked?

- > 1,000 structures solved
  - SGC now contributes >30% of global output of human structures annually and 15% of total output
  - SGC contributes >40% of global output of human parasite structures annually
  - SGC generates each structure for ~$150,000 (including Cap Ex)

- Making impact in science

  Nature Methods. 6:477 (2009); **PLoS Biology** 7:384 (2009); **EMBO J.** 28:969 (2009); **J. Med. Chem.** 52:3108 (2009); **Nature Chemical Biology** 5:436 (2009); **J. Med. Chem.** 51:7053 (2009); **Cell** 136:352 (2009); **J. Med. Chem.** 52:6369 (2009); **Nature Methods** 6:477 (2009); **J. Med. Chem.** 52: 3108 (2009); **J. Clin. Invest.** 119:1350 (2009); **PNAS** 106: 1039 (2009); **J. Med. Chem**. 52(24):7950-3. (2009); **PNAS** 106:20198 (2009); **J. Med. Chem.** 53:1810 (2010); **Nature Chemical Biology** 6:166 (2010), **Nature Mol and Struct Biol.** 17:596 (2010); **Nature Chemical Biology** 6:359 (2010); **Nature** 464:728 (2010), **Nature** 465:359 (2010)

Keys to PPP success?

- Clear and quantifiable objectives
- Output must have value for all participants (publications for academics, deliverables for industry aligned with their internal interests)
- Leadership: if you can’t find the right person, don’t start. Don’t run project “by committee” or consensus
- If pre-competitive, take a “no IP” position
- Assume the best in collaborators!

Moving the pre-competitive boundary

Open access chemistry to accelerate Target Discovery

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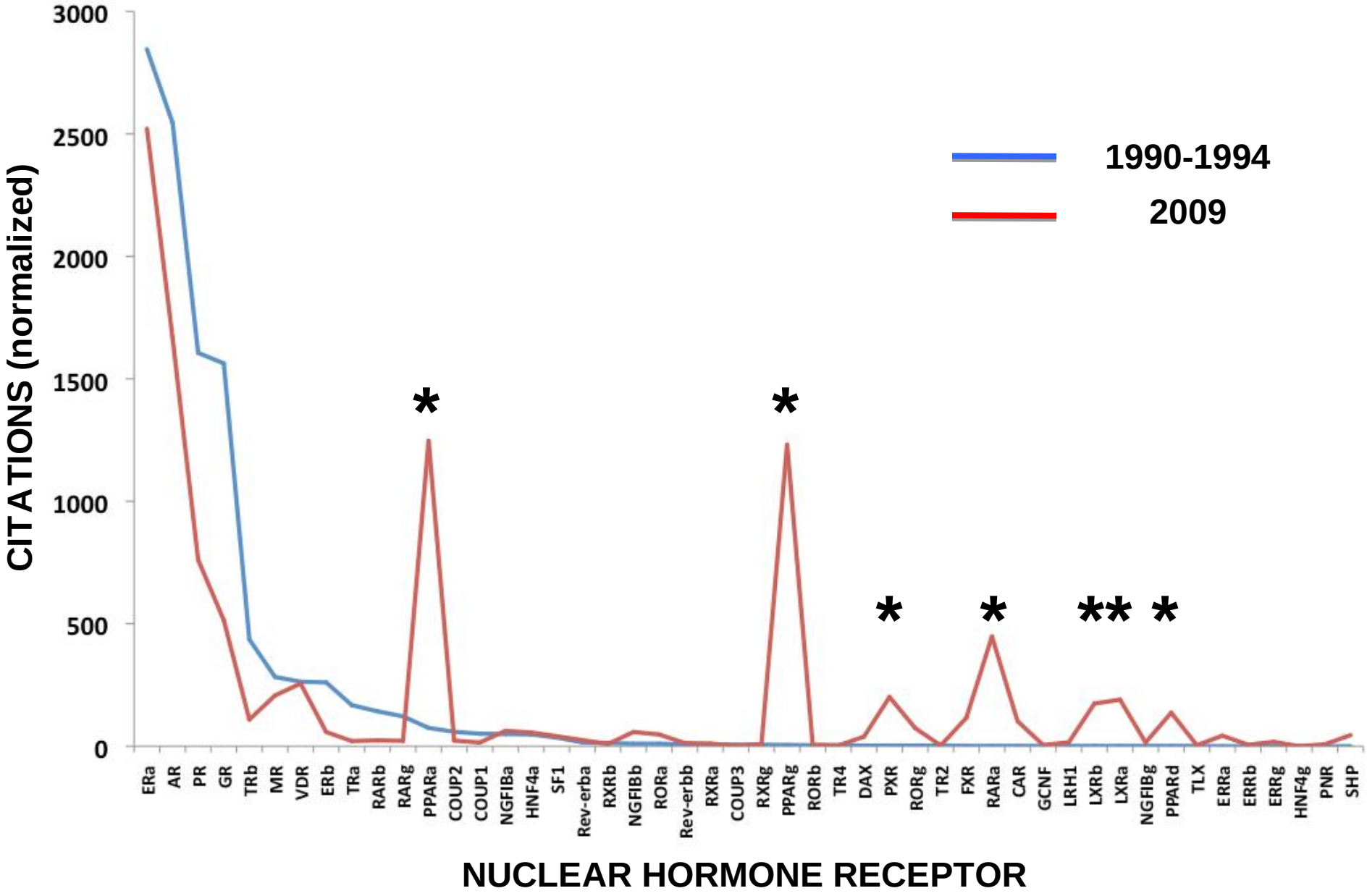
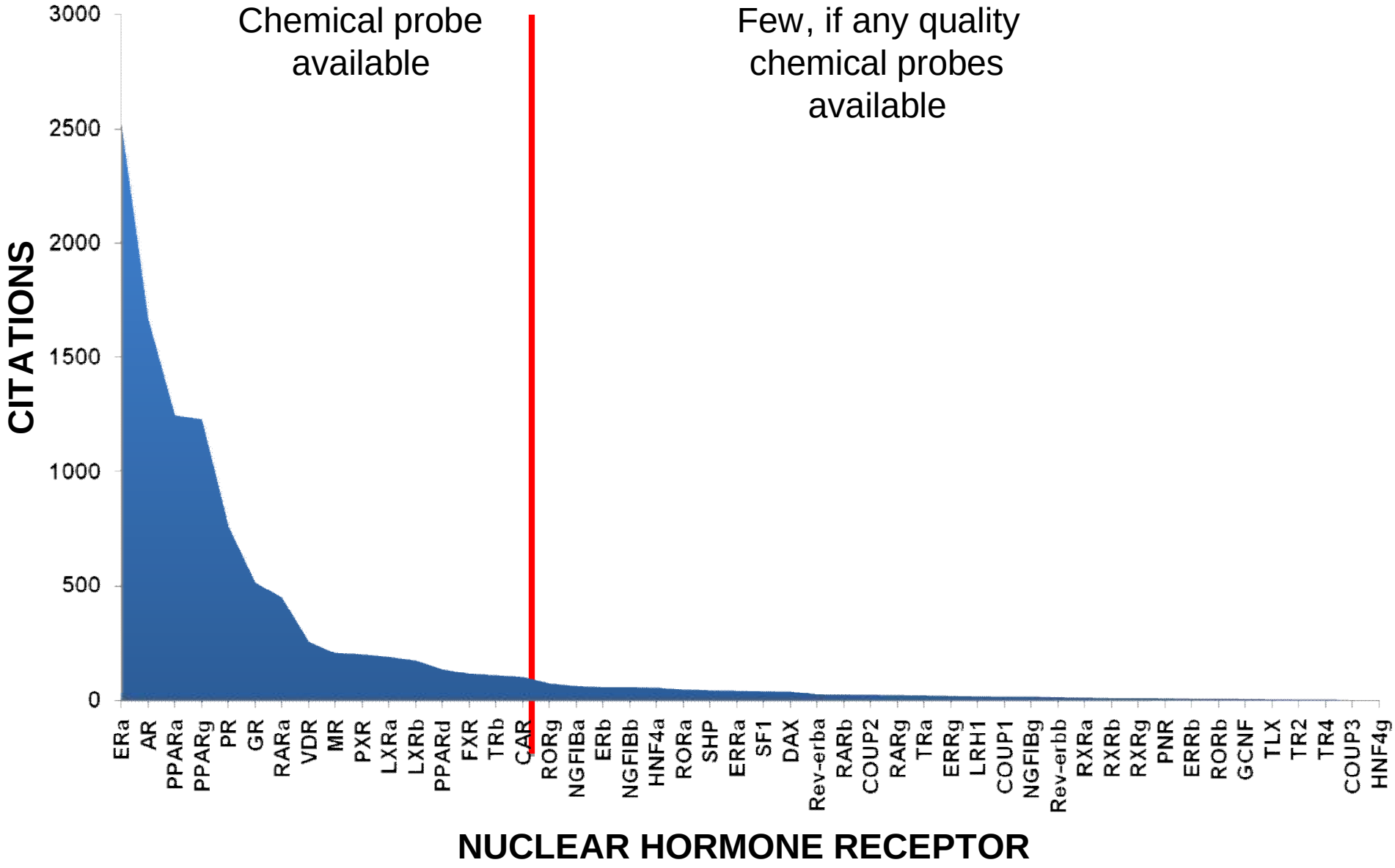
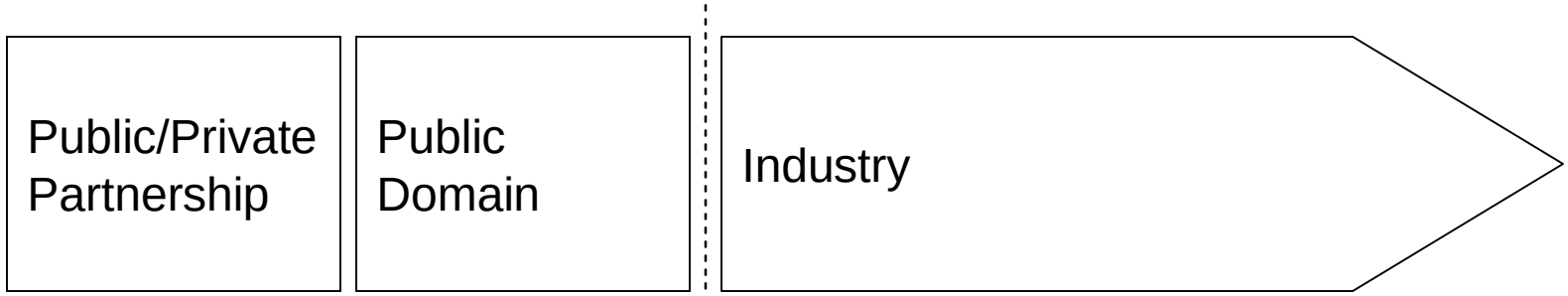
Nuclear receptors: The H-K Effect, with a twist



Tools may be the key to overcome the F-K Effect



The Model for Pre-Competitive Chemistry



Chemical Probes

Screening
Chemistry
Cell-based Assays

Target Exploration

No IP
No restrictions
Publication

Drug Discovery

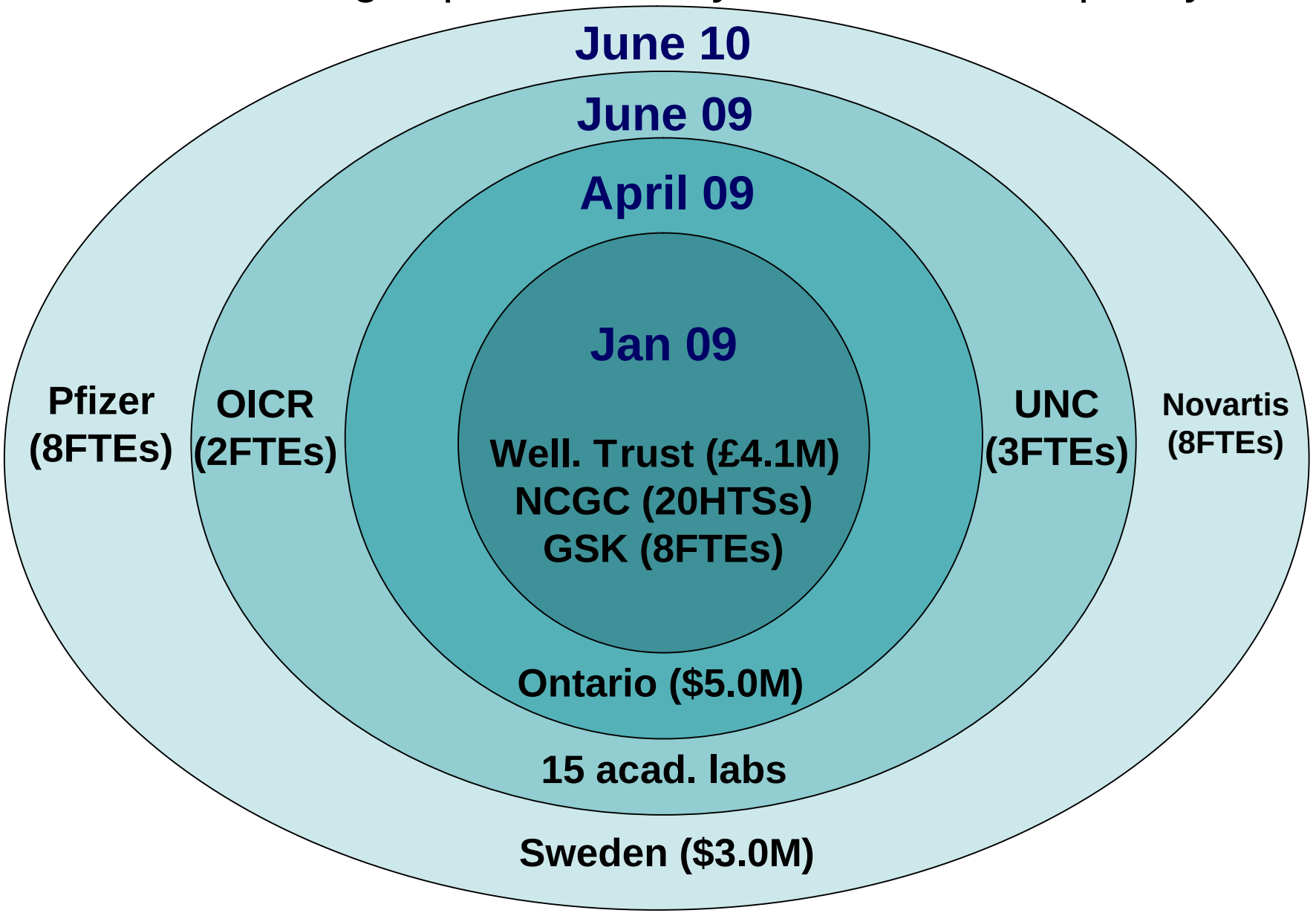
(re)Screening
Chemistry
Lead optimization
Pharmacology
DMPK
Toxicology
Chemical development
Clinical development

Creative commons

Proprietary

Epigenetics Chemical Probes Consortium

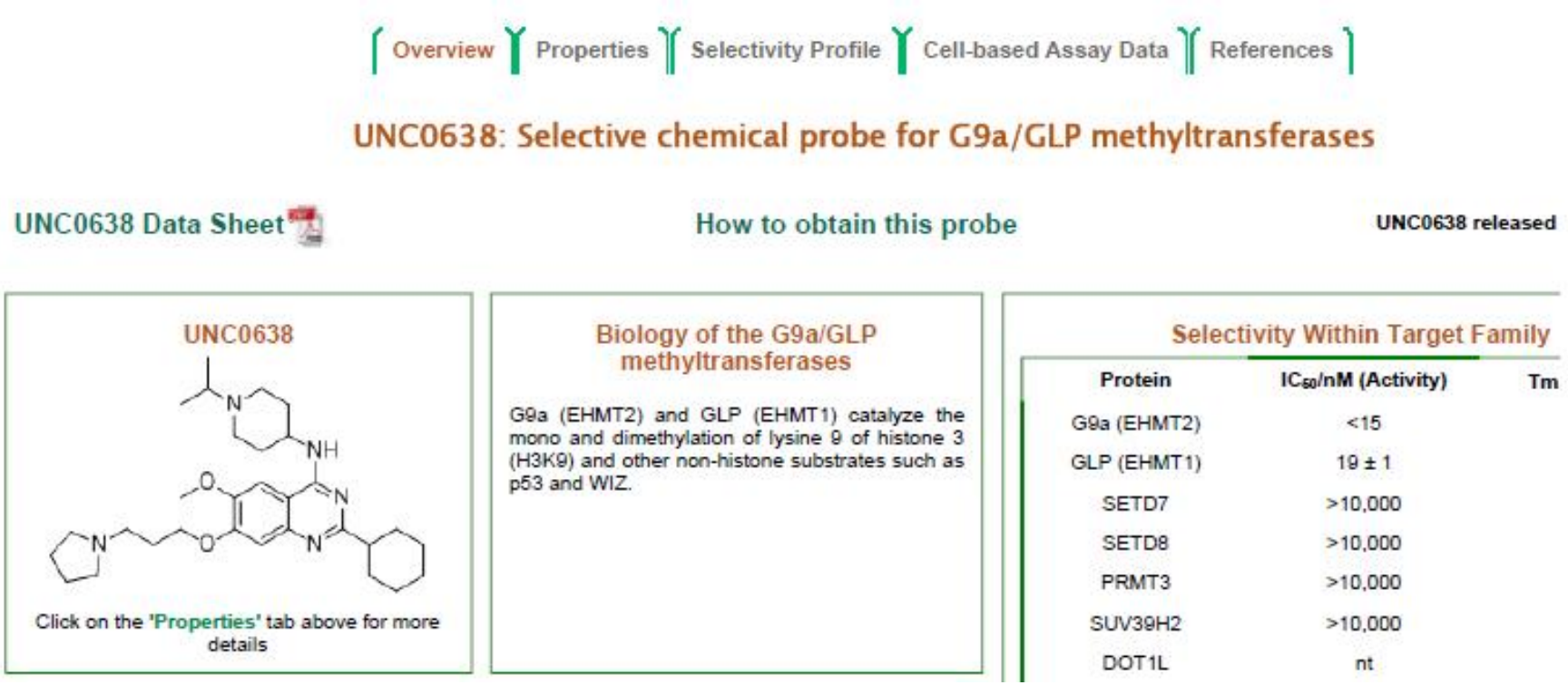
Accessing expertise, assays and resource quickly



….more than $50M of resource

Chemical Probe Consortium Released UNC0638 as a Chemical Probe on June 1st

http://www.thesgc.org/chemical_probes/UNC0638/#overview



- **Data released prior to publication. Living document that is updated as new data are generated**

Collaborators Who Are Using UNC0638

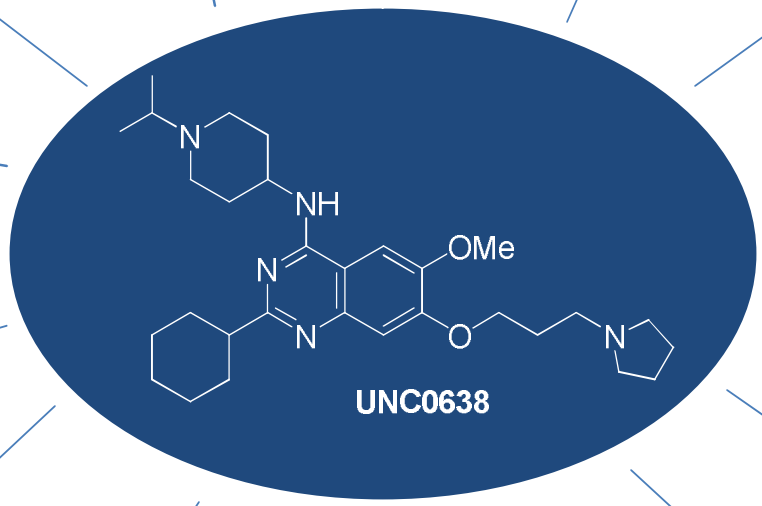
Mark Minden (OCI)
Test on EVI-1 expressing leukemia cells

Jayne Danska (Sick Kids, Toronto)
Test on large panel of ALL cells

Jay Bradner (Dana Farber/Broad Inst)
Test on MLL dependent leukemic cells
Effects on epigenetic markers

Rob Bristow (OCI)
Test on prostate cancer cell lines

Alex Tarakhovsky (Rockefeller)
IFN production after viral infection
Viral resistance
Changes of epigenetic markers



Ben Garcia (Princeton)
MS assessment of histone methylation levels

James Ellis (Sick Kids, Toronto)
iPS cell studies

David Margolis (UNC)
Effects on HIV-1 latency

Bryan Roth (UNC)
Effects on cocaine addiction

Michael Taylor (Sick Kids Hosp)
Test on DAOY cell line (meduloblastoma)

Martin Hirst (UBC)
ChIP-seq

Jing Huang (NCI, NIH)
Bill Janzen (UNC)
p53 methylation
Apoptosis of MCF7 cells

Rod Bremner (TWRI)
Assess effect on IFN expression

Open access PoC studies

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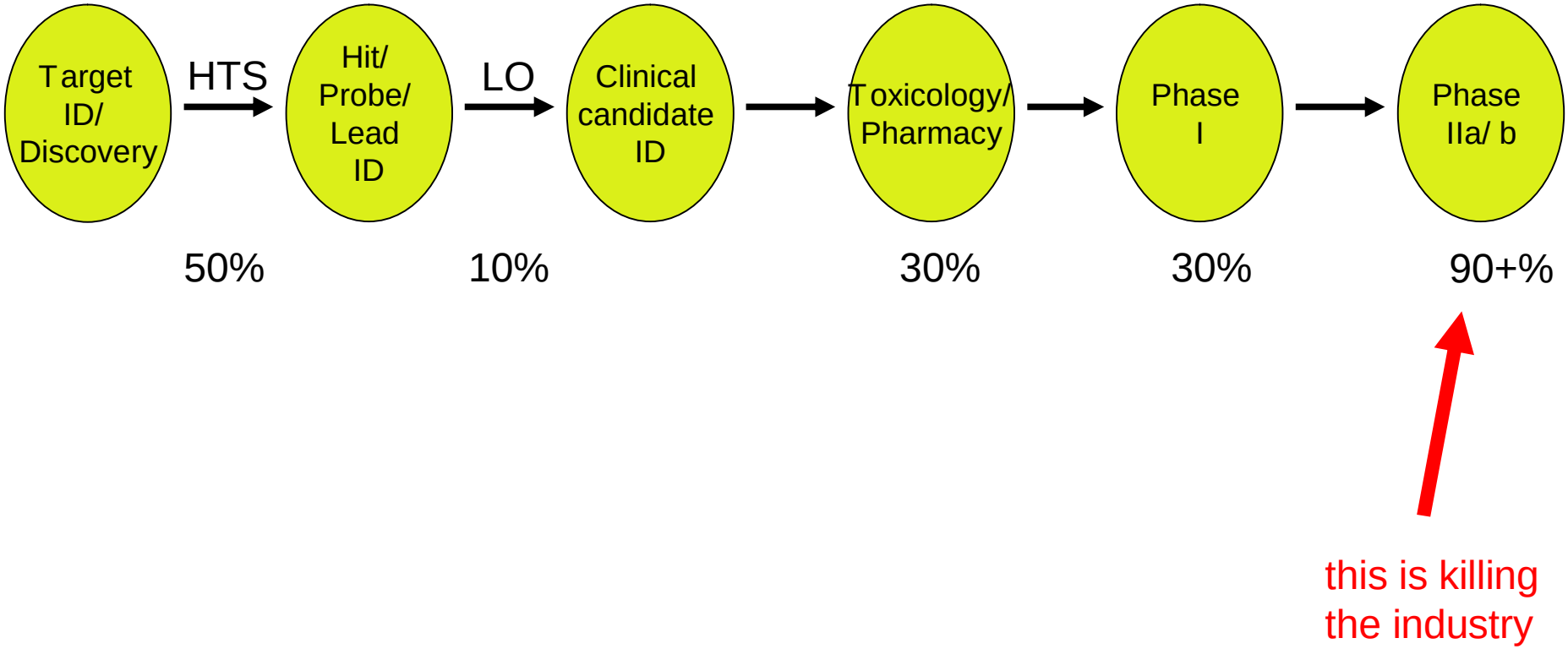
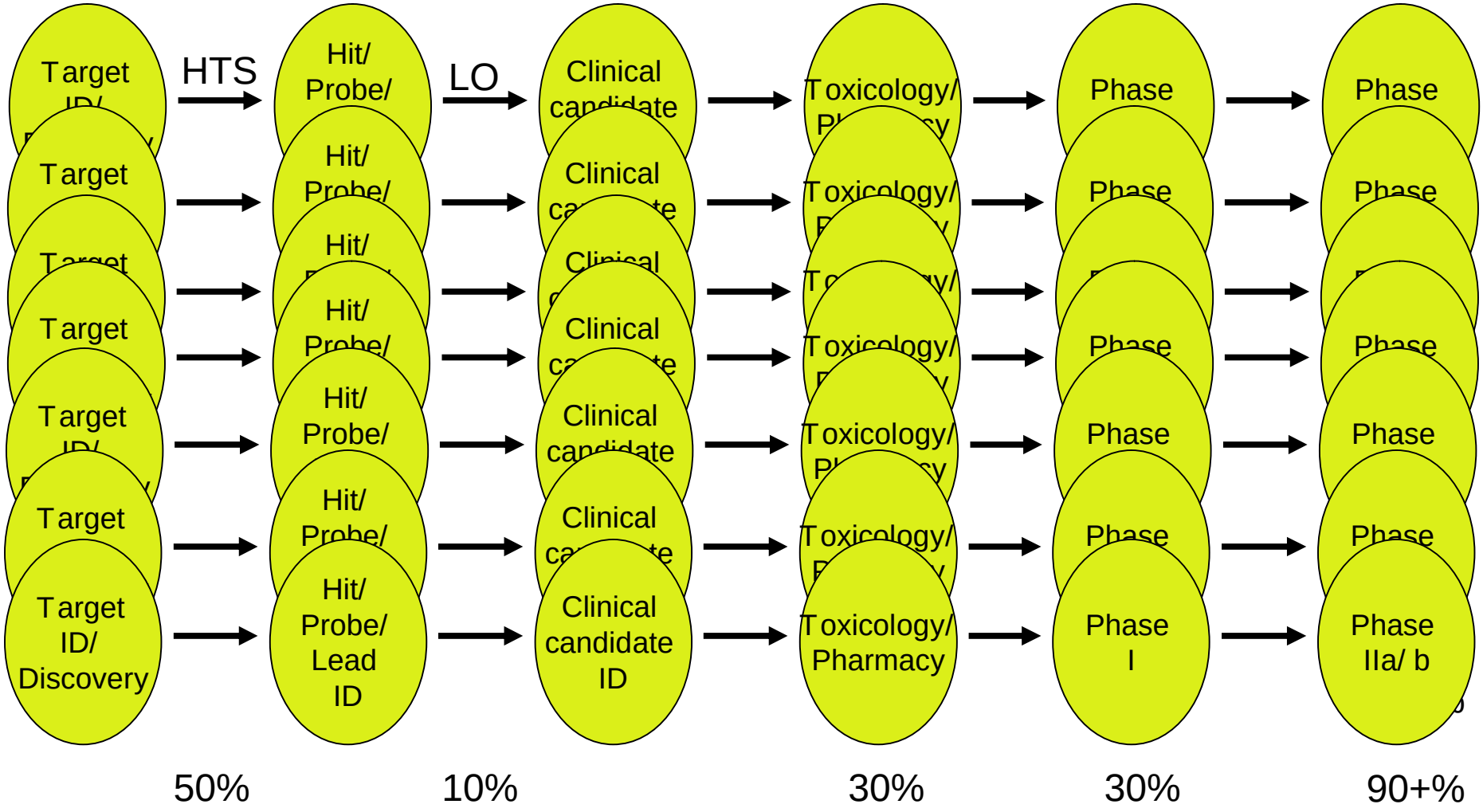
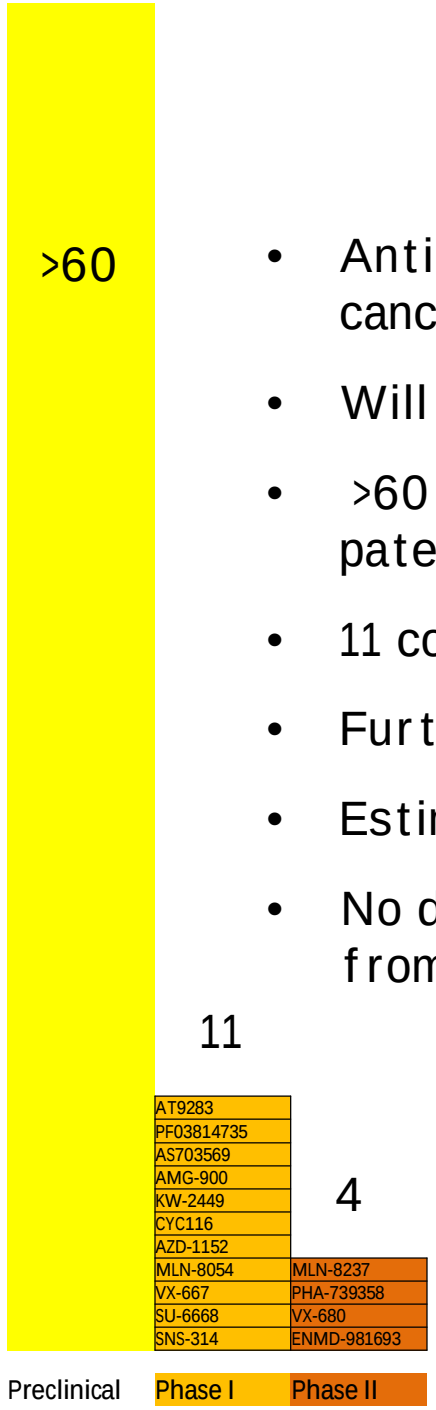
Largest attrition in drug discovery for novel targets is at clinical POC



And most drug programs are done in duplicate

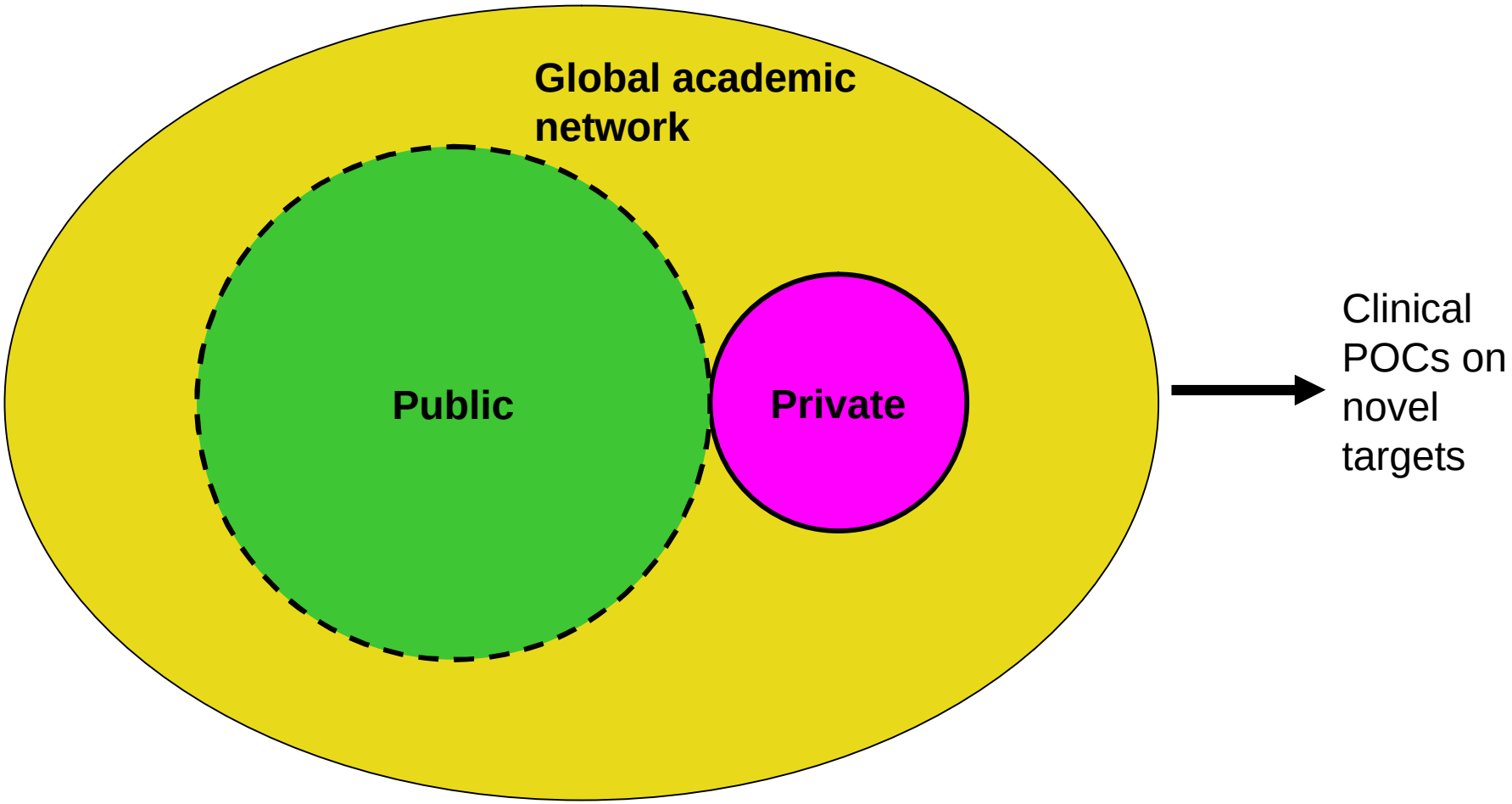


Aurora Kinase Inhibitors



- Antimitotic kinase – potential treatment for numerous cancer types
- Will also affect healthy proliferating cells – risk of low TI
- >60 separate organizations have pre-clinical programs with patents
- 11 compounds in Phase I
- Further 4 compounds in Phase II
- Estimated total expenditure >£200M
- No data available on outcomes of clinical studies, apart from rumours

Global PPP to deliver clinical PoCs on novel targets (with no IP)



How to organize it?

- A charitable consortium comprising public funders, charities, industry, regulators and patient groups
- All participants have voice in research priorities
- Top-down objective of PPP is to generate clinical PoC for 40 (?) novel targets by funding research anywhere
- All results into public domain, from med chem to PK/PD and tox to clinical data