

SGC:
catalysing the discovery of new medicines
through open access research

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SGC Toronto



SGC Oxford

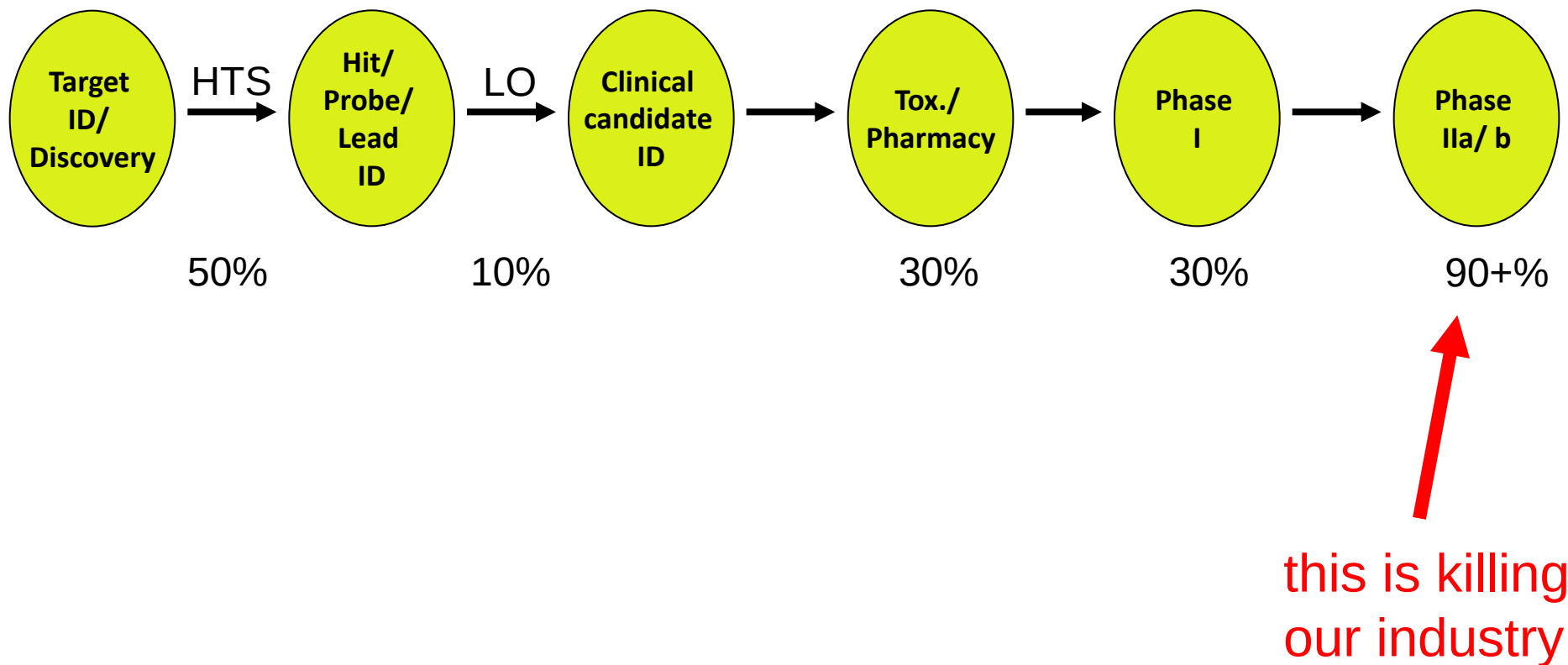
Situation 1

- R&D becoming unaffordable
- Many new medicines becoming unaffordable
- Need for new medicines is increasing
- Massive duplication in biomedical research
- Most targets/ assets fail in Phase II

Situation 2

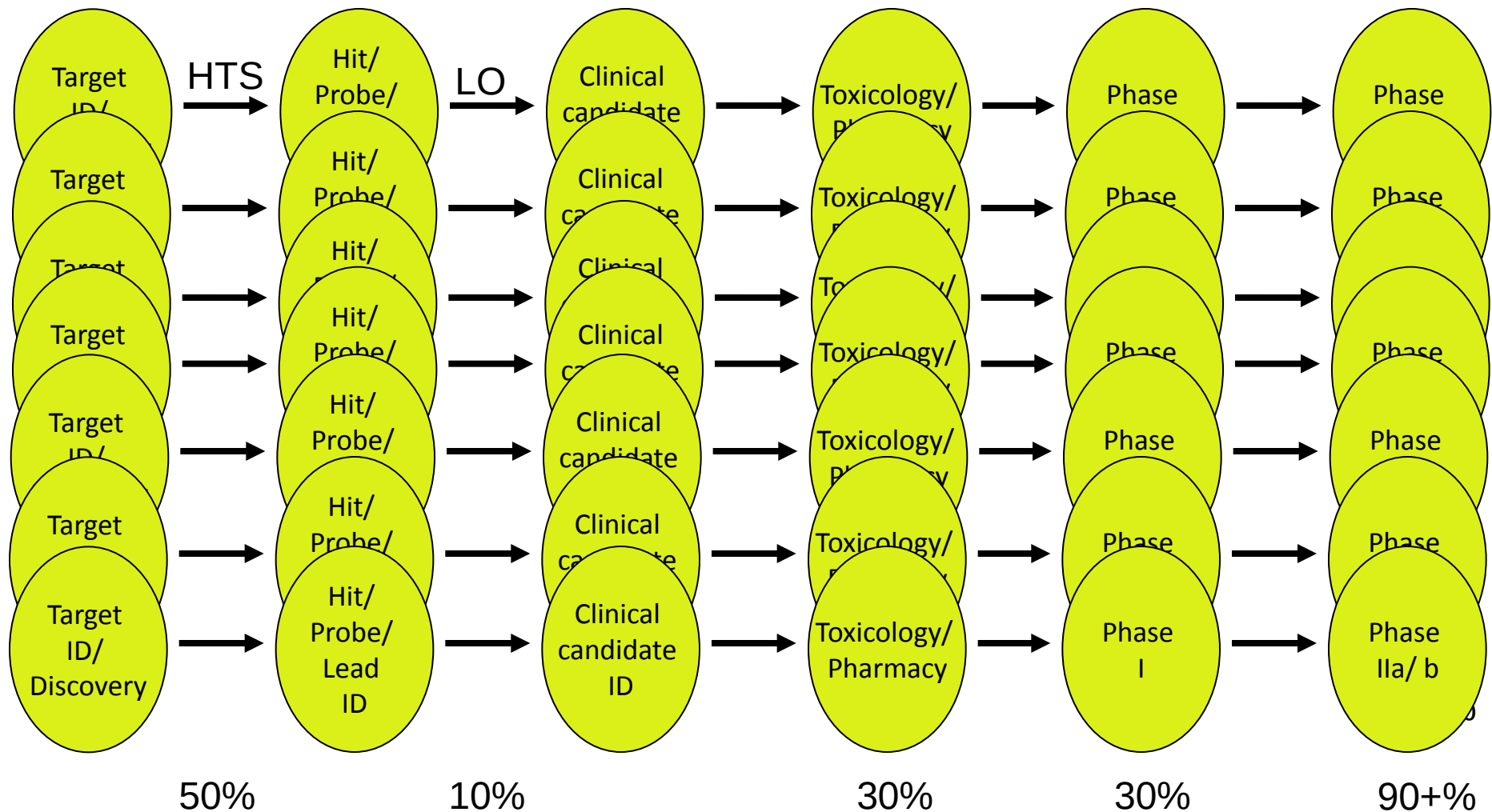
- Poor understanding of human disease: inadequate biomarkers, poorly predictive pre-clinical assays
- Pharma has many strengths: HTS, LO, Tox, ADME, Pharma dev, IIb/ III clinical studies
- Academia has better access to clinicians, patients, patient materials and patient databases, but lacks good tools

Nearly all novel targets fail at clinical POC



...we can generate “safe” molecules, but they are not developable in chosen patient group

This failure is repeated, many times



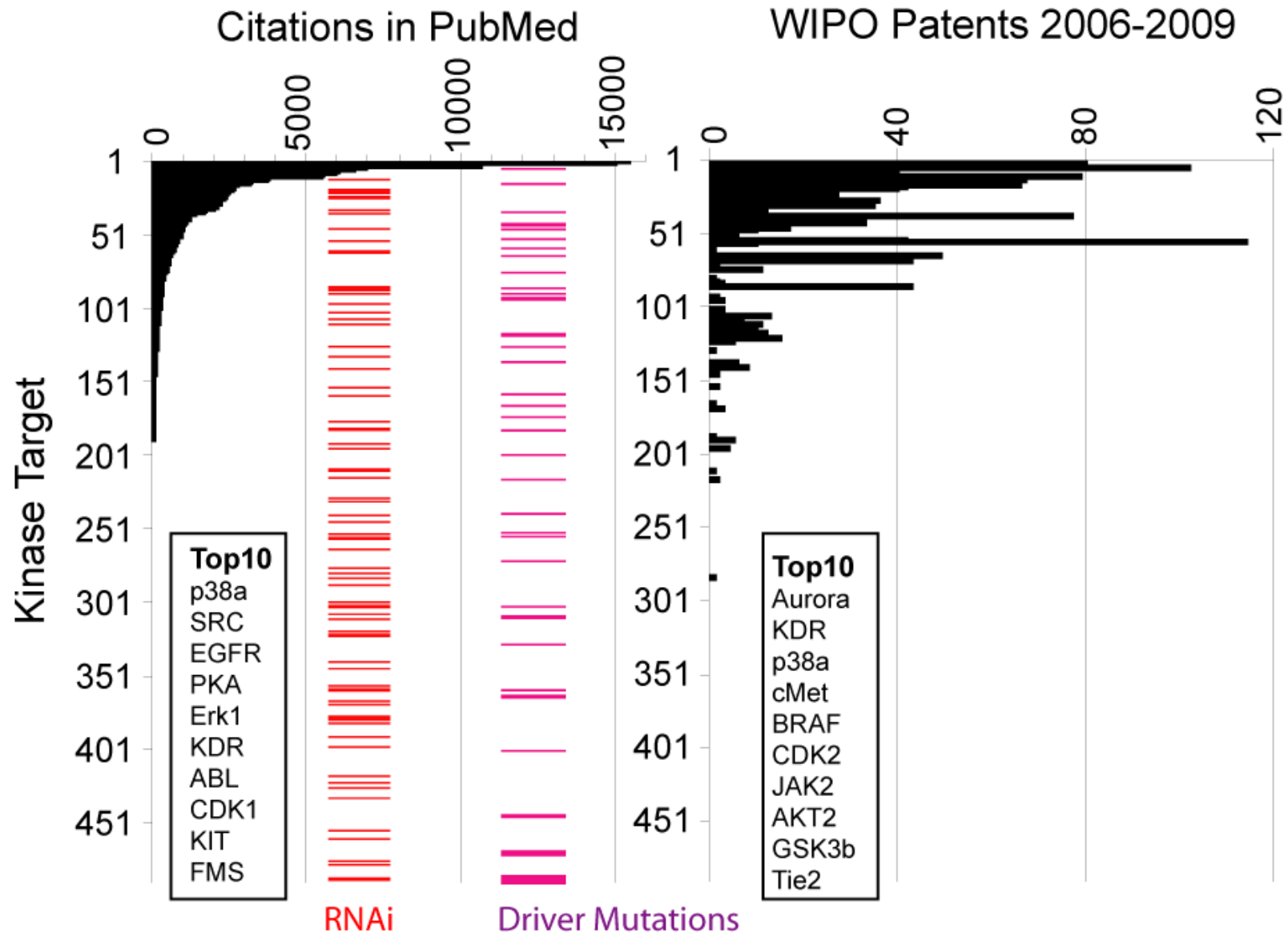
...and outcomes are not shared

All Phase III trials in AD have failed

<u>Agent</u>	<u>Target/Mechanism</u>	<u>Outcome</u>
Atorvastatin	HMG CoA reductase	Negative
Dimebon	Mitochondrial function	Negative
LY450139	Gamma secretase	Negative
NSAIDs	Inflammation	Negative
Phenserine	Cholinesterase/Amyloid	Negative
Rosiglitazone	PPAR gamma agonist	Negative
Simvastatin	HMG CoA reductase	Negative
Tarenflurbil	Gamma secretase	Negative
Xaliproden	Serotonin antagonist	Negative
Bapineuzumab	amyloid beta (passive immunization)	Negative
Solanezumab	amyloid beta (passive immunization)	Negative*
IVIG	amyloid beta (passive immunization)	Negative

* Benefit in mild: will be tested in A4 and DIAN trials (amyloid positive, pre-symptomatic and mild AD)

We tend to work under the lamp post



The solution is:

- Increase our knowledge-base
- Bring together best people irrespective of organisation
- Pool resources
- Do it quickly (delay IP)
- Identify the 1 in 10 target that shows efficacy in patients, then compete

SGC works on new human proteins

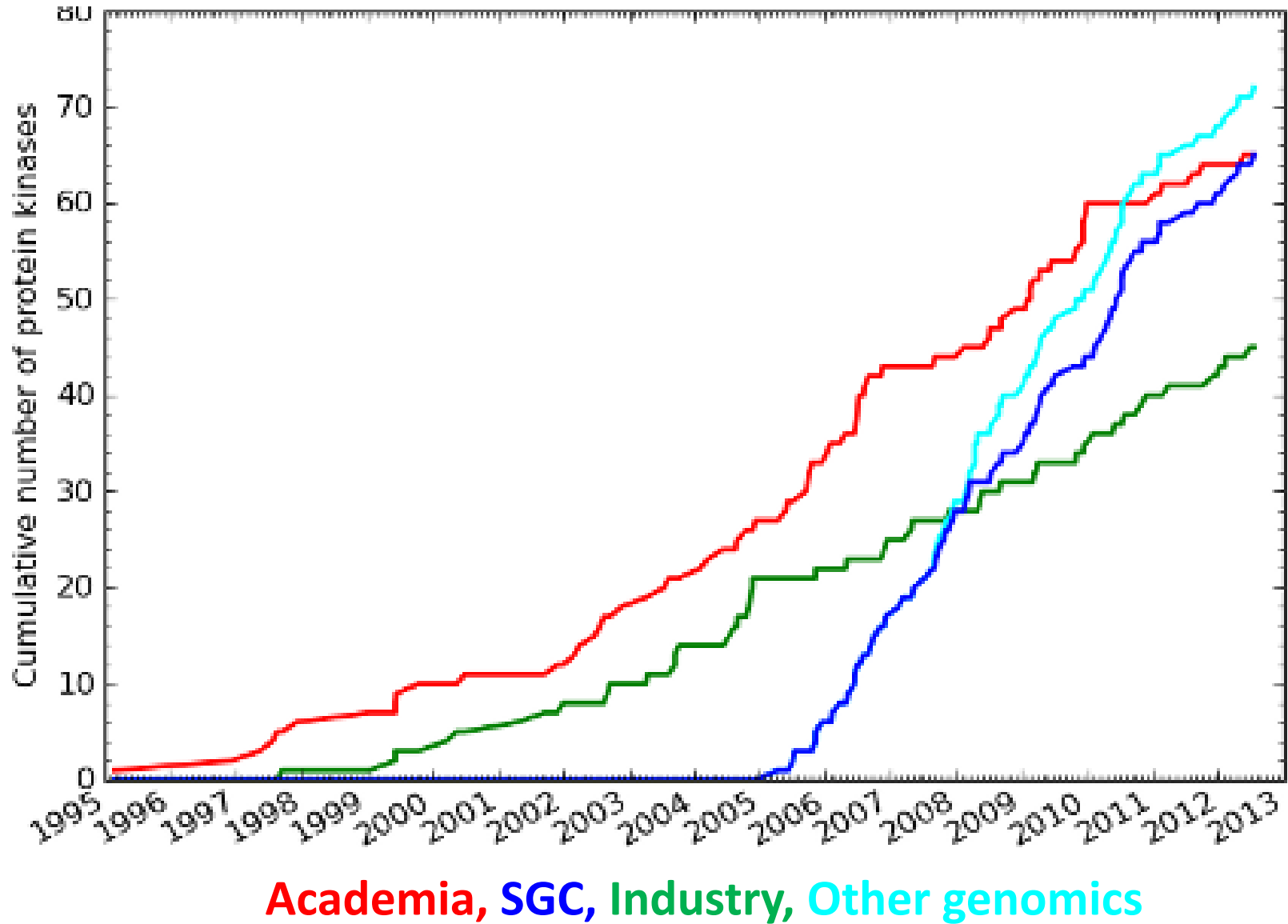
- Generate new target validation tools
  - Proteins
  - Assays
  - Inhibitors
  - Antibodies
  - Structures
- Everything made freely available

SGC has become a hub for:

- innovation
- pharma (9)
- academia (>250)

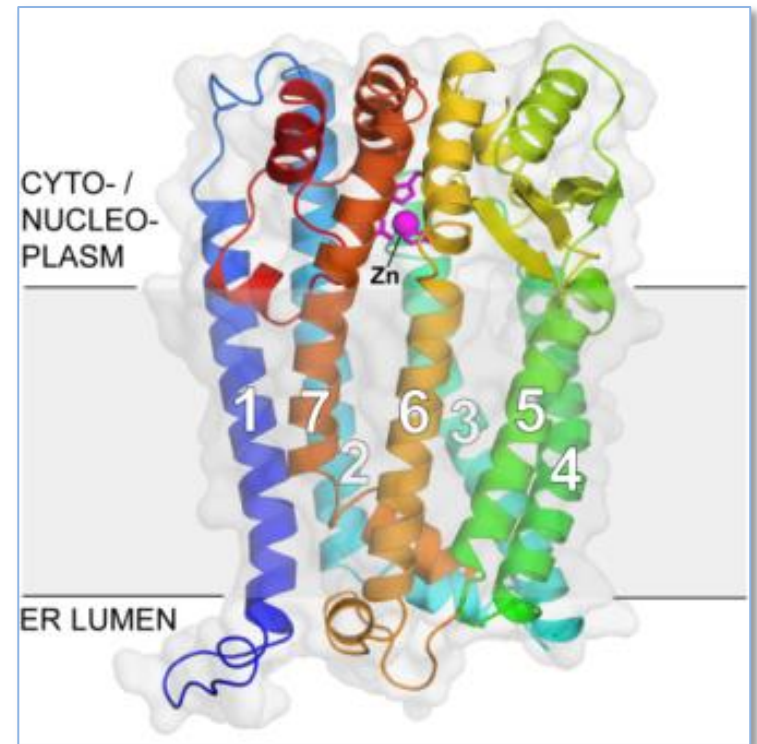
**...pool resources, share risk,
crowd-source early discovery**

Now solved as many kinase structures as rest of academia

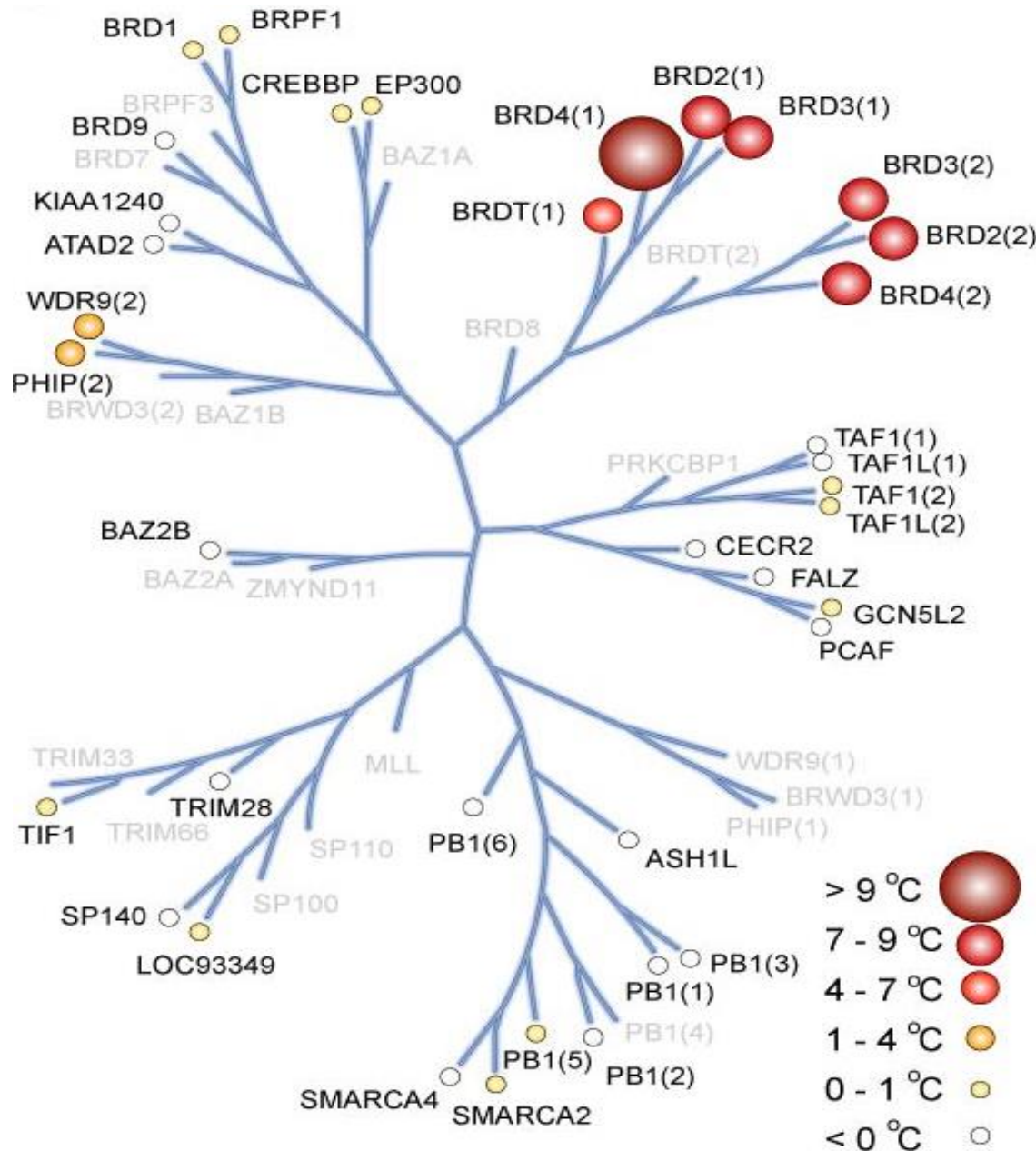
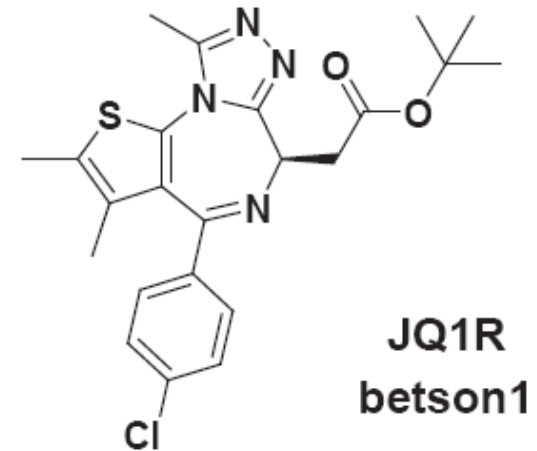
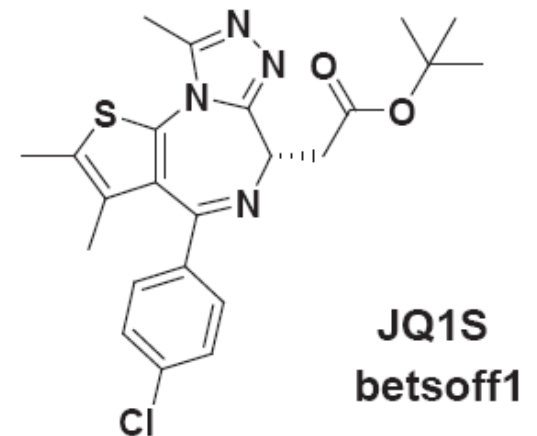


Rapid dissemination reduces wastage

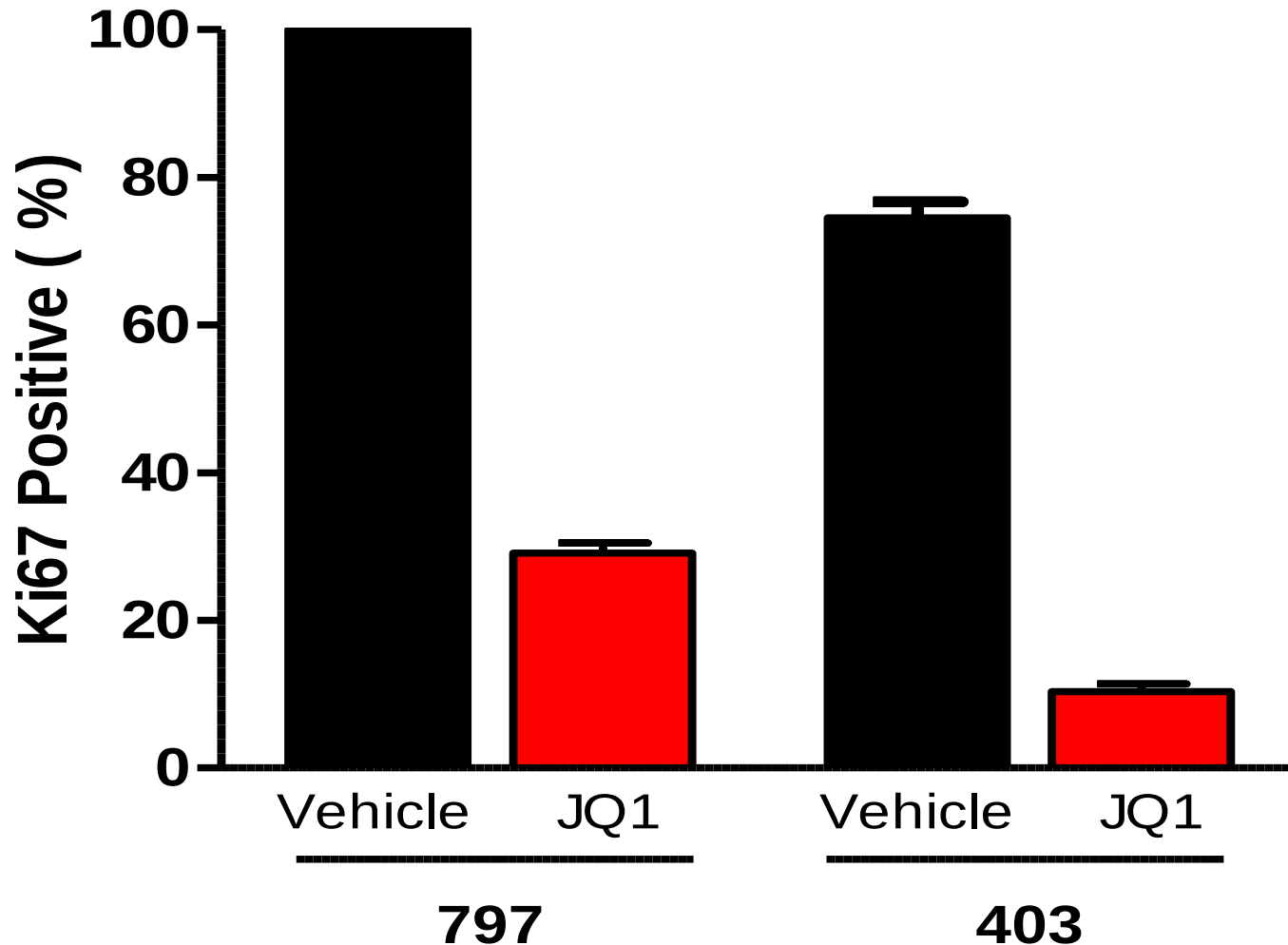
- **May 12**: Deposited structure of human membrane protein ZMPSTE24 (“premature ageing”)
- **Summer 12**: enabled another lab to solve yeast structure
- **Nov 12**: paper submitted
- **April 13**: both papers published together in Science



First inhibitor for BRD sub-family - JQ1

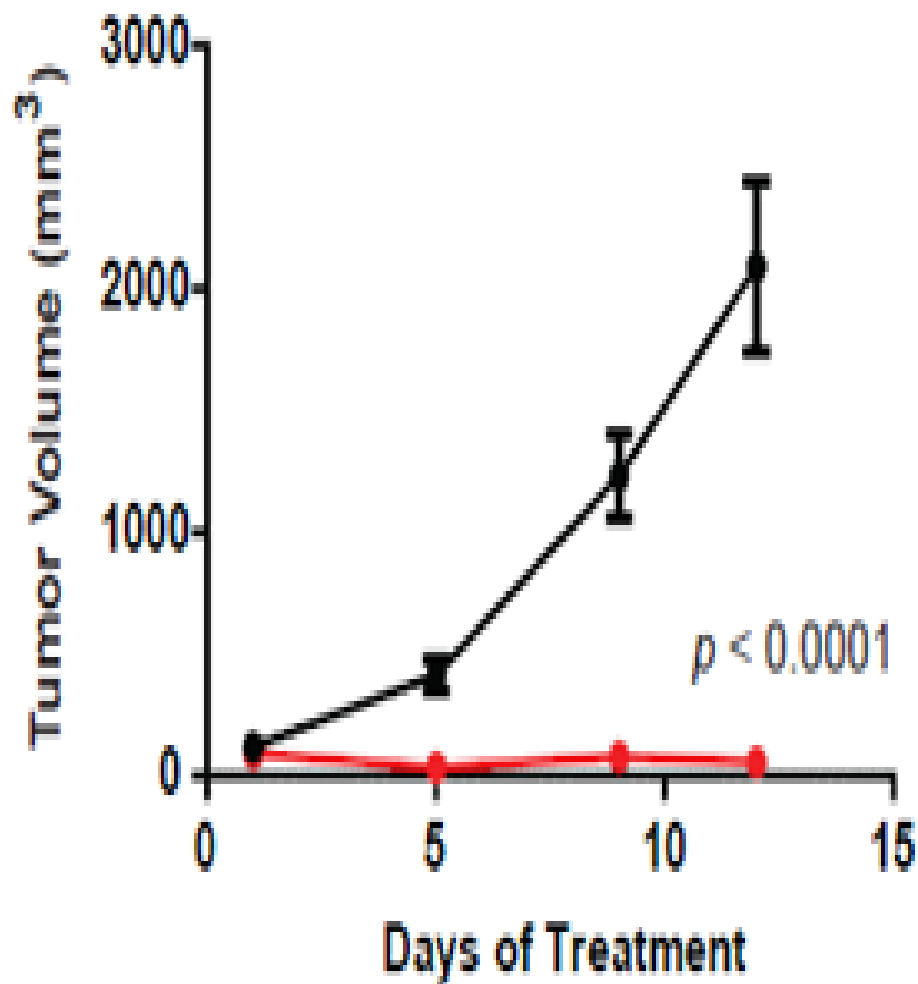
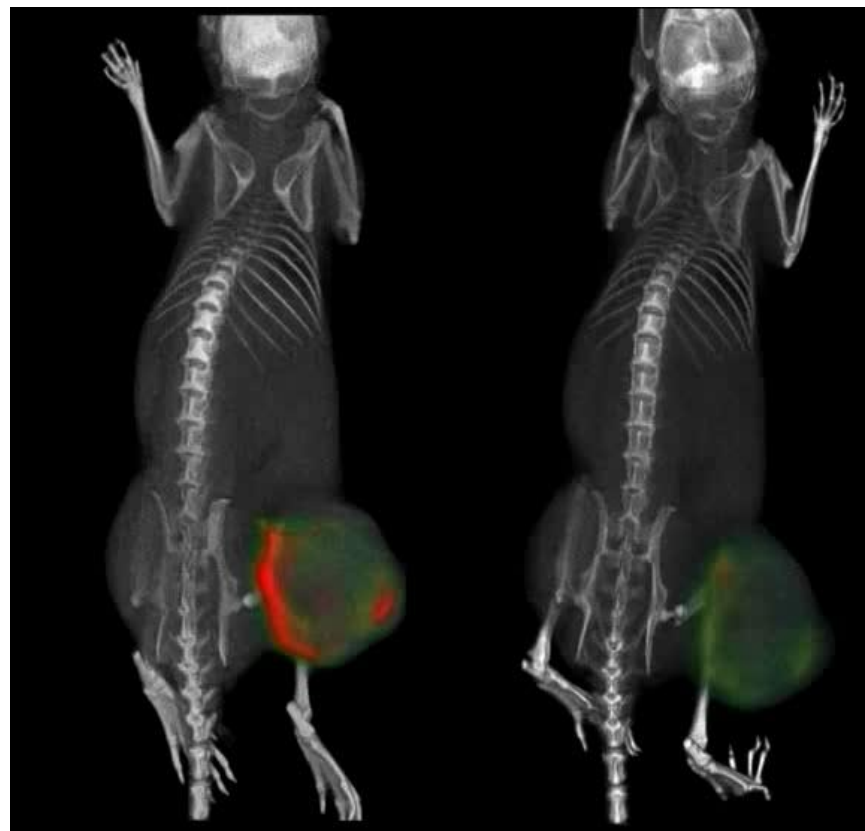


JQ1 reduces proliferation in NUT midline carcinoma



Ki67 positive = proliferating

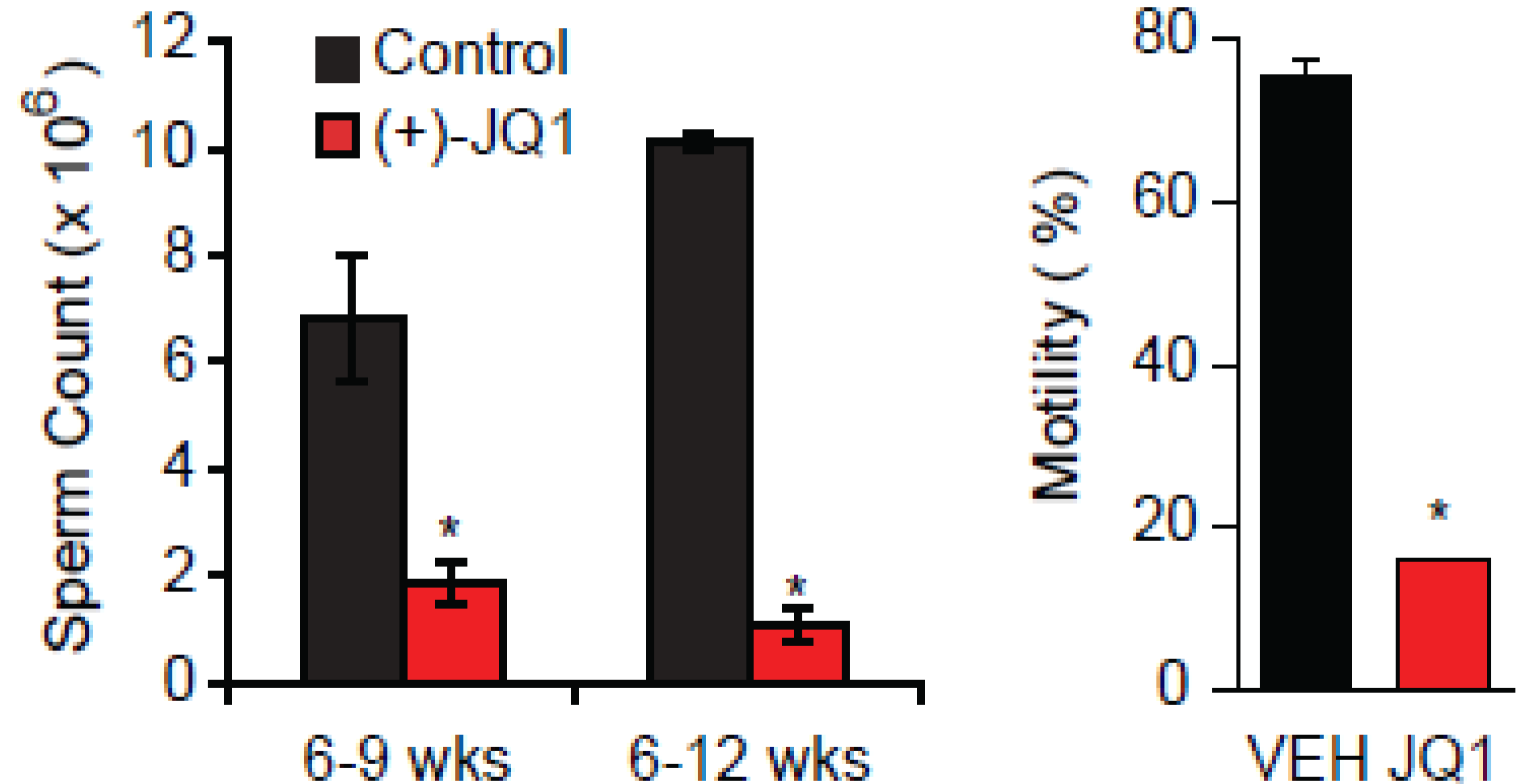
JQ1 reduces tumour size



JQ1 cancer publications

- NUT midline carcinoma
- AML/ CML
- Multiple myeloma
- Burkitts lymphoma
- B cell ALL
- B cell non Hodgkins lymphoma
- Erythroleukaemia
- Lung adenocarcinoma
- Merkel cell polyomavirus
- Papillomavirus
- Epstein Barr virus
- Glioblastoma
- Neuroblastoma
- B cell lymphoma
- Prostate
- Primary effusion lymphoma
- Metastatic melanoma

JQ1 reduces sperm count and motility

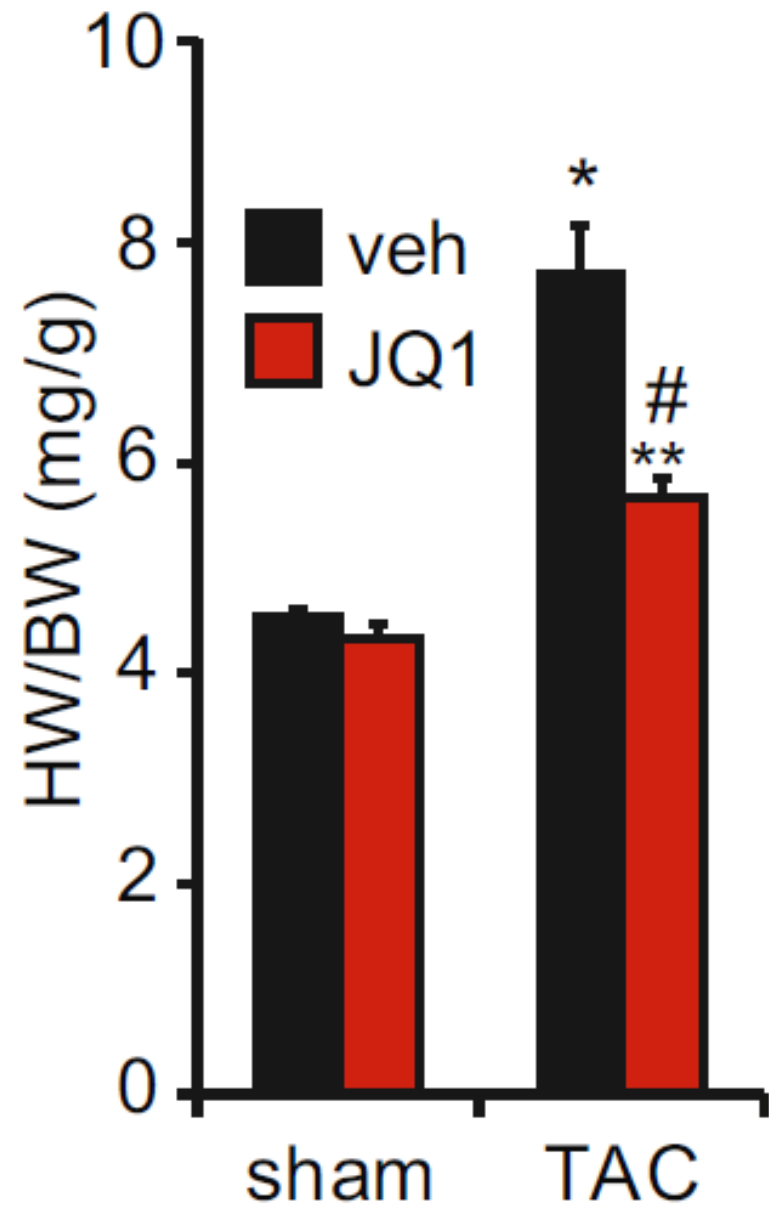


JQ1 reverses cardiac hypertrophy

JQ1: 1.5-28 days post TAC

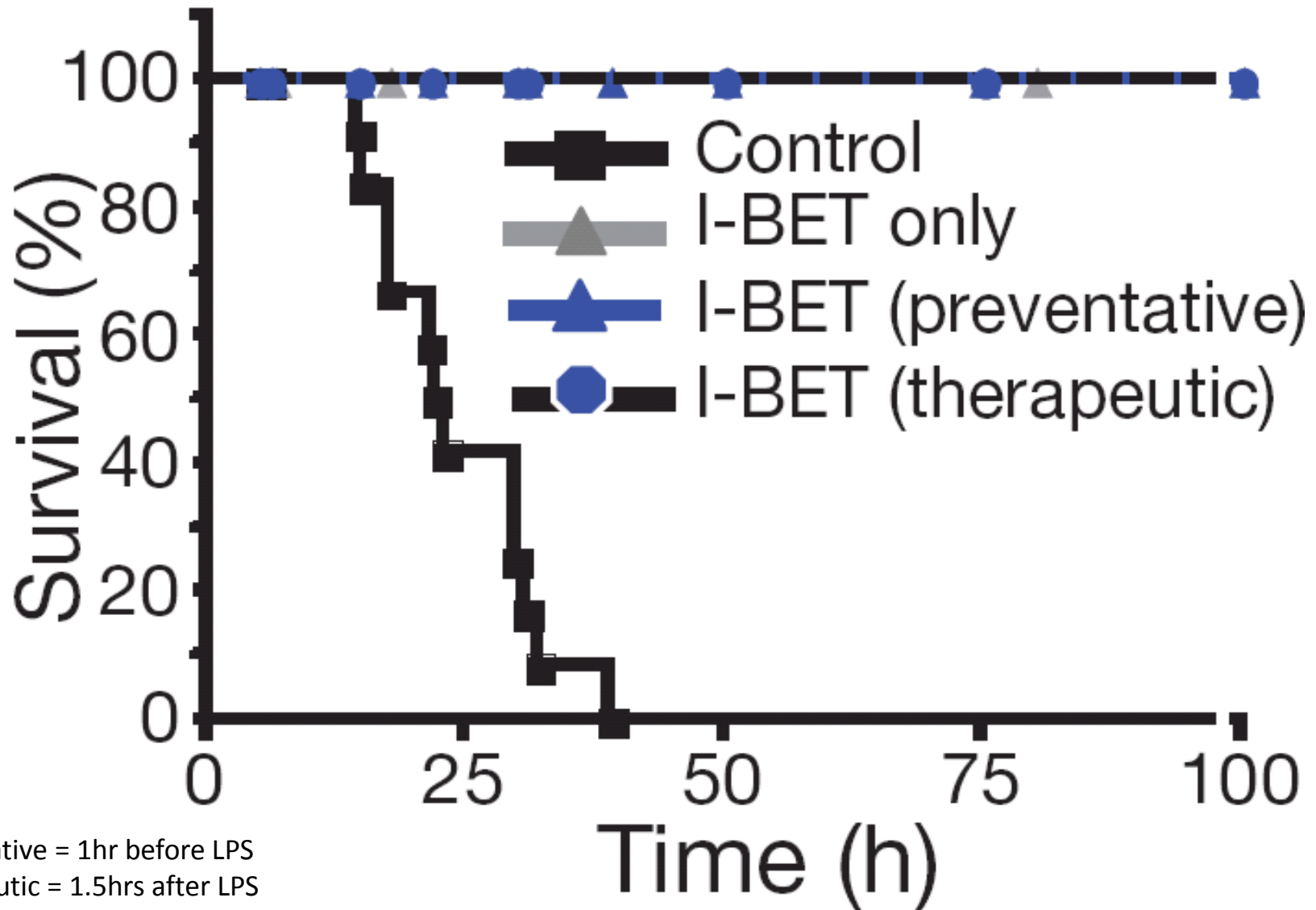
HW: heart weight

BW: body weight



Anand (2013), Cell, 154, 569

I-BET762 prevents and inhibits LPS induced endotoxic shock



Preventative = 1hr before LPS
Therapeutic = 1.5hrs after LPS
C57BL/6 mice

JQ1: Impact on science & drug discovery

- Distributed to >400 labs/companies
- Published Dec 2010. By May 2013
  - cited >200 times
  - further 172 papers
- Started proprietary efforts
  - now 6 molecules in clinic
- Collaborator created spin off
  - Tensha: \$15 M seed funding

Pipeline (Nov 13)

Screening / Chemistry

Probe/
Tool

Potent &
Selective

Potent

Weak

None

2 PRMT3

BRPF1B SUV39H2 53BP1
PCAF SUV420H1 L3MBTL1
FALZ SETD2 SPIN1
PB1/SMARCA
EP300

MLL LSD1
3 MMSET UHRF1
NSD3 2 SND1
SETDB1

BAZ1B SMYD3 JMJD2B
WDR9 MLL3 JMJD2C
EZH1 PRMT1 JMJD2A
SUV420 PRMT8
NSD1 PRMT6

In vitro assay

BRD9
FBXL11

CECR2 SETD8
BAZ2B/A 2nd JMJD2 3rd
CREBBP 3rd JARID1C
TIF1α 2nd JMJD3 3rd
CECR2

ATAD2
PHIP

BRD7
JARID1A

Cell assay

BET G9a/GLP JMJD3
BET 2nd G9a/GLP 2nd L3MBTL3
CREBBP G9a/GLP 3rd WDR5
CREBBP 2nd DOT1L Pan 2-OG
SMARCA4 SETD7 PHD2
BAZ2B/A EZH2
Bromosporine EZH2 2nd

TIF1α
SMYD2
PRMT5
LSD1
JMJD2

BRD1
JMJD1
JMJD2 2nd

Cell activity

BRD

HAT

(H)MT

KDM

Me Lys Binders

TUD

WD Domain

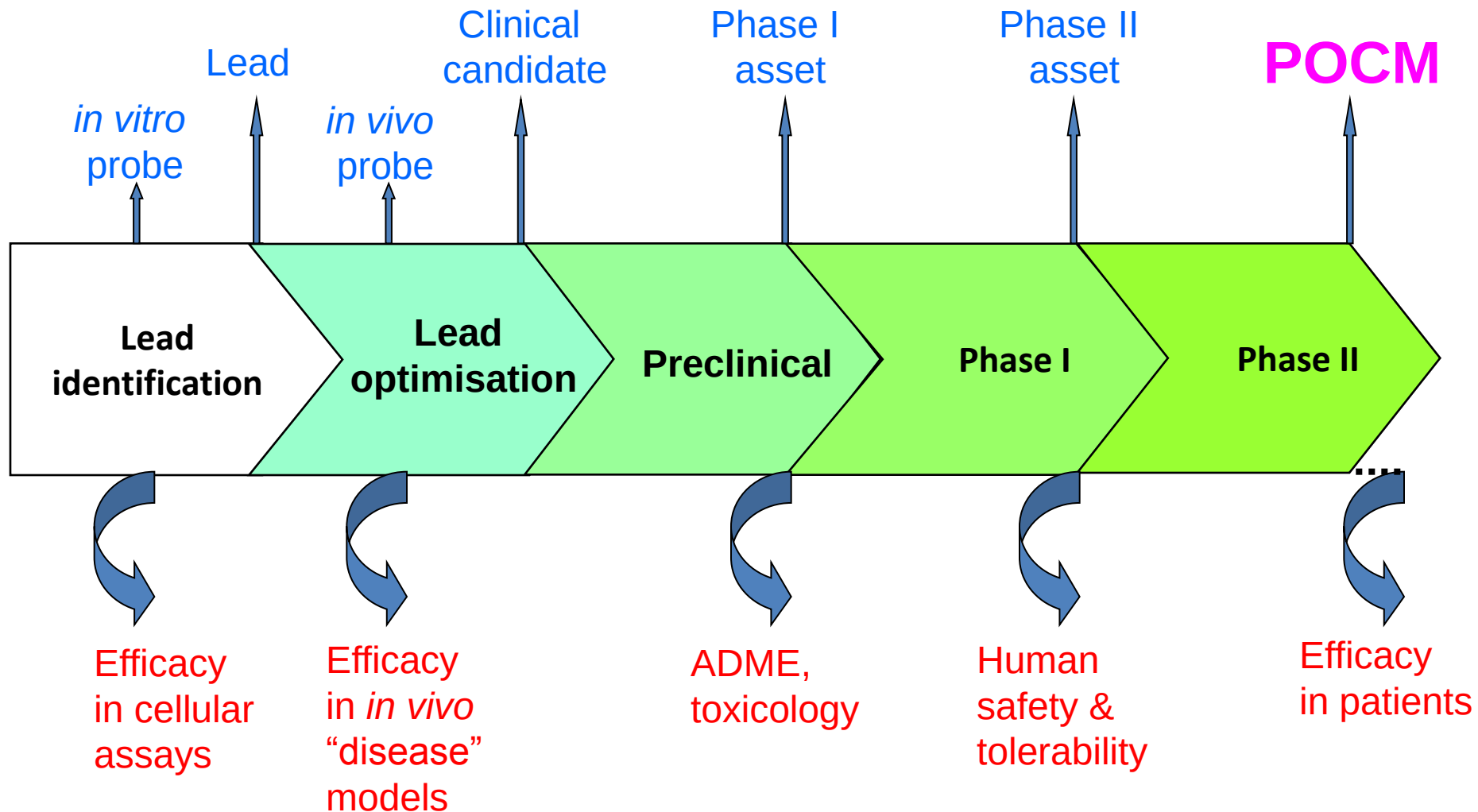
2OG Oxygenase

Pharma partner

Proposal: PPP to validate pioneer targets in patients

- Generate open clinical probes
- Evaluate in patients
- Identify 1/10 target that has potential to be a medicine
- Industry will then create proprietary assets
- Benefit for industry and patients

Reagents and **publications** will facilitate collaboration, leveraged funds, and **POCMs**



Patient groups will:

- facilitate recruitment
- minimise payments

Regulators will:

- help design new clinical studies
- help validate new biomarkers
- help pave path for new targets

Status

- Project initiated in cancer
  - with CRUK
- Takeda will fund new target for AD
  - (5 Feb 2014)
- Writing business plan for neuro-psychiatry
  - CIHR will seed with up to \$30M

Creating a new ecosystem for medicines discovery (in Oxford)

- **Biotechs** freely giving access to proprietary platforms
- **Patient groups** want to advance our outputs
- **CROs** want to commercialise our outputs
- Building **BioEscalator** to catalyse the creation of new biotechs
- Enabled creation of a new **Target Discovery Institute**
- Have facilitated funds for a **Big Data Institute**
- Have aggregated activity in **rare diseases**
- Are planning a new **Brain Institute**, a **Chemistry for Medicine Centre** and **human disease assay platforms** for improved target discovery

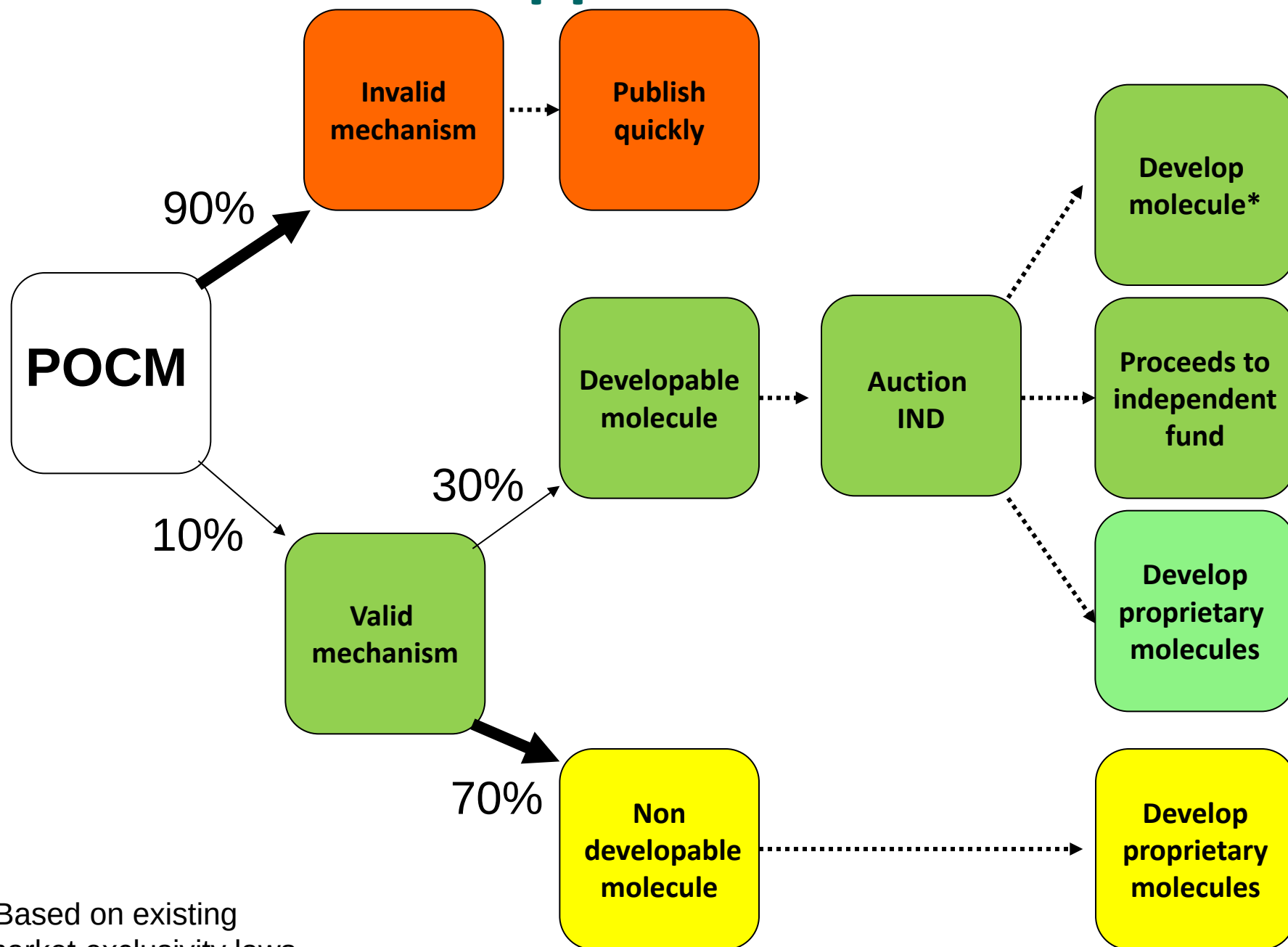
Summary

- Open reagents and rapid publications enable
  - Partnering with multiple companies
  - Fast collaborations with academics
  - Easier access to patient materials and patient databases
  - Reduces duplication and wastage
  - Catalyses science and drug discovery
  - Allows pooling of resources and sharing of risk

Acknowledgements

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- **GSK, Novartis, Pfizer, Lilly, Abbvie, Takeda, Janssen, BI, Bayer**

What happens after POCM?



*Based on existing market exclusivity laws

Crowd sourcing early discovery and target validation in patients

