How can we work together to discover new clinically validated targets for pain?

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Outline

- Status
- What we are doing and its impact
- What we are planning in Schizo/ Autism (AD/ Depression?)
- Could this model be applicable to Pain?

We have not been very successful in delivering novel analgesics

- Rational design success: Triptans
- Accidental success: Gabapentin
- Very limited success: COX2, topicals
- Potential success: NGF, P38

- Failures: NK1, TRPV1,
- Ongoing: Na, Ca, CB……

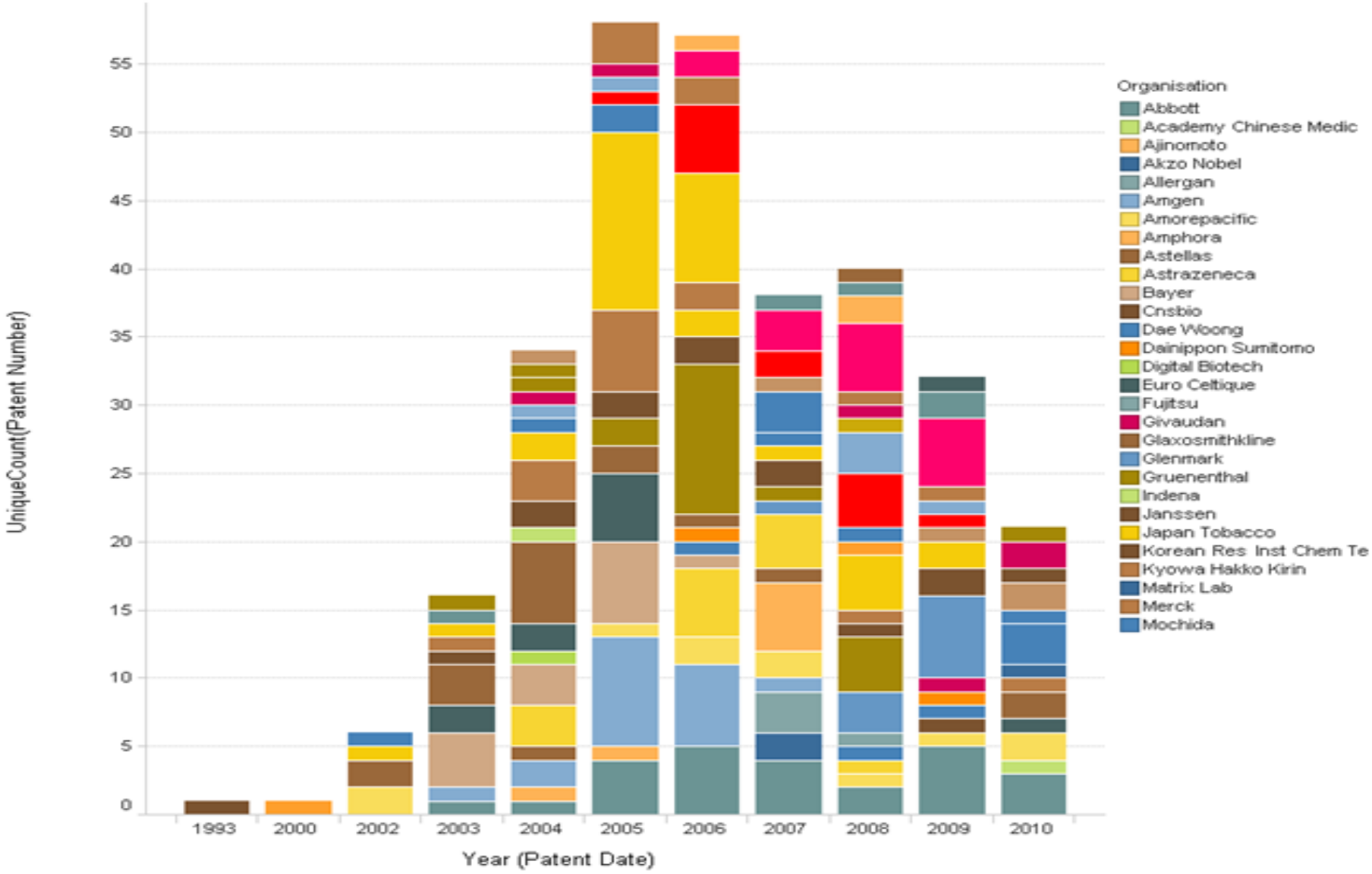
Challenges, questions, post clinical study debates

- Wrong target/ too many targets to choose from
- More selective molecule/ more “dirty” molecule
- Wrong dose
- Insufficient exposure/ target engagement
- Poor CNS penetration
- Animal models are not predictive
- Wrong biomarker
- Placebo response
- Wrong patient group……..

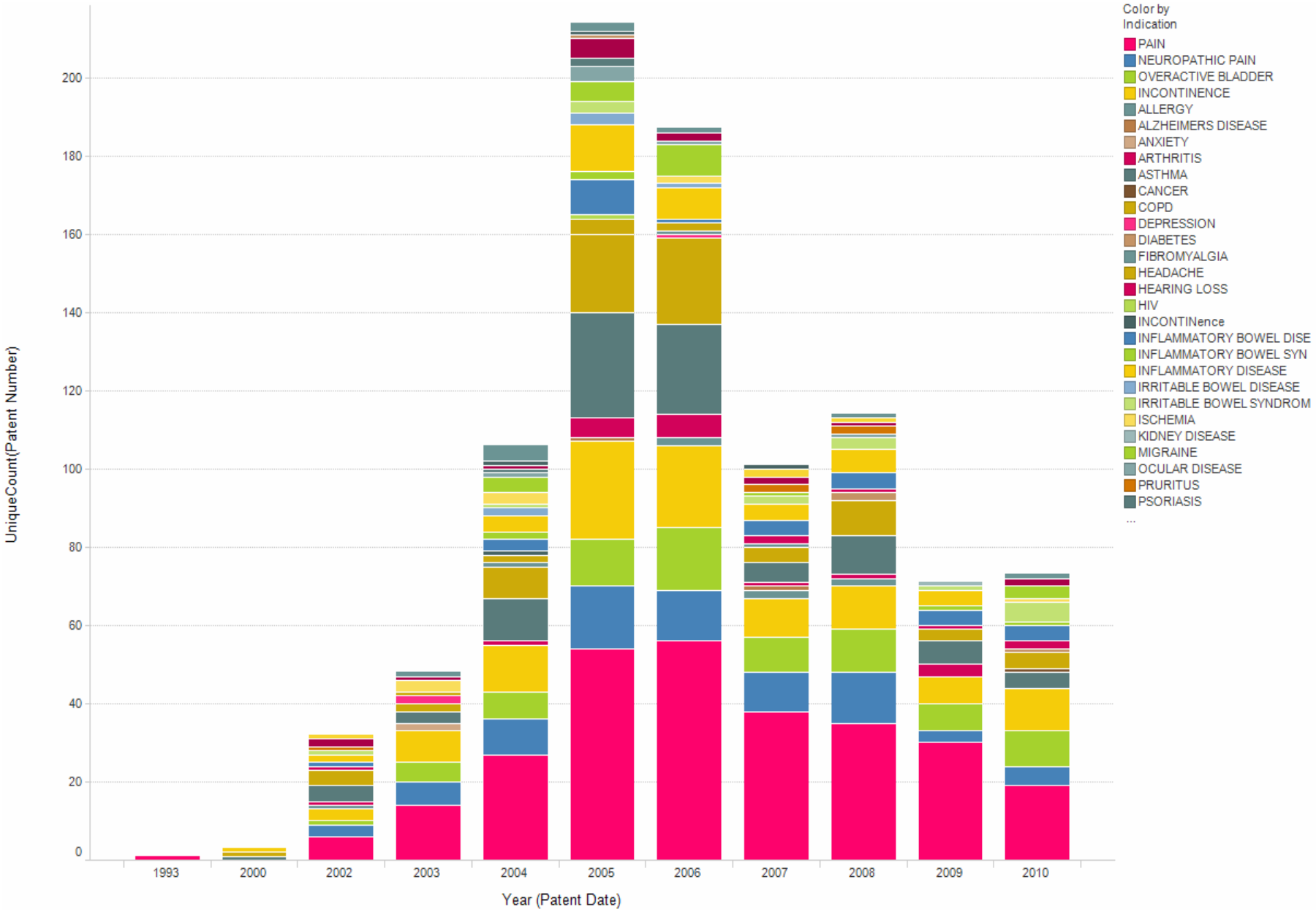
Duplication in science is wasteful, in drug discovery it is unethical

- Many groups work on same target in parallel and in competition (NK1, TRPV1, CB, Na…..)
- Most novel targets are destined for failure at Phase II
- Patients are being exposed to molecules that other groups already know are destined for failure

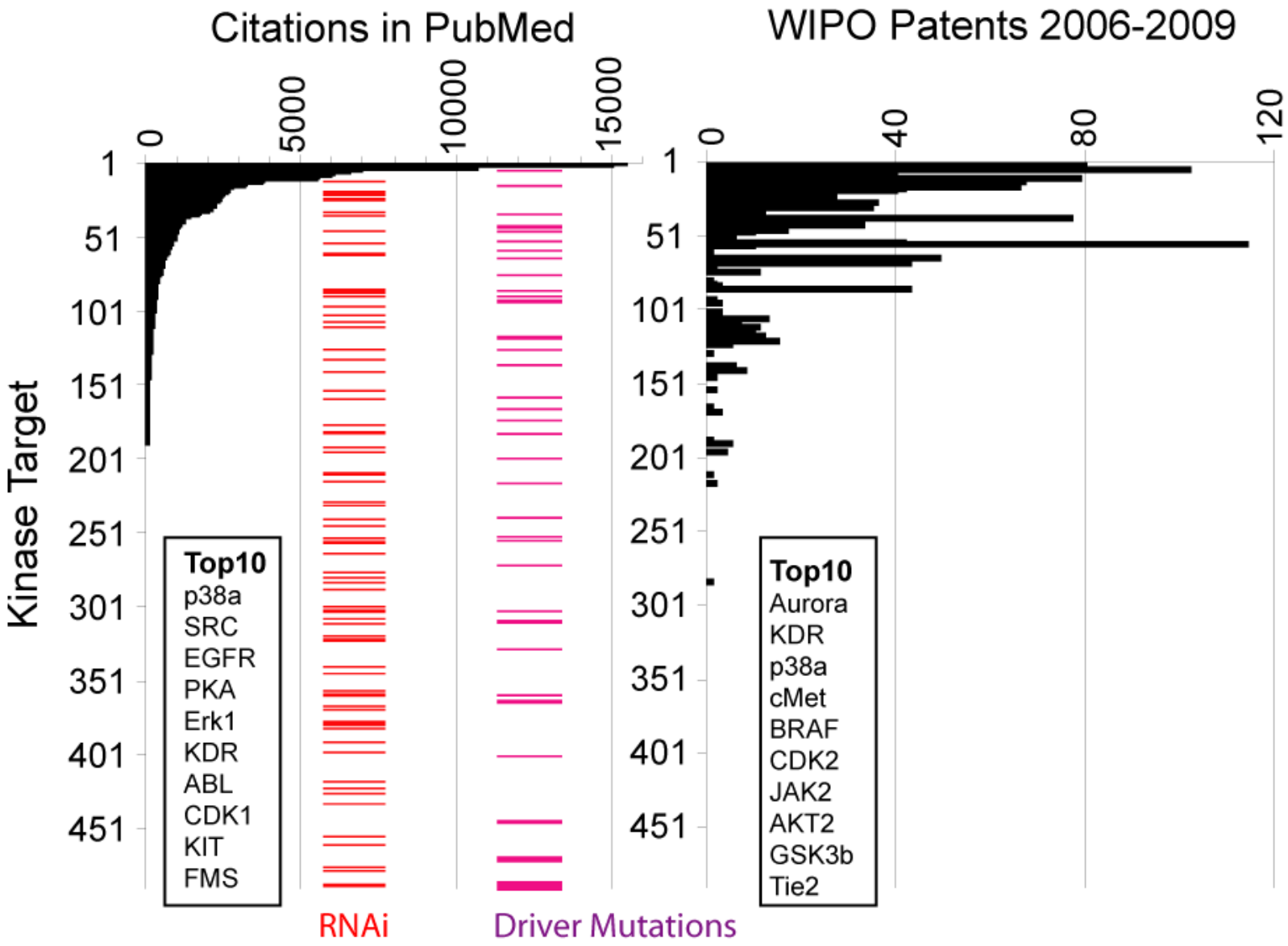
Most companies have patents for TRPV1



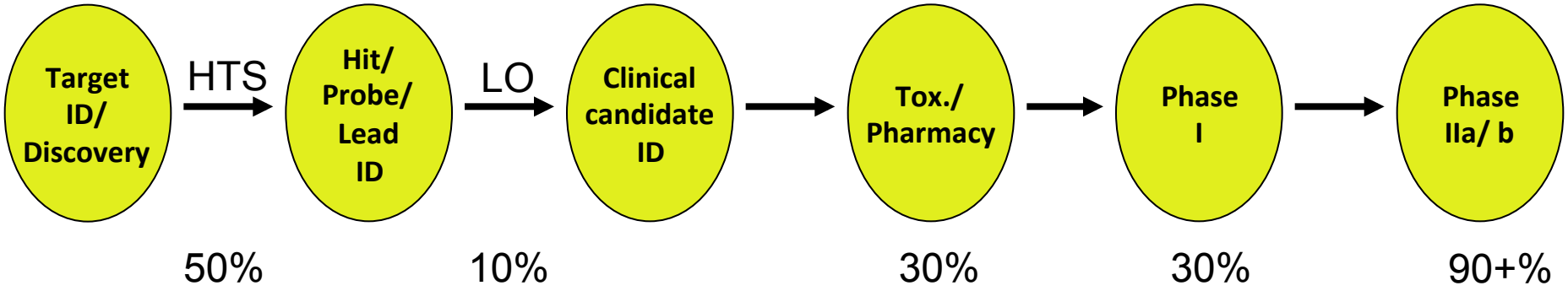
…in probably all therapeutic areas



We need novel targets



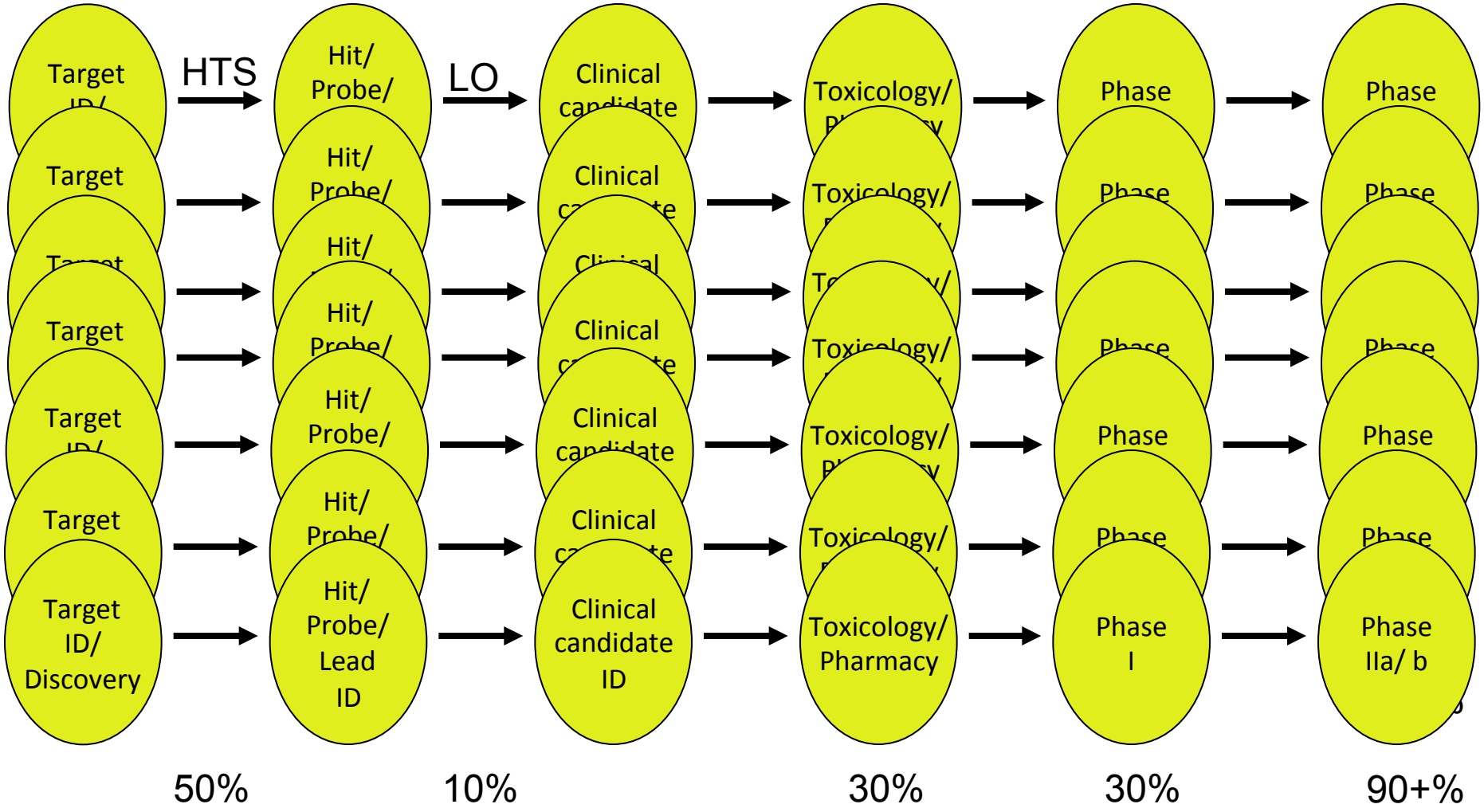
Nearly all novel targets fail at clinical POC



this is killing our industry

…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

Target validation occurs in patients

- Lets
  - get there as quickly as possible
  - do the experiment once
  - do it well
  - share the data quickly

- Consequence
  - save money
  - save careers
  - save patients

AT_2 receptors do not control blood pressure

Angiotensinogen

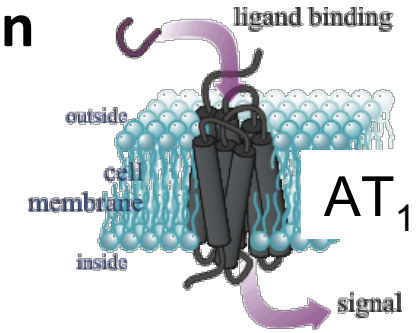
Renin

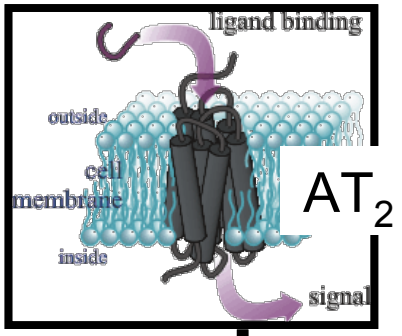
Angiotensin I

Angiotensin converting enzyme (ACE)

Angiotensin II

AT_1 antagonists for hypertension e.g. losartan





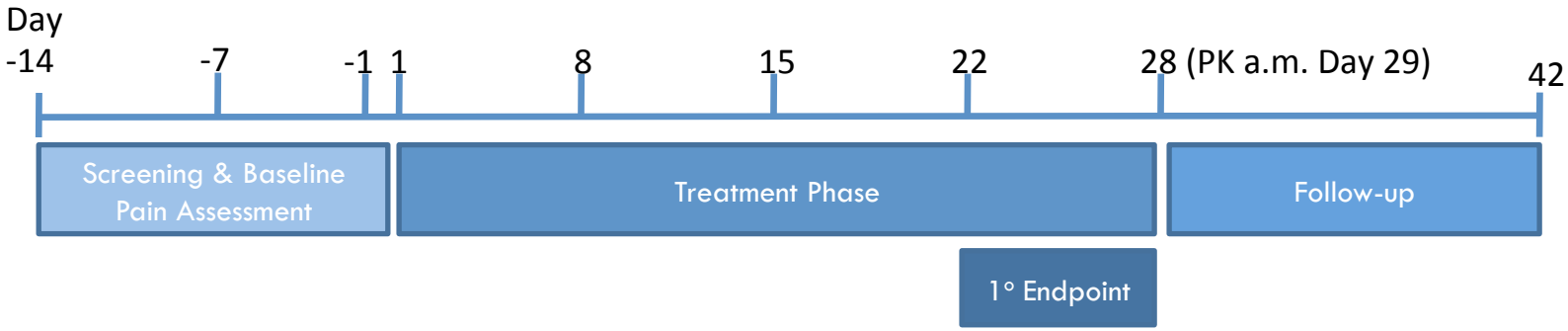
Physiological responses

- Blood-pressure regulation
- Salt and volume homoeostasis
- Cardiovascular function and structure

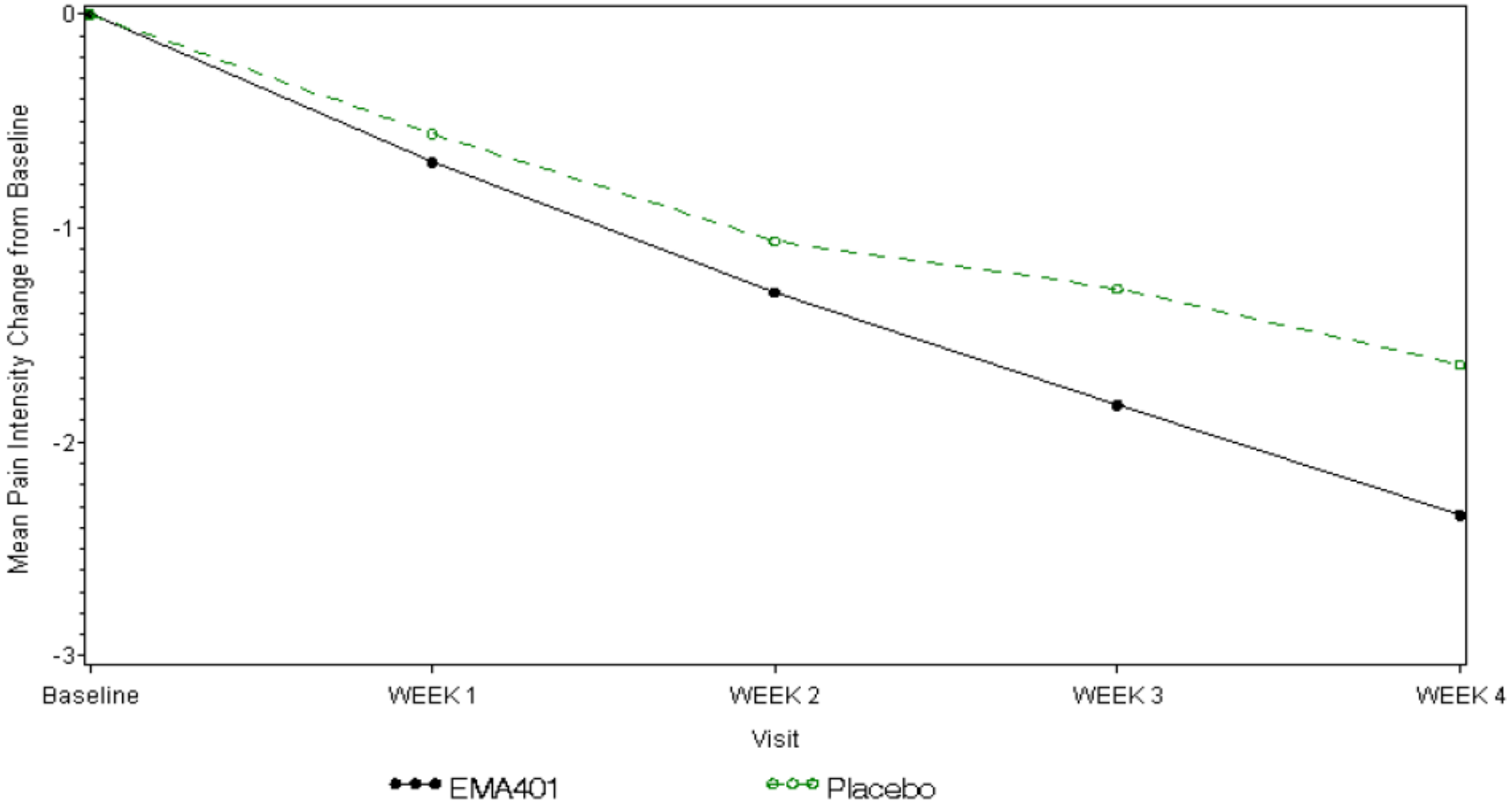
30-40% homology with AT1

Design of PHN efficacy study

- Randomised, double-blind, placebo controlled
- Multicentre - 6 countries
- Single dose level of EMA401 [100mg b.i.d.] for 28 days
- 183 patients
- Patients were not receiving *or* not responding to single agent
- Allowed to continue taking one agent



EMA401 reduces mean pain intensity at 4 weeks (primary endpoint)



EMA401 decreases Mean Pain Intensity

Description	Per Protocol		Intent to Treat	
	EMA401	Placebo	EMA401	Placebo
Baseline Mean (SD) [number of patients]	6.298 (1.057) [79]	6.353 (1.115) [79]	**6.306** (1.024) [92]	**6.325** (1.086) [91]
Week 4 Mean (SD) [number of patients]	3.817 (2.069) [79]	4.767 (1.951) [79]	3.975 (2.046) [90]	4.714 (1.916) [89]
Change from Baseline (SD)	-2.481 (1.741)	-1.586 (1.700)	**-2.340** (1.738)	**-1.637** (1.662)
Difference of Adjusted LS Means (SE)	-0.8950 (0.2747)		-0.7085 (0.2546)	
95% CI for Difference of Adjusted LS Means	Not available	Not available	-1.2111 , -0.2059	
p value	0.0014		**0.0060**	

EMA401 increases 30% responder rate

Description	Per Protocol		Intent to Treat	
	EMA401	Placebo	EMA401	Placebo
Responders (%) [number of patients]	63.3 [50/79]	34.2 [27/79]	**56.5** [52/90]	**34.1** [31/89]
Odds Ratio	0.300		0.391	
95% CI	0.1554 , 0.5785		0.2099 , 0.7281	
p value	0.0003		**0.0031**	

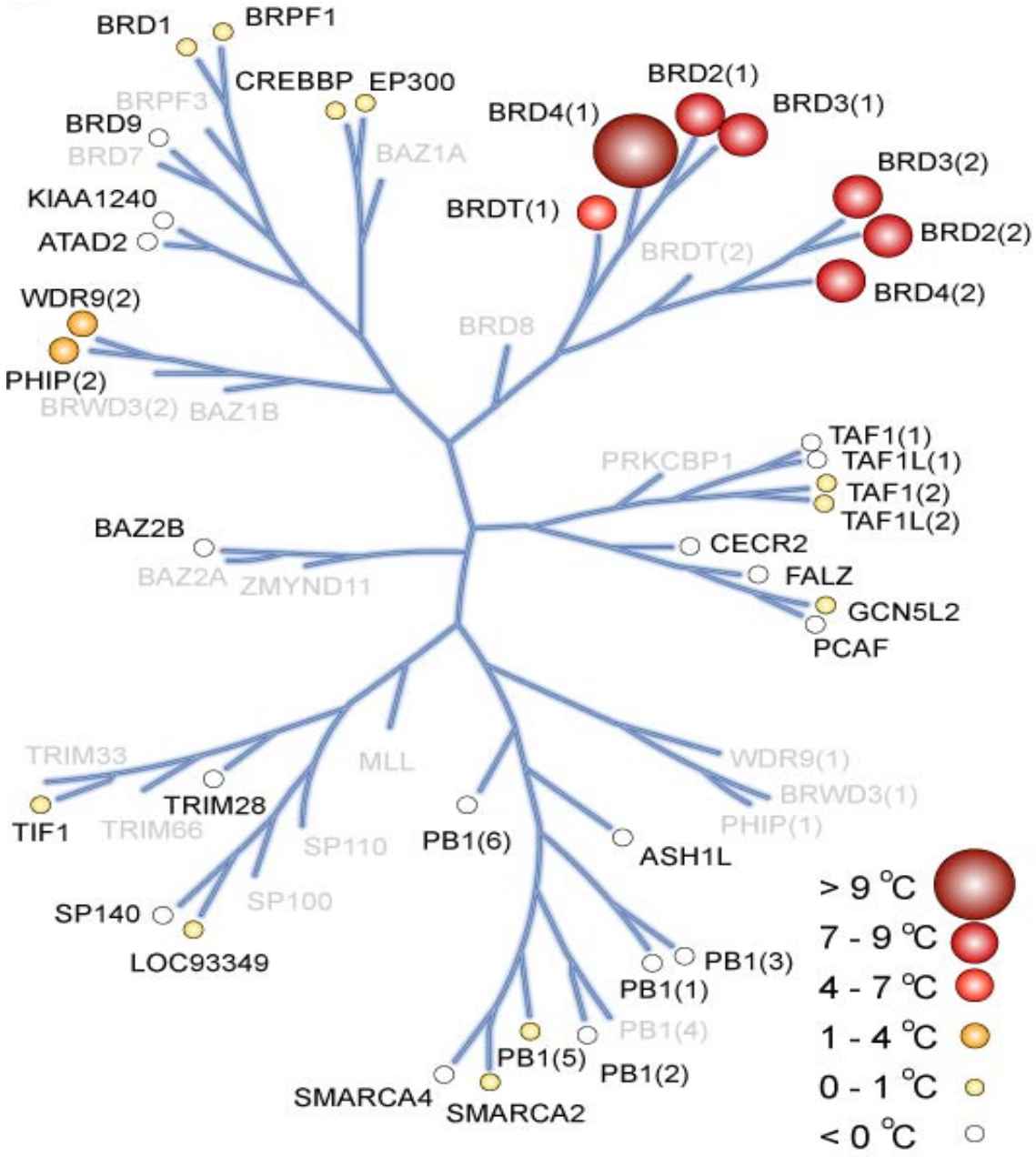
What is SGC?

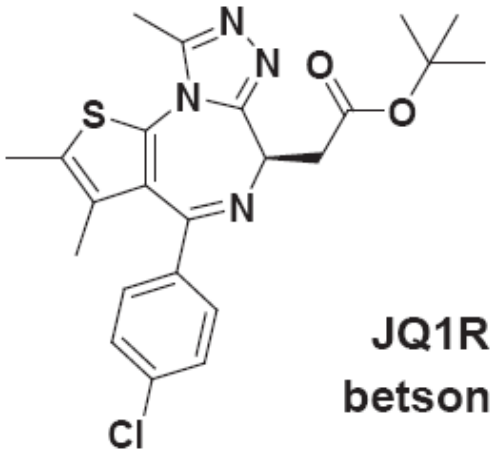
- PPP - GSK, Pfizer, Novartis, Lilly, Abbott, Takeda, BI, Janssen
  - GC, Ontario, CIHR, Wellcome Trust
- Other pharmas wanting to join
- Private funding: $64M
- 200 scientists in Universities of Toronto and Oxford
- Academic network: >250 labs

Output

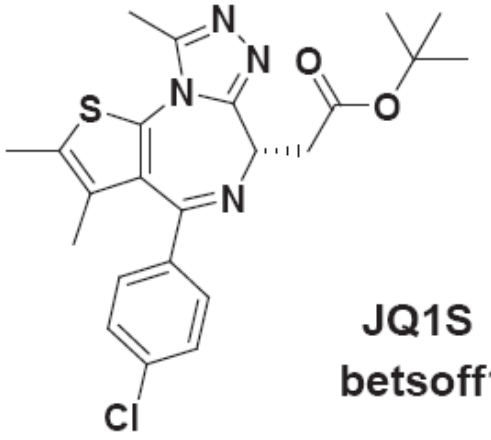
- Generate freely available novel reagents:
  - human therapeutically relevant proteins,
  - assays,
  - structures,
  - inhibitors,
  - antibodies
- Focus on epigenetics
- Give to collaborators to discover new targets for drug discovery

A selective inhibitor for BET sub-family





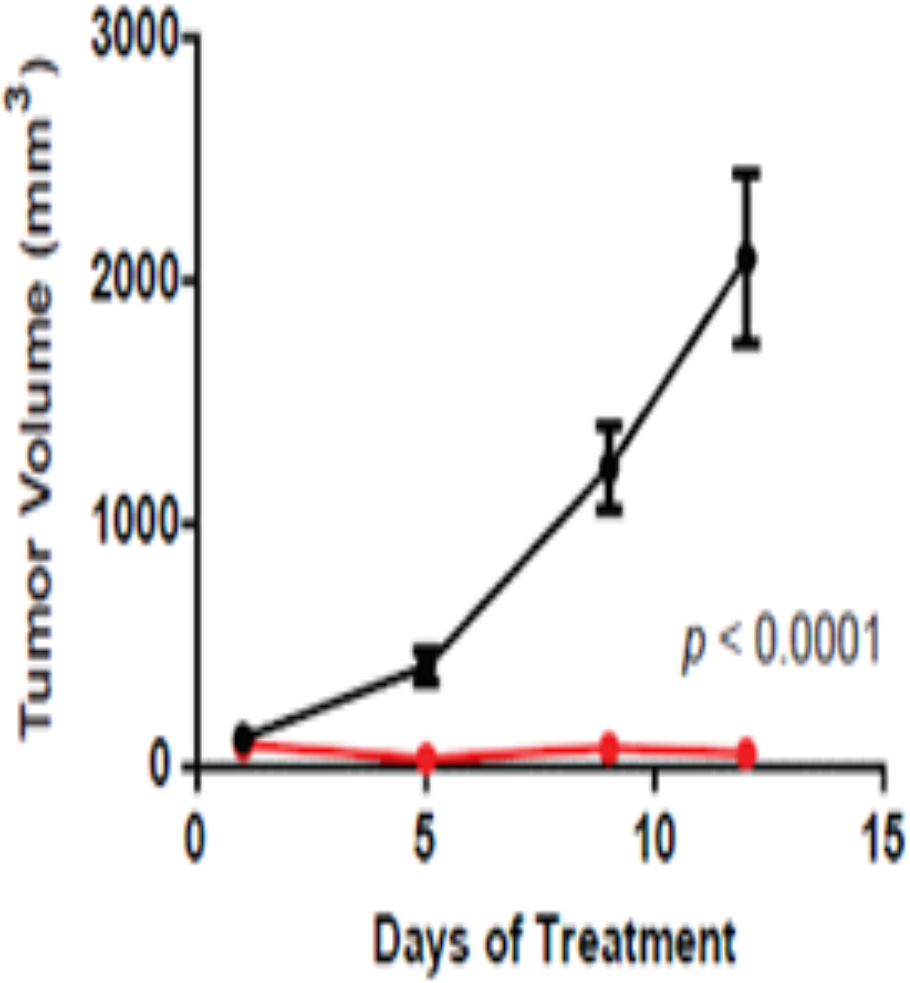
JQ1R
betson1

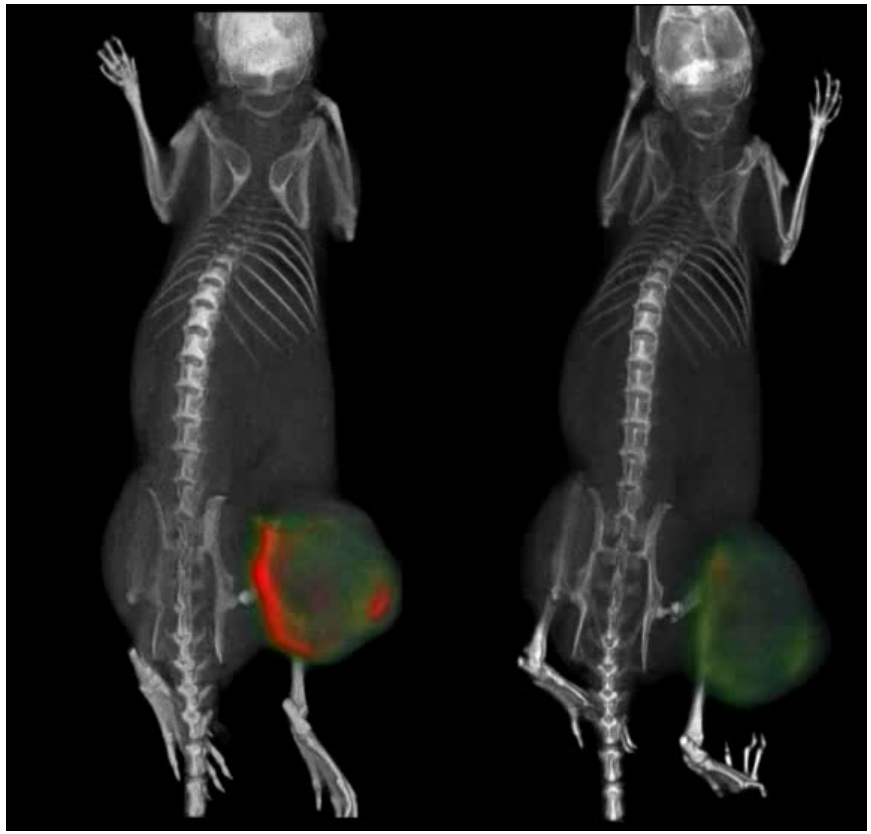


JQ1S
betsoff1

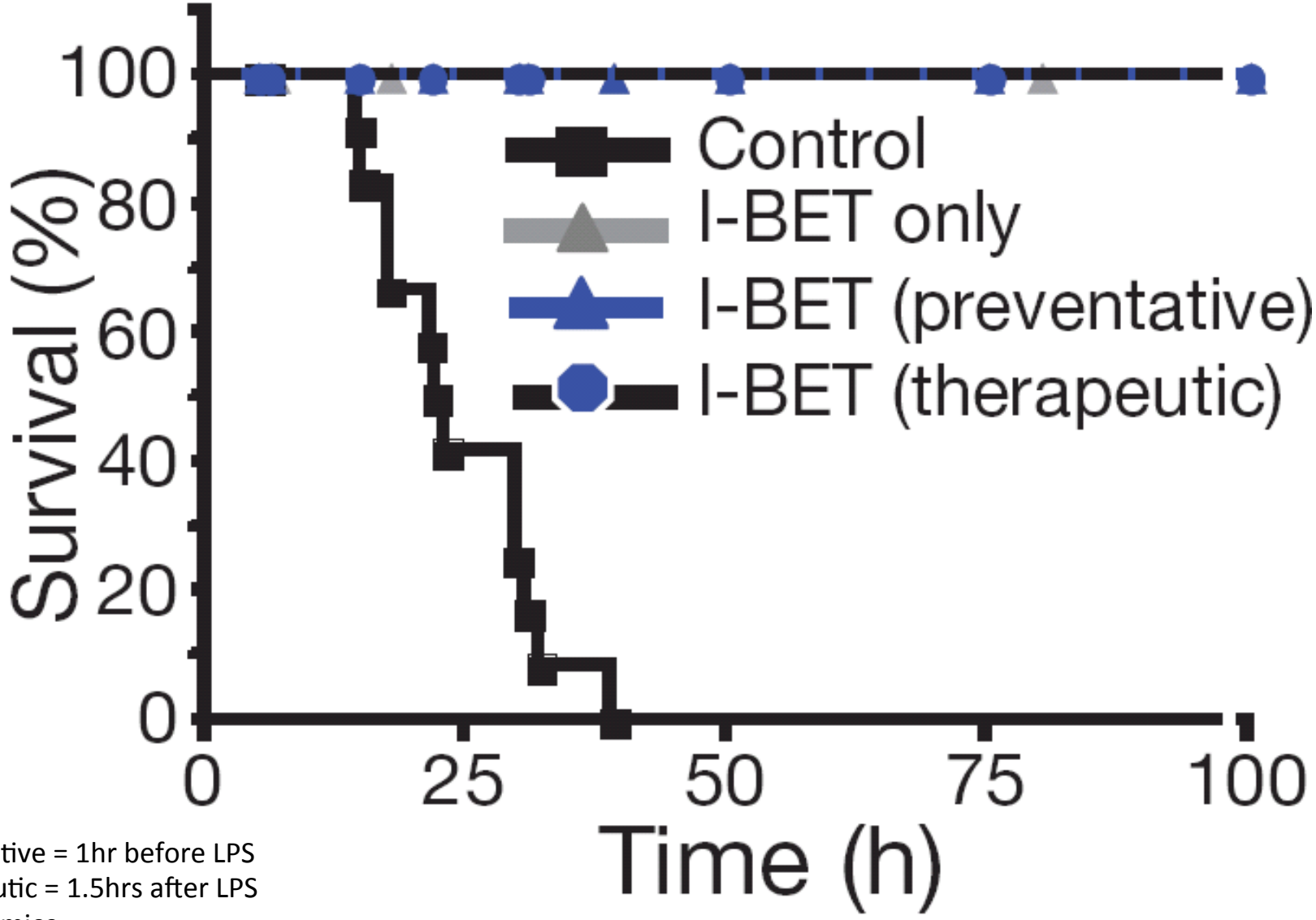
Nature, Dec 23, 2010

JQ1 reduces tumour size



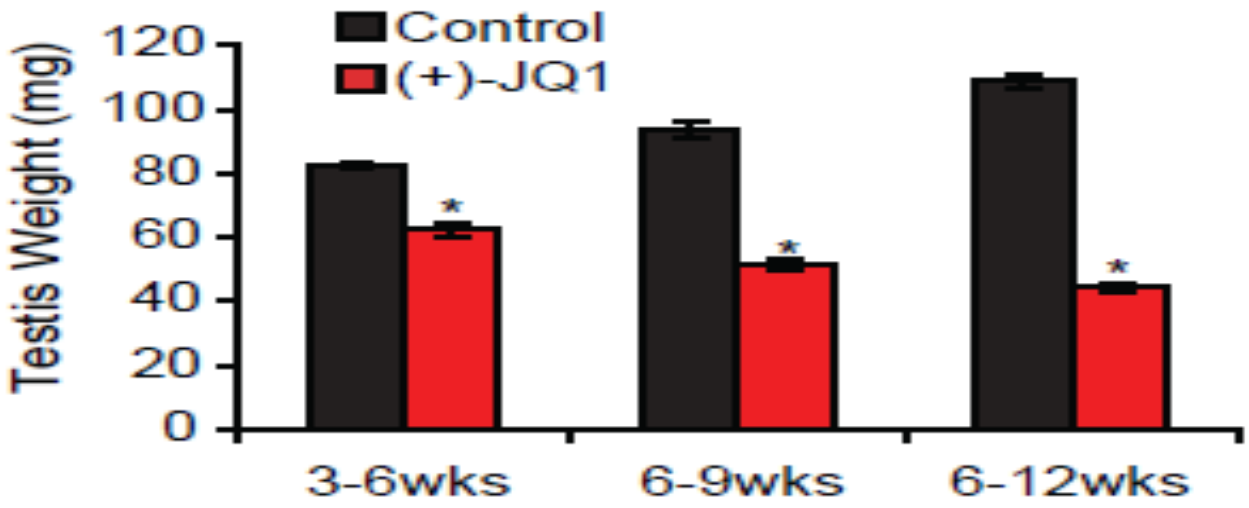


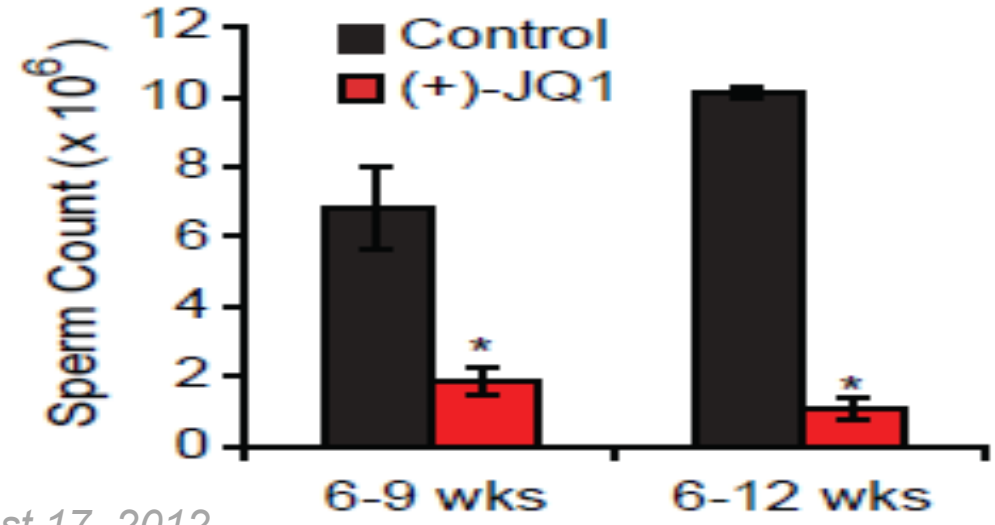
I-BET762 prevents and inhibits LPS induced endotoxic shock

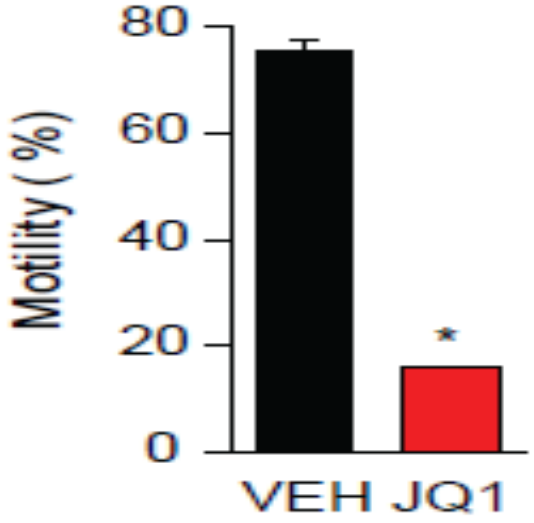


Preventative = 1hr before LPS
Therapeutic = 1.5hrs after LPS
C57BL/6 mice

JQ1 reduces testes weight, sperm count and motility







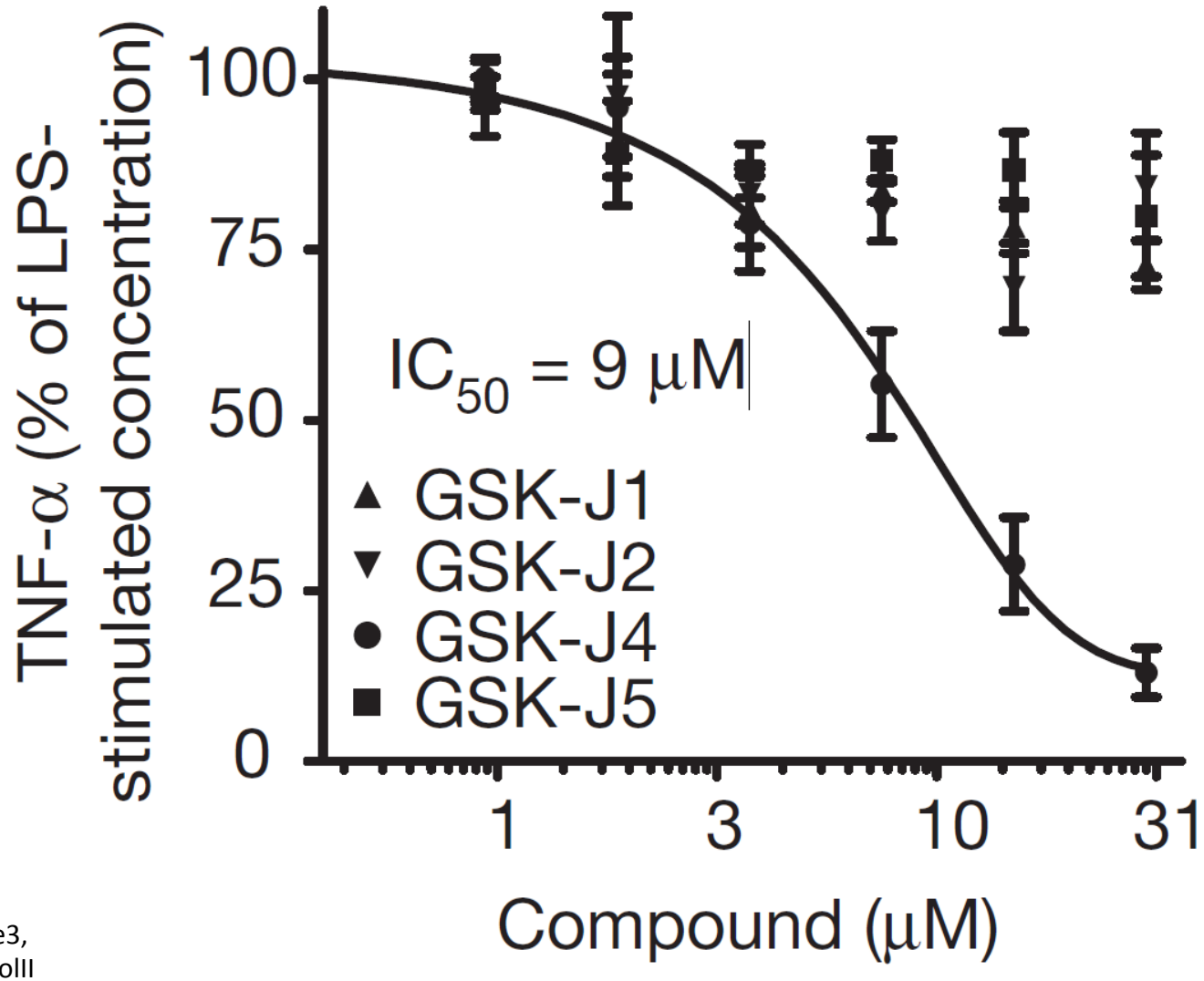
Cell August 17, 2012

Impact on science & drug discovery

- Published Dec 23 2010 - already cited >100 times
- Distributed to >300 labs/companies - profile in several therapeutic areas
- Pharmas - started proprietary efforts
- Harvard spin off - $15 M seed funding
- Opened new area:

Zuber et al :	BRD4 as target in acute leukaemia	**Nature**, 2011 Aug 3
Delmore et al:	JQ1 suppresses myc in multiple myeloma	**Cell**, 2011 Volume 146, 904-917, 16
Dawson et al:	BRD4 in MLL (isoxazole inhibitor)	**Nature** 2011, Oct 2.
Blobel et al:	Novel Targets in AML	**Cancer Cell**, 2011, Sep 13
Mertz et al :	Myc dependent cancer	**PNAS**, 2011, Oct 4
Zhao et al:	Post mitotic transcriptional re-activation	**Nature Cell Biology**, 2011 Oct 9

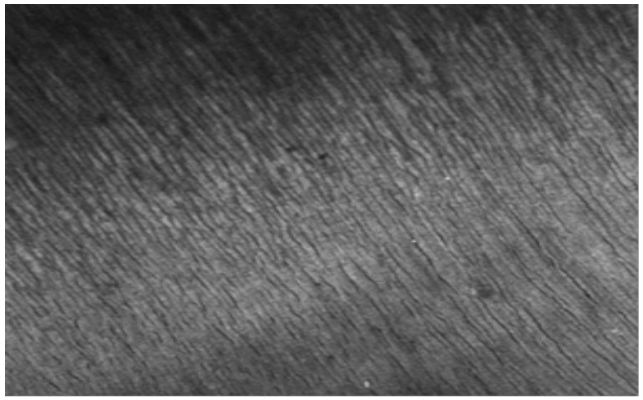
GSK-J1 produces dose related inhibition of LPS stimulated TNF release from human macrophages



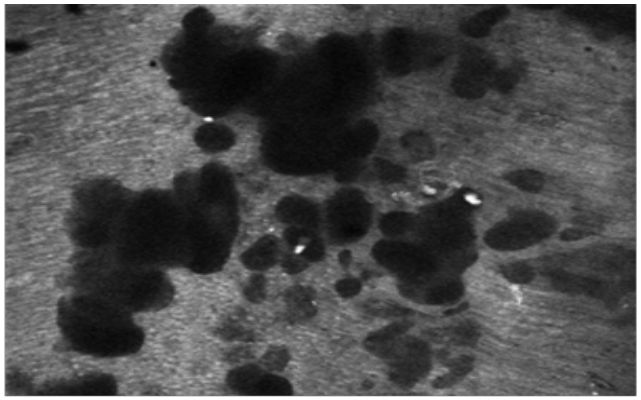
Inhibitor

- increases K27me3,
- decreases RNApolII
- no change in H3

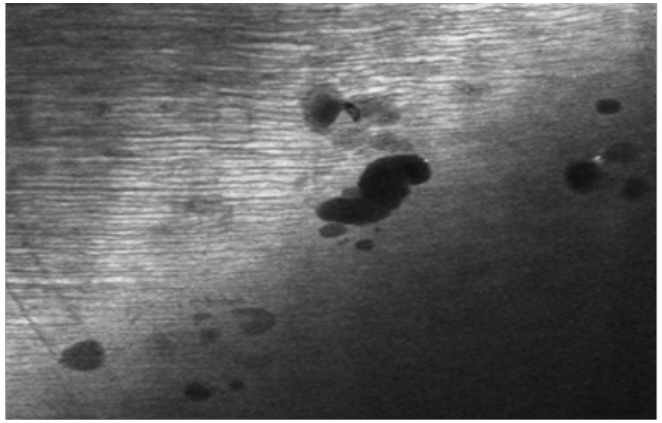
GSK-J1 reduces RANKL induced bone resorptive activity in osteoclasts



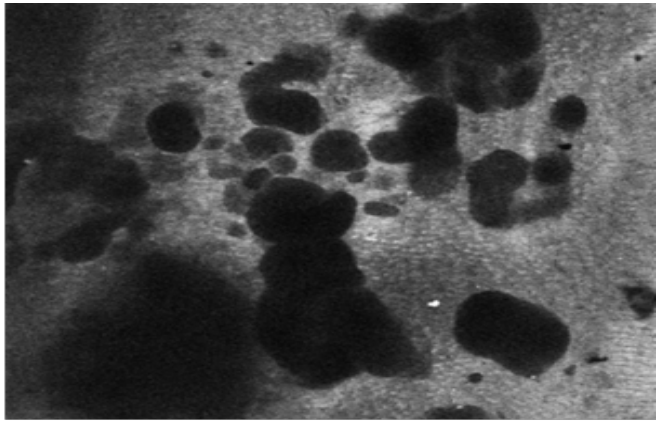
- RANKL



+ RANKL



+ RANKL
+ GSK-J4

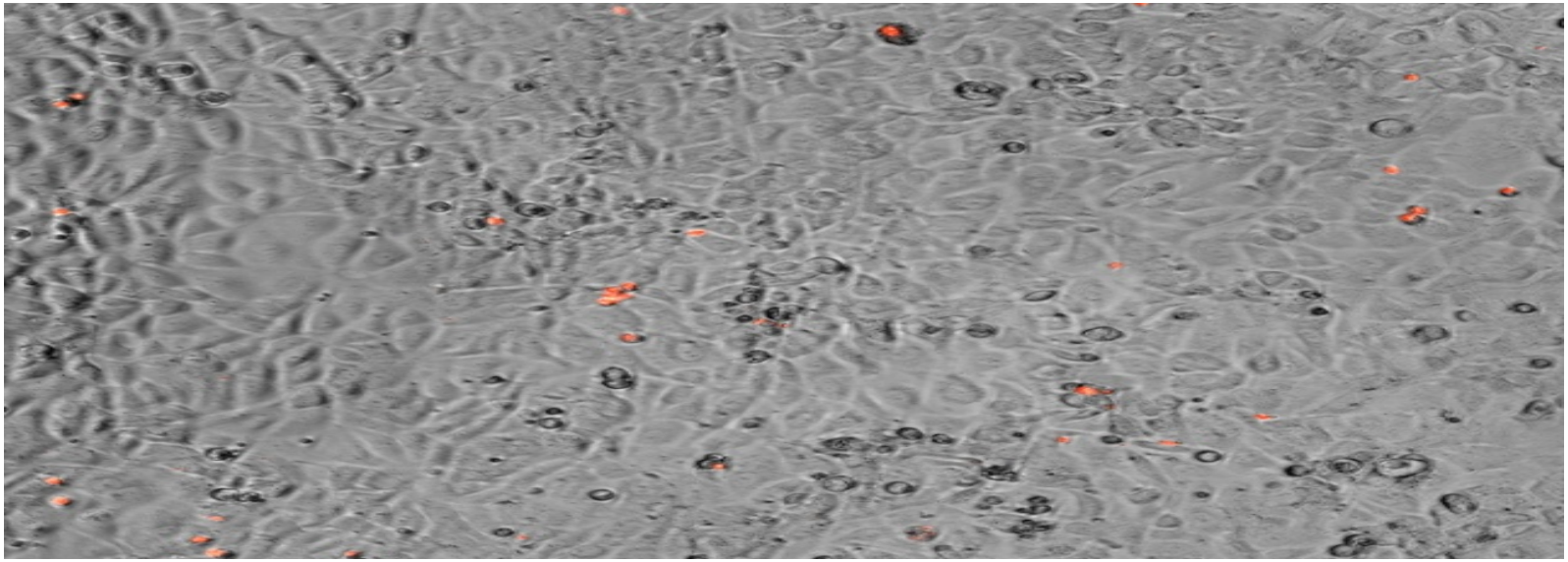


+ RANKL
+ GSK-J5

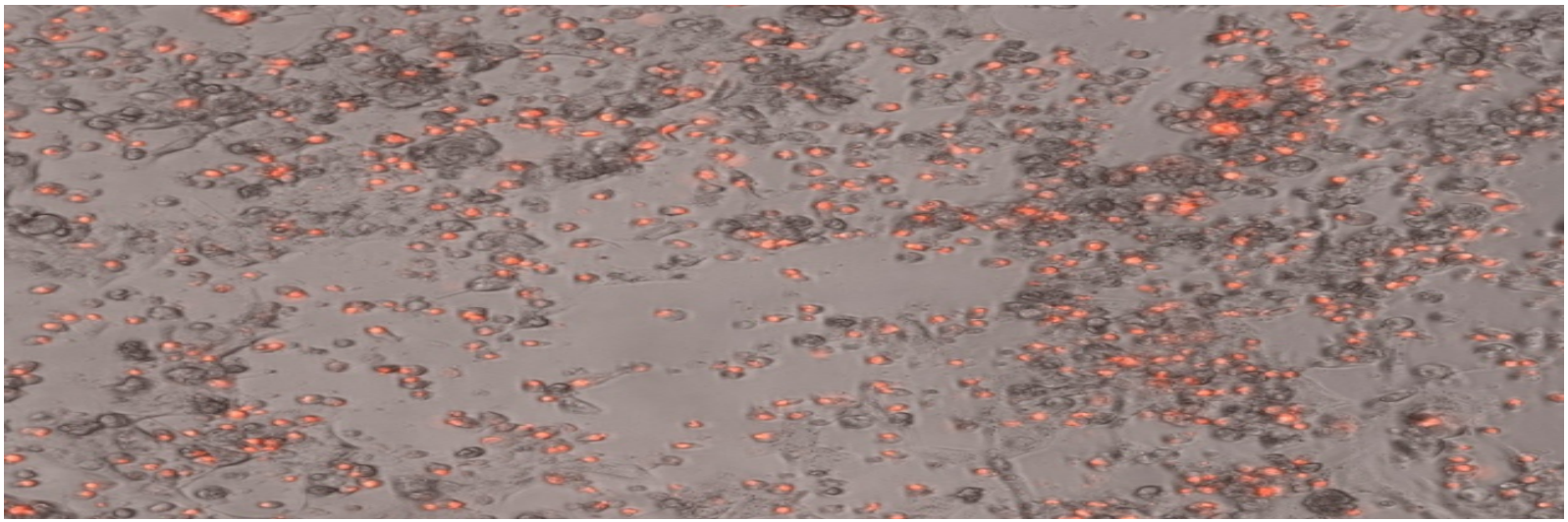
RANKL = receptor activator of nuclear factor KB ligand
RANK = osteoclast cell surface receptor

GSK-J1 increases apoptosis in human breast cancer cells (MCF7)

Vehicle



D3 inhib

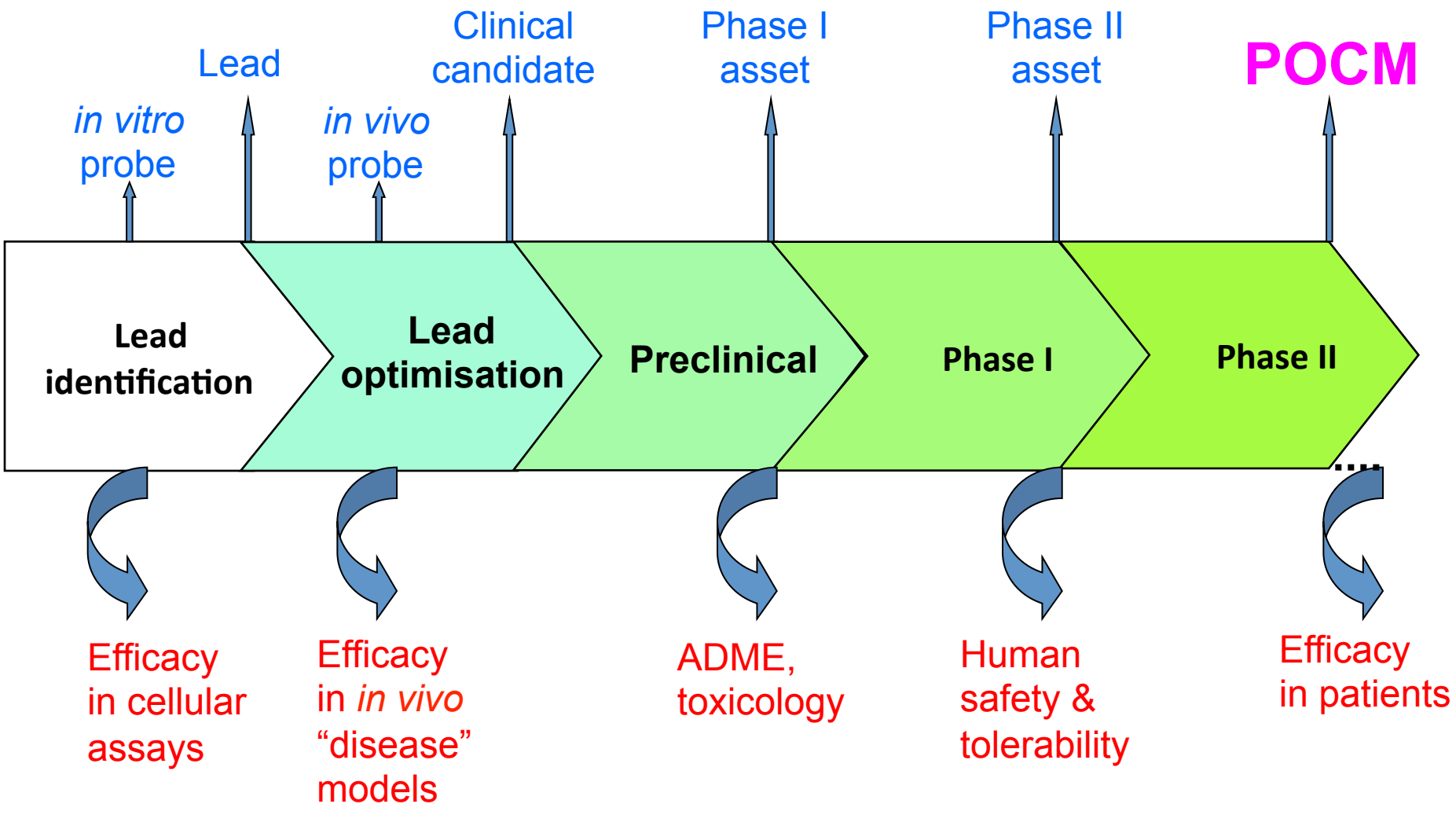


Red dots: propidium iodide stained apoptotic cells
D3 inhibition, increases K27me3, decreases BCL2, increases apoptosis

Building a new PPP to validate novel targets in patients

- Academics, regulators, citizens, health industry, through to Proof Of Clinical Mechanism (Phase IIa)
- Regulators and patient groups want to be active participants
- Knowledge creation endeavour
- All reagents will be freely shared

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



Patient groups

- Will facilitate recruitment

- Will minimise payments

Regulators

- Have access to large clinical datasets

- Wish to
  - help design new clinical studies
  - help validate new biomarkers
  - pave path for new targets
  - host Arch2POCM data

Status

- Established SAB (Bell, Feldman, Hyman, Ford Hutchison)
- Project started in cancer
- Project soon to start in neuroscience
  - schizo, autism, depression, AD
  - CIHR earmarked $30M, likely get other public funds
  - 6 pharmas interested
  - high level meeting being arranged in Ottawa
- Discussions ongoing re inflammation

Lessons

- Academia needs quality probes to help discover new targets
- Pre-competitive efforts catalyse competitive endeavours
- Based on cellular data it is difficult to predict which patients will benefit
- Target validation occurs in patients with quality molecules
- Industry needs new validated targets, biomarkers and ways to stratify patients: we in academia must help generate.

Acknowledgements

- SGC : Aled Edwards, Stefan Knapp, Udo Oppermann
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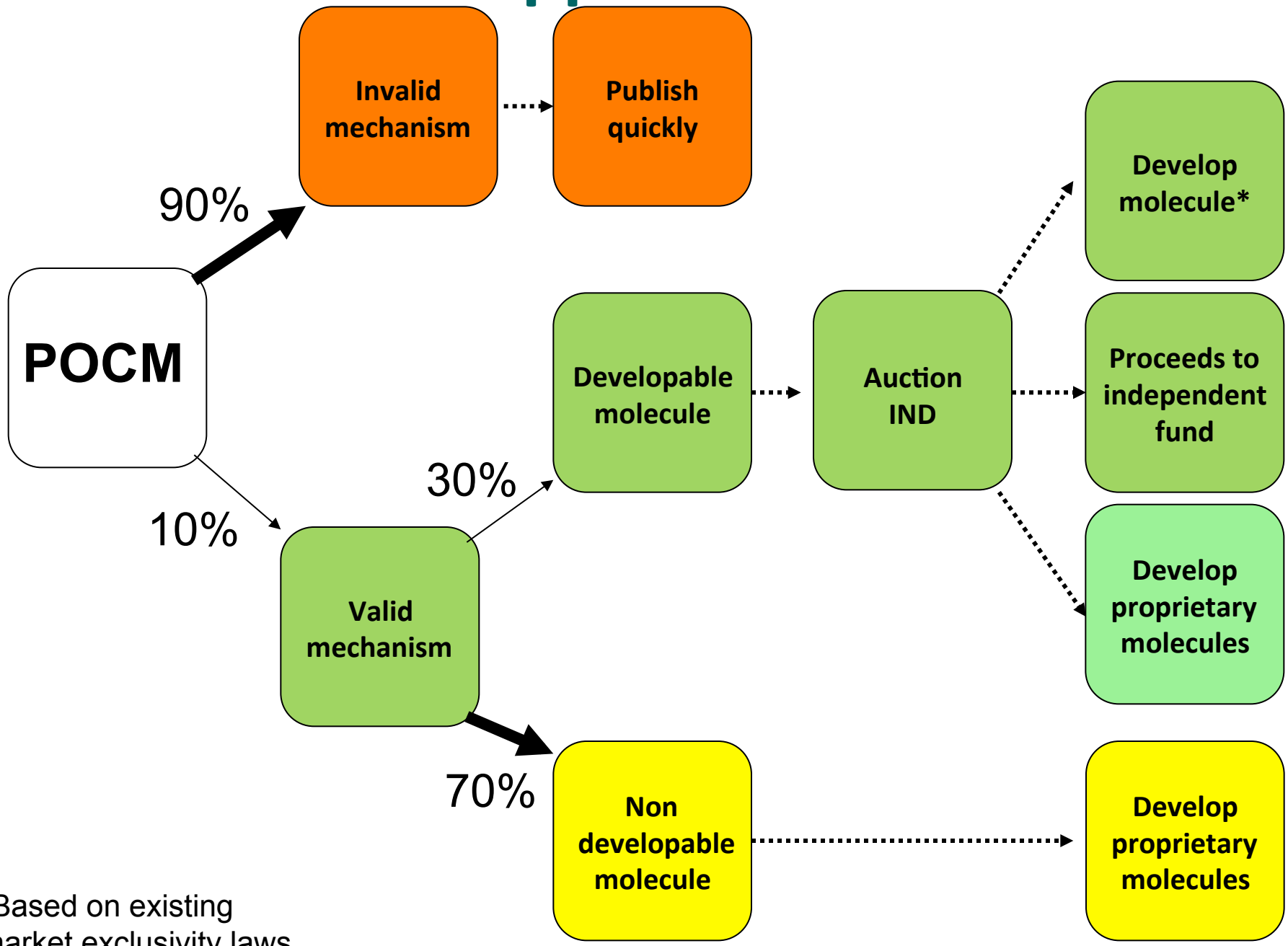
- Imperial College: Praveen Anand
- Spinifex: Tom McCarthy, Bob Dworkin, Andrew Rice
- CIHR, Genome Canada, Ontario, Wellcome Trust
- GSK (Rab Prinjha, David Wilson), Novartis, Pfizer (Kevin Lee), Lilly, Abbott, Takeda, Janssen, BI

What happens after POCM?



*Based on existing market exclusivity laws