SGC and Arch2POCM:

open access PPPs to develop research tools and de-risk novel targets in oncology

Drug discovery scene

1. Novel medicines and different treatment strategies are needed for many of society's unmet needs

2. Both public and private sector spending for health research has increased, but numbers of new medicines has remained constant

3. Industry, having let go 110,000 people in past two years, is looking to academia for "innovation" (and many are leaving important areas entirely, such as neuroscience)

4. Novel medicines are key to industry success

Issues with drug discovery

1. The greatest attrition is at clinical proof-of-concept – if a “target” is linked to a disease in the clinic, the risk of failure is far lower

2. Most novel targets are pursued by multiple companies in parallel in secret (and most fail at clinical POC)

3. Early IP is making it even harder (makes process slower, harder and more expensive)

4. The complete data from failed trials are rarely, if ever, released to the public

Conclusions

1. New targets probably fail at clinical PoC because we have a poor understanding of human disease

2. The current ways to support biomedical research and measure success are a big part of the problem

We need to build a path:

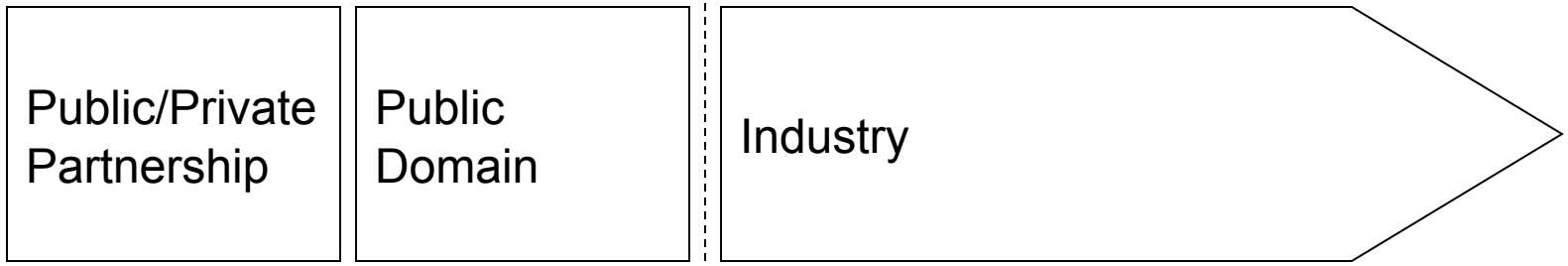
(1)to generate open access research tools to drive science (SGC)

(2) to de-risk new disease mechanisms in the clinic before the pharmaceutical industry starts their proprietary work (Arch2POCM)

Structural Genomics Consortium:
A PPP For Open Access Chemical Biology

- PPP: Members
  - GSK, Pfizer, Novartis, Lilly, Abbott, Takeda
  - Genome Canada, Ontario, CIHR, Wellcome Trust
- Based in Universities of Toronto and Oxford
- 200 scientists
- Academic network of more than 250 labs
- Generate freely available reagents (proteins, assays, structures, inhibitors, antibodies) for novel, human, therapeutically relevant proteins
- Give these to academic collaborators to dissect pathways and disease networks, and thereby discover new targets for drug discovery

Our Model for Pre-Competitive Chemistry



Chemical Probes

Screening
Chemistry
Structure
Cell activity

Target Validation

No IP
No restrictions
Publication

Drug Discovery

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

Creative commons

Proprietary

Some achievements thus far

- Structural impact
  - SGC contributed ~25% of global output of human structures annually
  - SGC contributes >40% of global output of human parasite structures annually

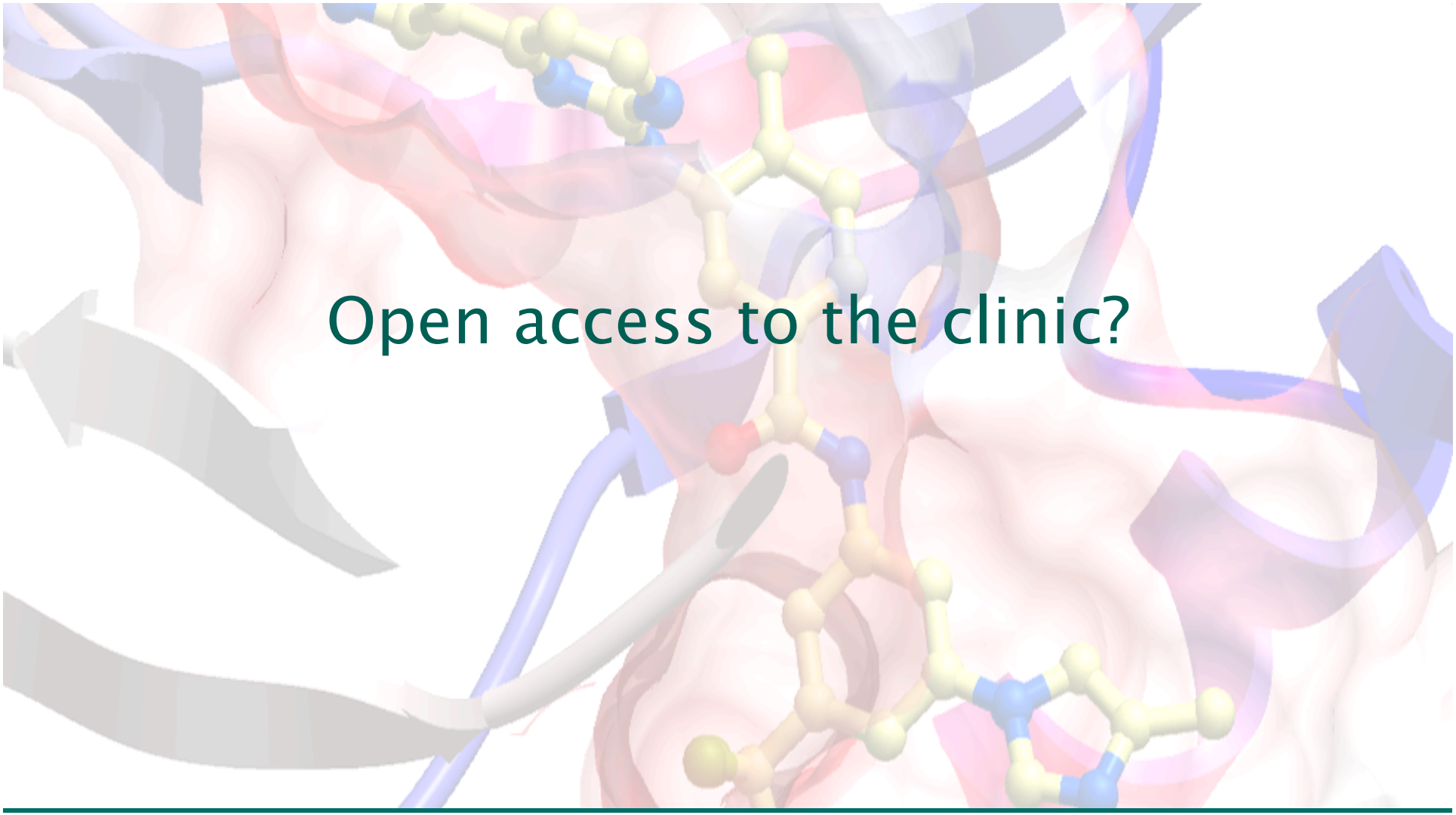
- High quality science (some publications from 2011)

  Vedadi et al, **Nature Chem Biol**, in press (2011); Evans et al, **Nature Genetics** in press (2011); Norman et al **Science Transl Med**. 3(88):88mr1 (2011); Kochan G et al **PNAS** 108:7745 (2011); Clasquin MF et al **Cell** 145:969 (2011); Colwill et al, **Nature Methods** 8:551 (2011); Ceccarelli et al, **Cell** 145:1075 (2011; Strushkevich et al, **PNAS** 108:10139 (2011); Bian et al **EMBO J** in press (2011) Norman et al **Science Trans. Med**. 3:76cm10 (2011); Xu et al **Nature Comm**. 2: art. no. 227 (2011); Edwards et al **Nature** 470:163 (2011); Fairman et al **Nature Struct, and Mol. Biol**. 18:316 (2011); Adams-Cioaba et al, **Nature Comm**. 2 (1) (2011); Carr et al **EMBO J** 30:317 (2011); Deutsch et al **Cell** 144:566 (2011); Filippakopoulos et al **Cell**, in press; **Nature Chem. Biol**. in press, **Nature** in press

Impact of open access JQ1 BET Probe

- SGC paper published Dec 23 has already been cited >60 times
- Harvard spin off (15 M$ seed funding raised)
- > 5 pharma have launched bromodomain programs
- JQ1/SGCB01 has been distributed to >100 labs/companies
- Already used by some to link Brd4 to new areas of science

Zuber et al :	BRD4 as target in acute leukaemia	**Nature**, 2011
Delmore et al:	JQ1 suppresses myc in multiple myeloma	**Cell**, 2011
Dawson et al:	BRD4 in MLL (isoxazole inhibitor)	**Nature** 2011,
Blobel et al:	Novel Targets in AML	**Cancer Cell**, 2011,
Mertz et al :	Myc dependent cancer	**PNAS**, 2011,
Zhao et al:	Post mitotic transcriptional re-activation	**Nature Cell Biol.** 2011



Open access to the clinic?

Target Validation and Drug Discovery are high risk

- We must therefore
- pool resources and capabilities
- rapidly disseminate findings
- delay IP until after target is validated in patients

- If we do not WE will
- have few new drugs
- will continue to waste money
- will continue to harm patients
- further erode the pharma industry

Solution: Arch2POCM

- PPP to clinically validate (IIa = POCM) pioneer targets
- Pharma, public, academia, regulators and patient groups are active participants
- Knowledge creation endeavour/avoid patents filing to maximize rapid information sharing
- All reagents freely shared

Arch2POCM: scale and scope

- Proposed Goal: Initiate 2 programs. One for Oncology/Epigenetics/ Immunology. One for Neuroscience/Schizophrenia/Autism. Both programs will have 8 drug discovery projects (targets) - ramped up over a period of 2 years

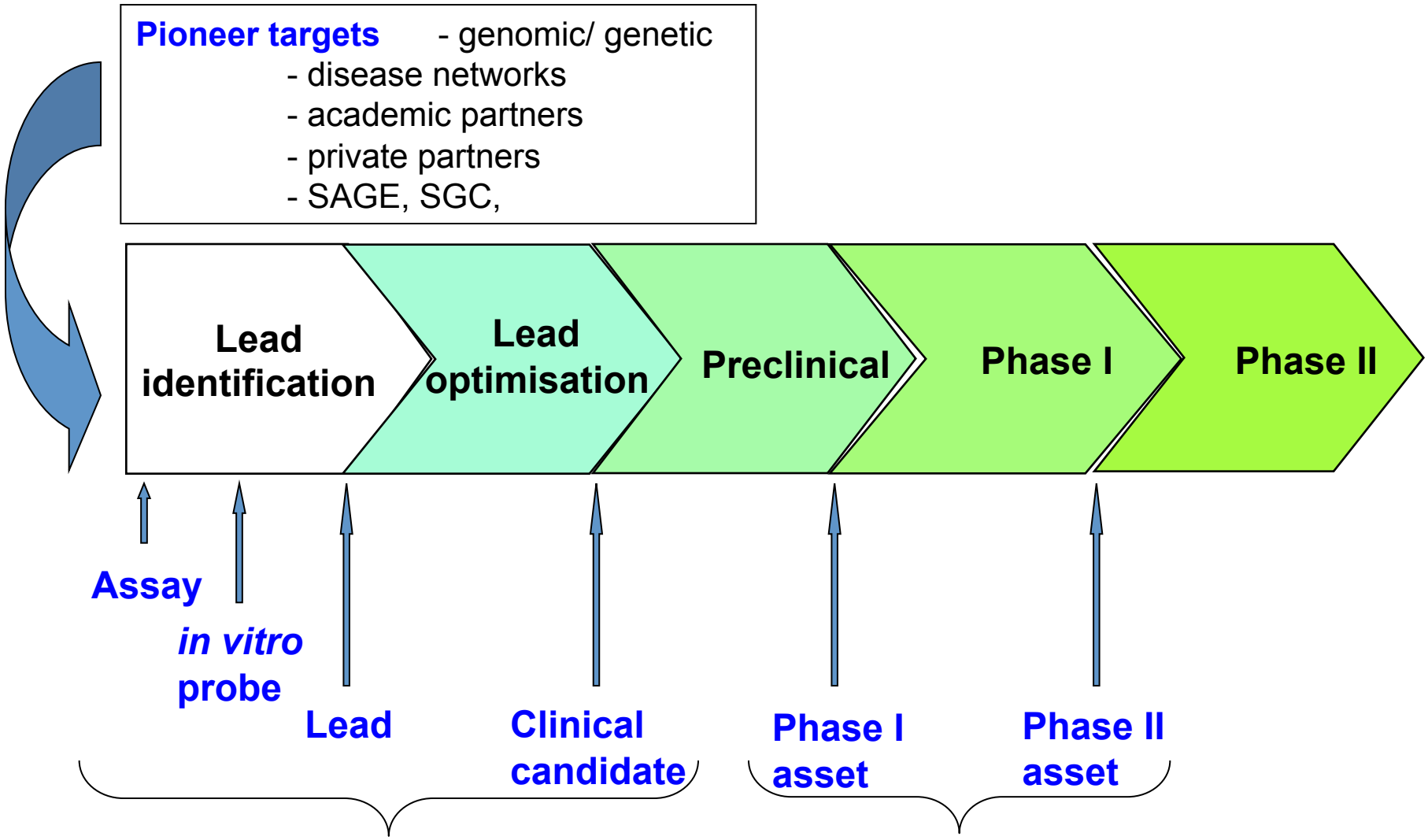
- These will be executed over a period of 5 years making a total of 16 drug discovery projects

  –Projected pipeline attrition by Year 5 (assuming 12 targets loaded in early discovery)

  - 30% will enter Phase 1
  - 20% will deliver Ph 2 POCM data

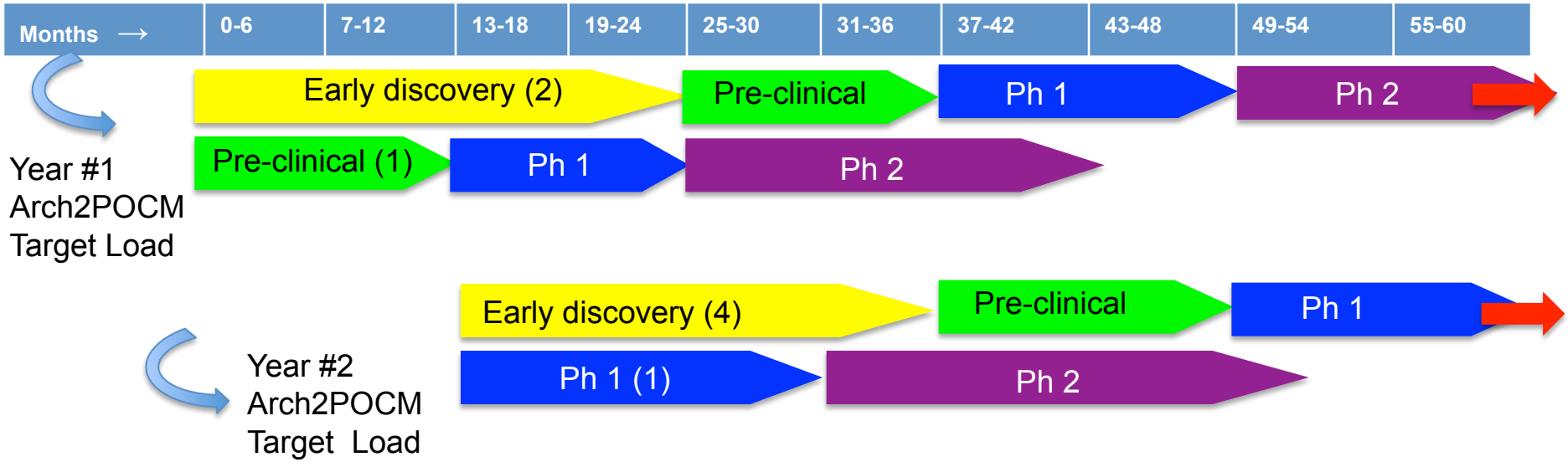
Entry points for Arch2POCM programs:

Two compounds (different chemotypes) will be advanced per target



Pipeline flow for Arch2POCM

Five Year Objective: Initiate ≈ 8 drug discovery projects with 6 entering in Early Discovery, one entering in pre-clinical and one entering in PH I



- Early discovery (45% PTRS)
- Pre-clinical (70% PTRS)
- Ph I (65% PTRS)
- Ph II (10% PTRS)

*PTRS = Probability of technical and regulatory success

Arch2POCM Snapshot at Year 5	
Targets Loaded	8
Projected INDs filed	3-4
Ph 1 or 2 Trials In Progress	2
Projected Complete Ph 2 (POCM) Data Sets	1