SGC

A Public Private Partnership facilitating Drug Discovery

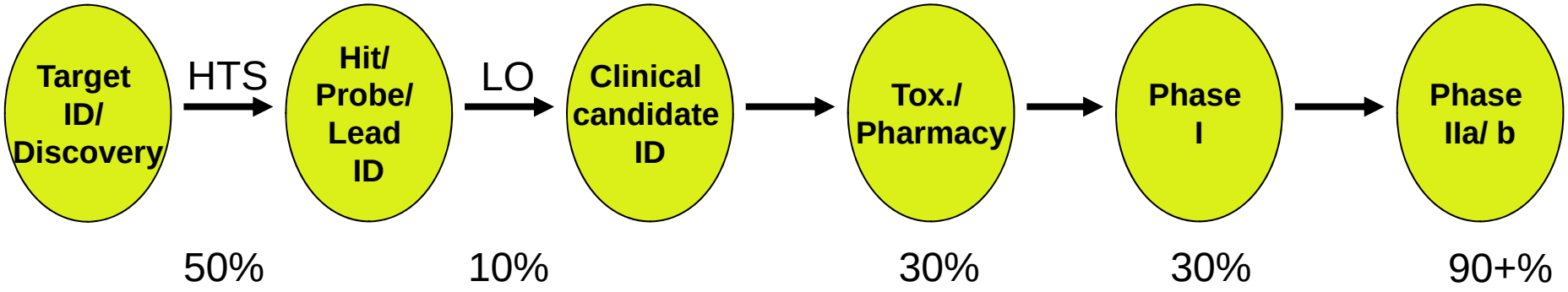
SGC Toronto

SGC Oxford

Outline

- Challenges in Drug discovery: science and organisational/ process
- We do not know how to pick the right targets
- Epigenetic proteins are likely to be better choices
  - injury or tissue damage/pain,
  - stress or early life experiences/depression,
  - toxins/inflammation,
  - diet/ respiratory disease,
  - glucose/ vascular disease
- We are generating quality reagents and using these to do target discovery in human cells
- Plans:
  - short term: human cell platform
  - medium term: Phase IIa

Most 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

How can we make drug discovery more successful?

Challenges	Consequence	Solution
Poor knowledge of human disease	• Preclinical assays rarely translate • Poor target selection/ biomarkers/ clin. POC • High attrition at IIa	More human biology
Slow or no publication of failures/ data, in academia and industry	• Duplication • Waste of resources/ careers/ patients	Publish rapidly
No organisation has all necessary capabilities		Pool capabilities
Early IP	• Slower, harder and more expensive	Treat as knowledge creation
Poorly characterised reagents in academia (not strong in med. chem.)	• Do not leverage strengths of academia	PPP to generate novel reagents and build med. chem. in academia

Science, Organisational/ process

SGC

- Public private partnership
  - large academic network
  - large pharma network
  - multiple funders: share risk
  - no IP
    - collaborate quickly and freely
    - disseminate data rapidly

- Generate
  - freely available, well characterised reagents
  - focus on knowledge creation & human target discovery

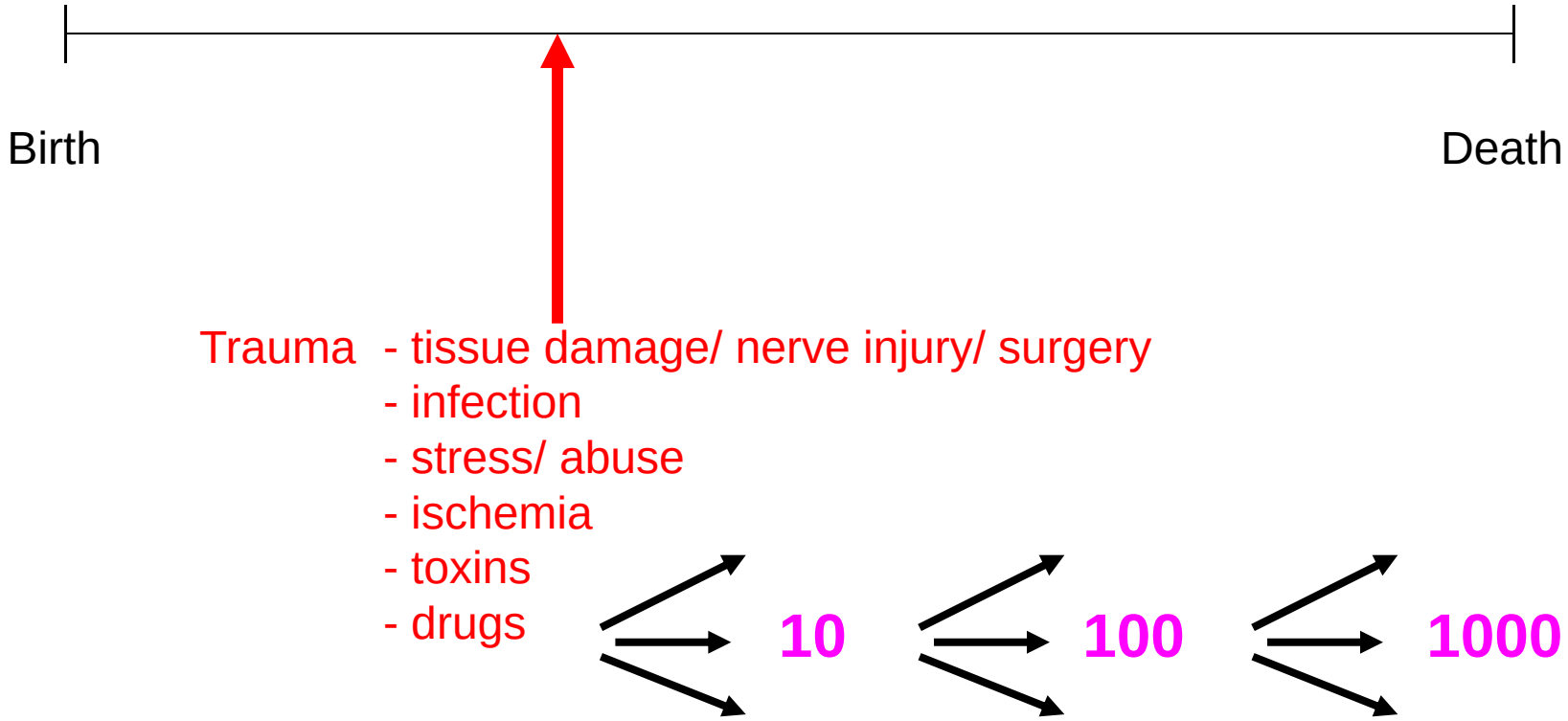
How do we pick the right target?

- Genetics - monogenic
  - oncology

- Network biology????

- Well characterised reagents in human
  - disease cells and tissues
  - Phase II studies

Modulating a late stage mediator is unlikely to be effective



Nos of genes/ proteins, up/down regulated

PNI induced epigenetic gene silencing

Peripheral nerve injury (PNI)

↓

Increase Neurone Restrictive Silencer Factor (NRSF) in DRG

↓

Bind to Neurone Restrictive Silencer Element (NRSE)

↓

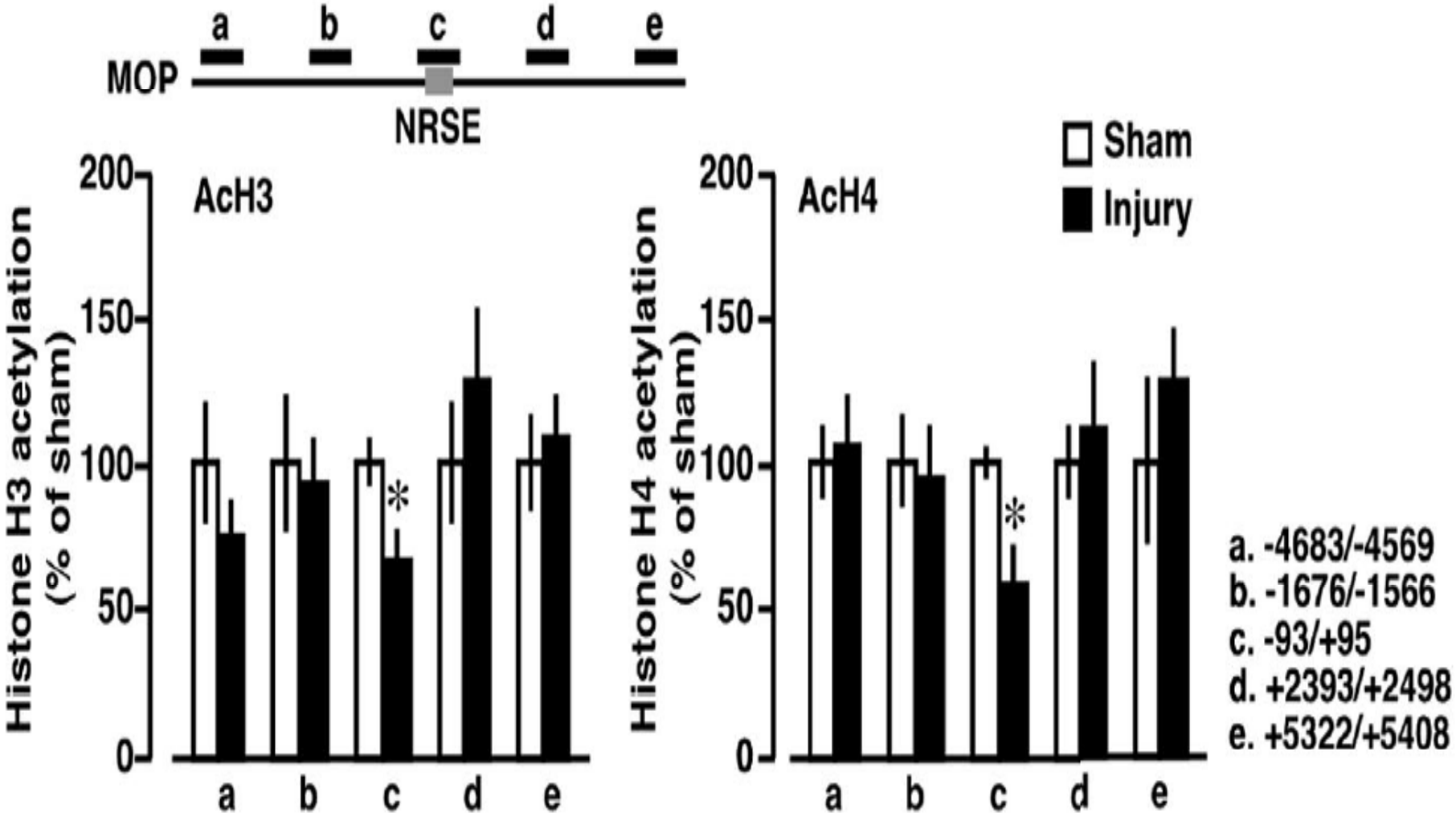
Decreased histone acetylation

↓

Decreased transcription of mu opioid receptor, Nav1.8, Kv4.3

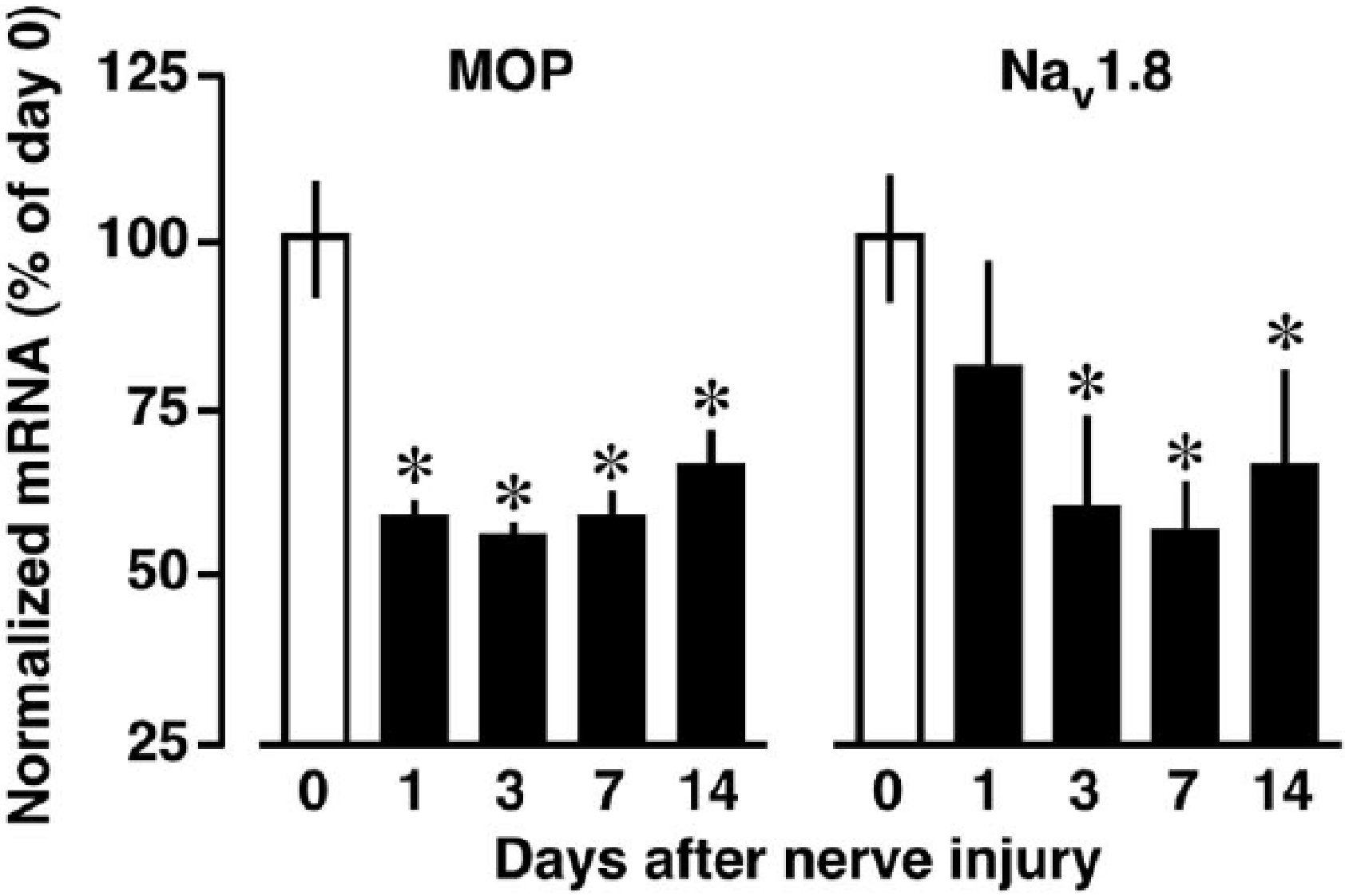
Uchida et al 2010, J of Neuroscience, Uchida et al 2010, Neuroscience

Decreased acetylation of mu opioid receptor through NRSF binding



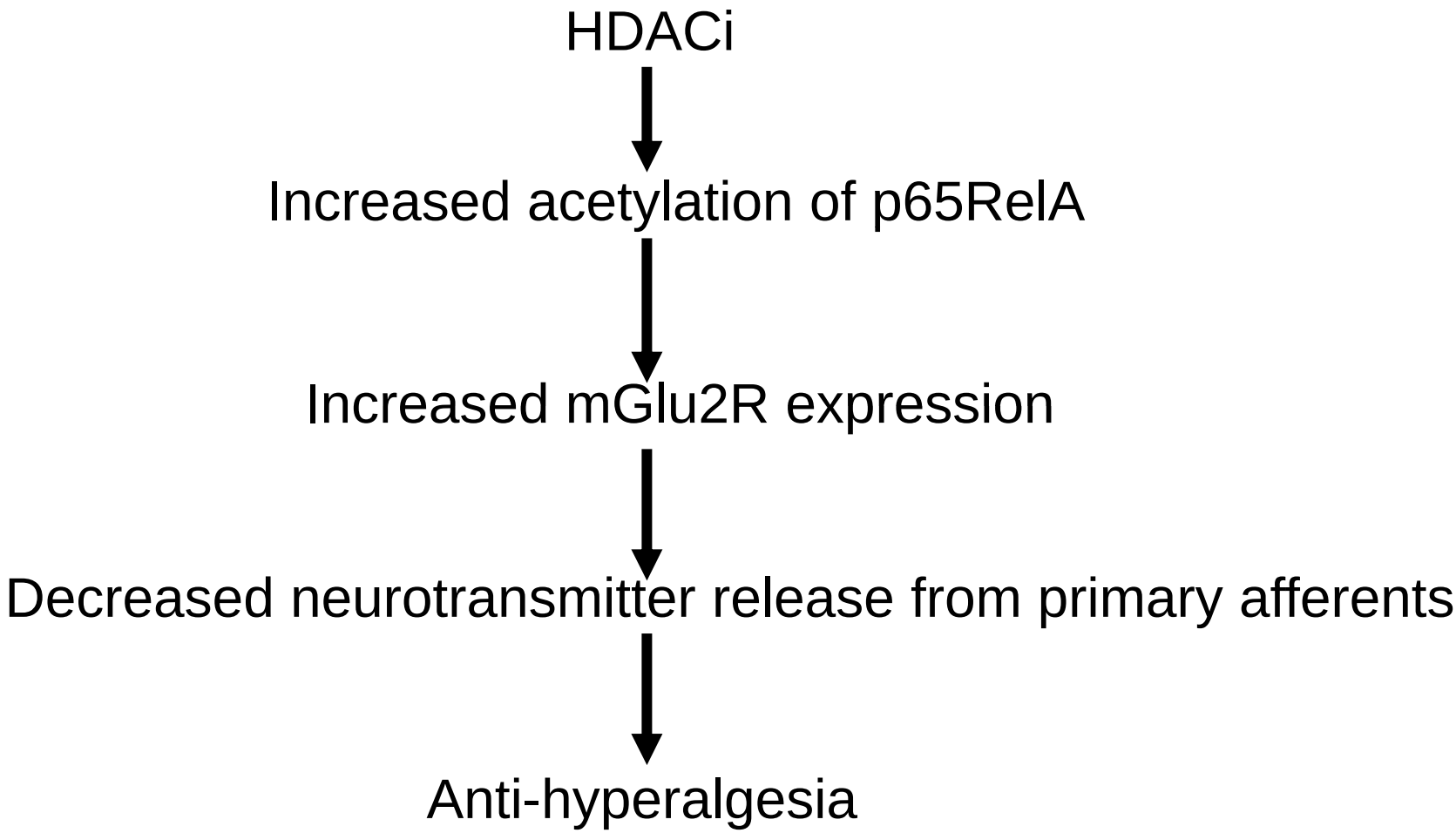
Uchida et al 2010, J of Neuroscience

PNI reduces mu opioid receptor and NaV1.8 in DRG



Uchida et al 2010, J of Neuroscience

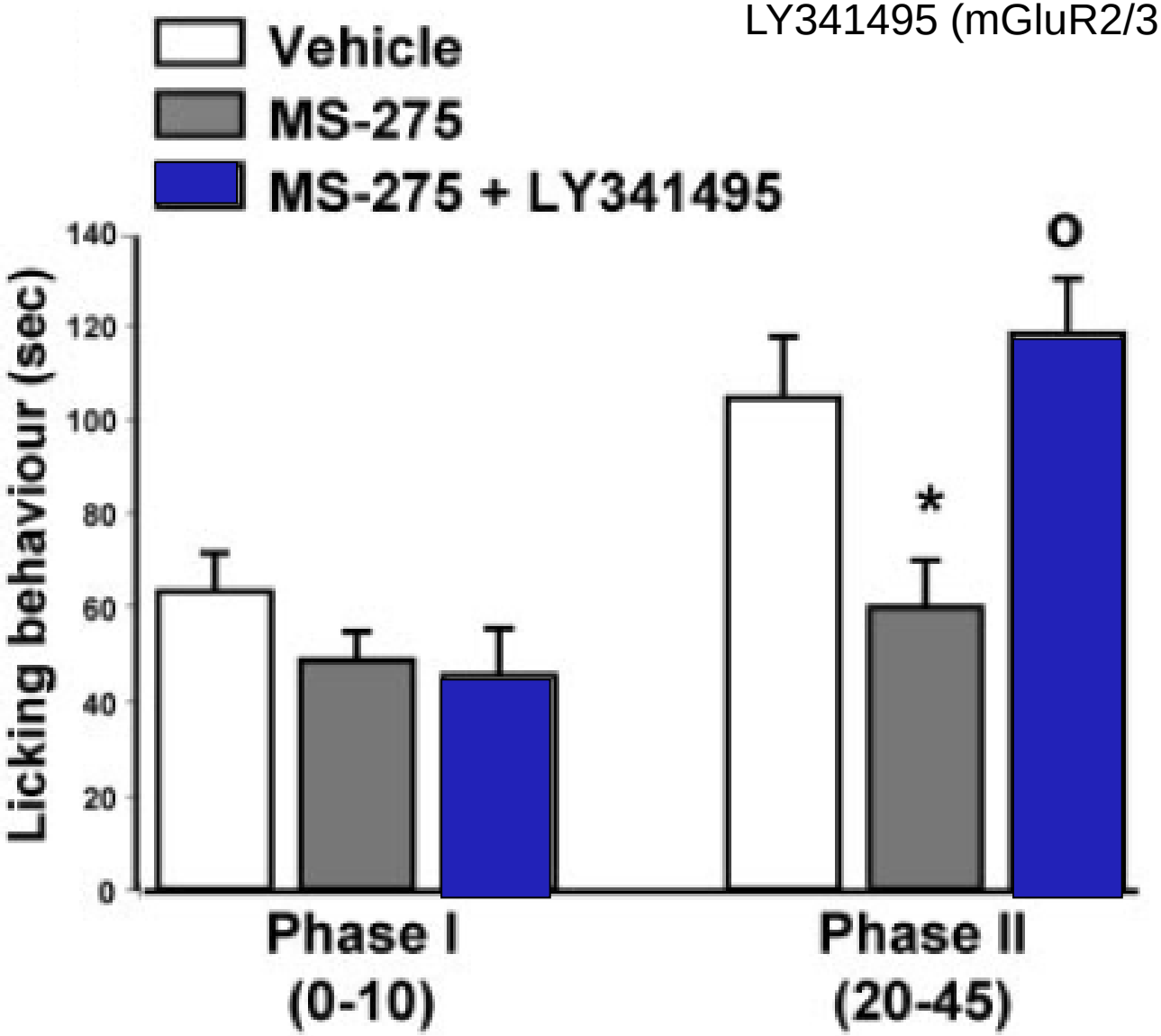
HDACi are anti-hyperalgesic



Chiechio et al 09

HDACi inhibitor is anti-hyperalgesic

MS275 (HDAC inhib): 5 days, 3m/kg sc
LY341495 (mGluR2/3 antag): -30min, 1mg/kg ip

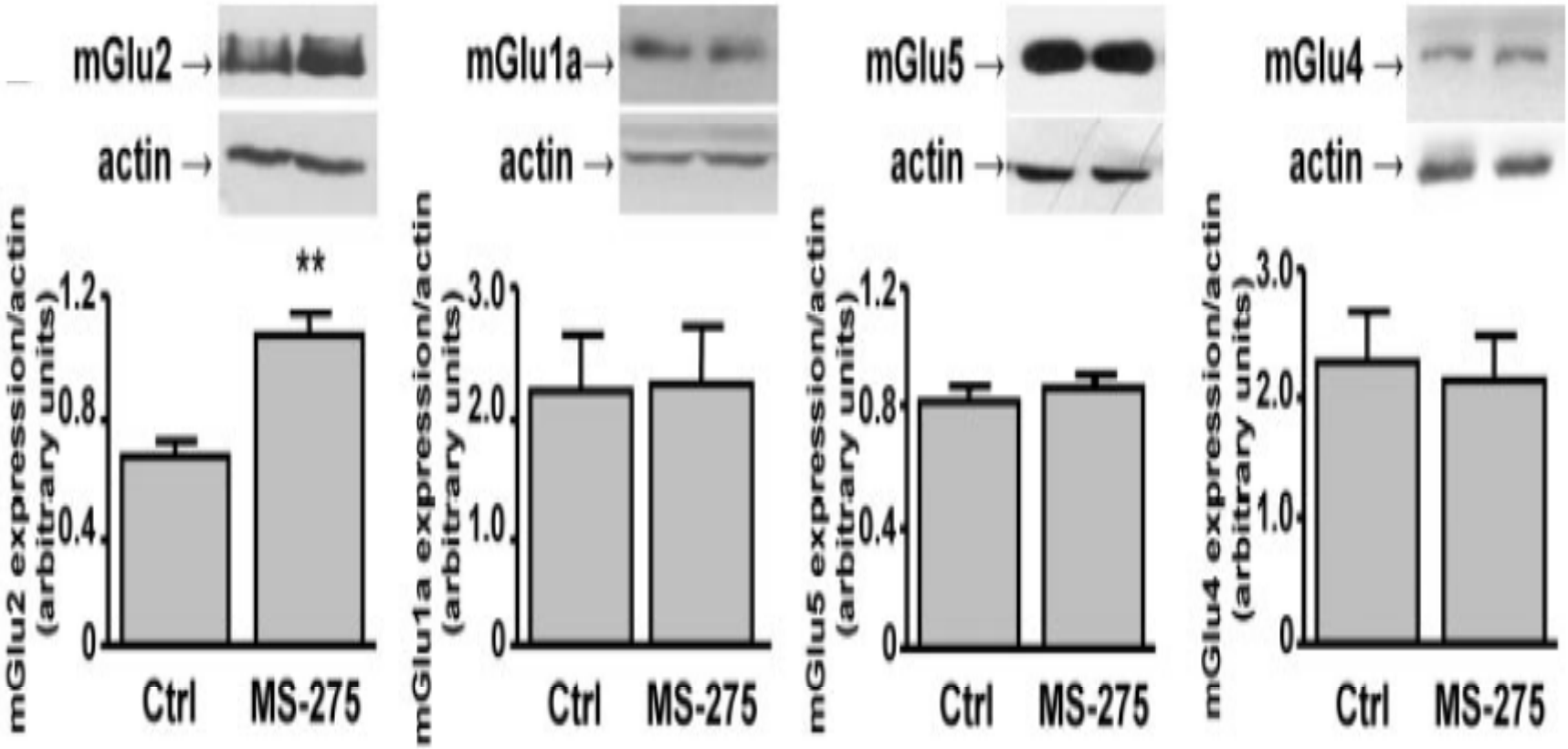


Anti-hyperalgesia prevented by mGluR2/3 antag

Chiechio et al 09

HDACi increases expression of mGluR2 in lumbar cord (not 1a, 5 and 4)

MS275 (HDAC inhib): 5 days, 3mg/kg sc



Chiechio et al 09

HDAC inhibitors are analgesic in NRM

Persistent inflammatory or neuropathic insult

↓

Hypoacetylation of Gad2

↓

Suppress Gad2 transcription

↓

Decreases glutamic acid decarboxylase (GAD65)

↓

Impaired GABA inhibition

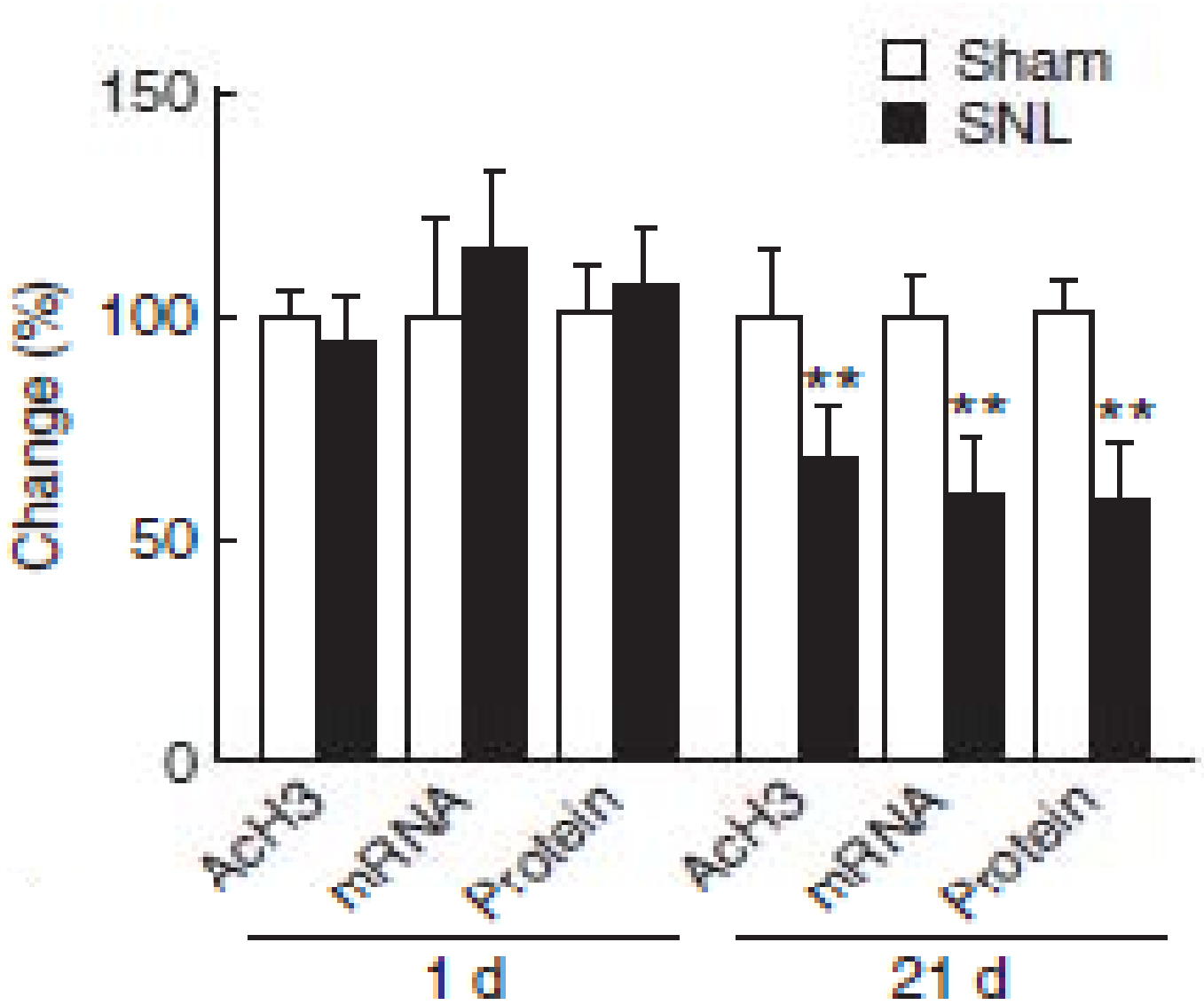
↓

Hyperalgesia

All effects reversed by HDAC inhibitors

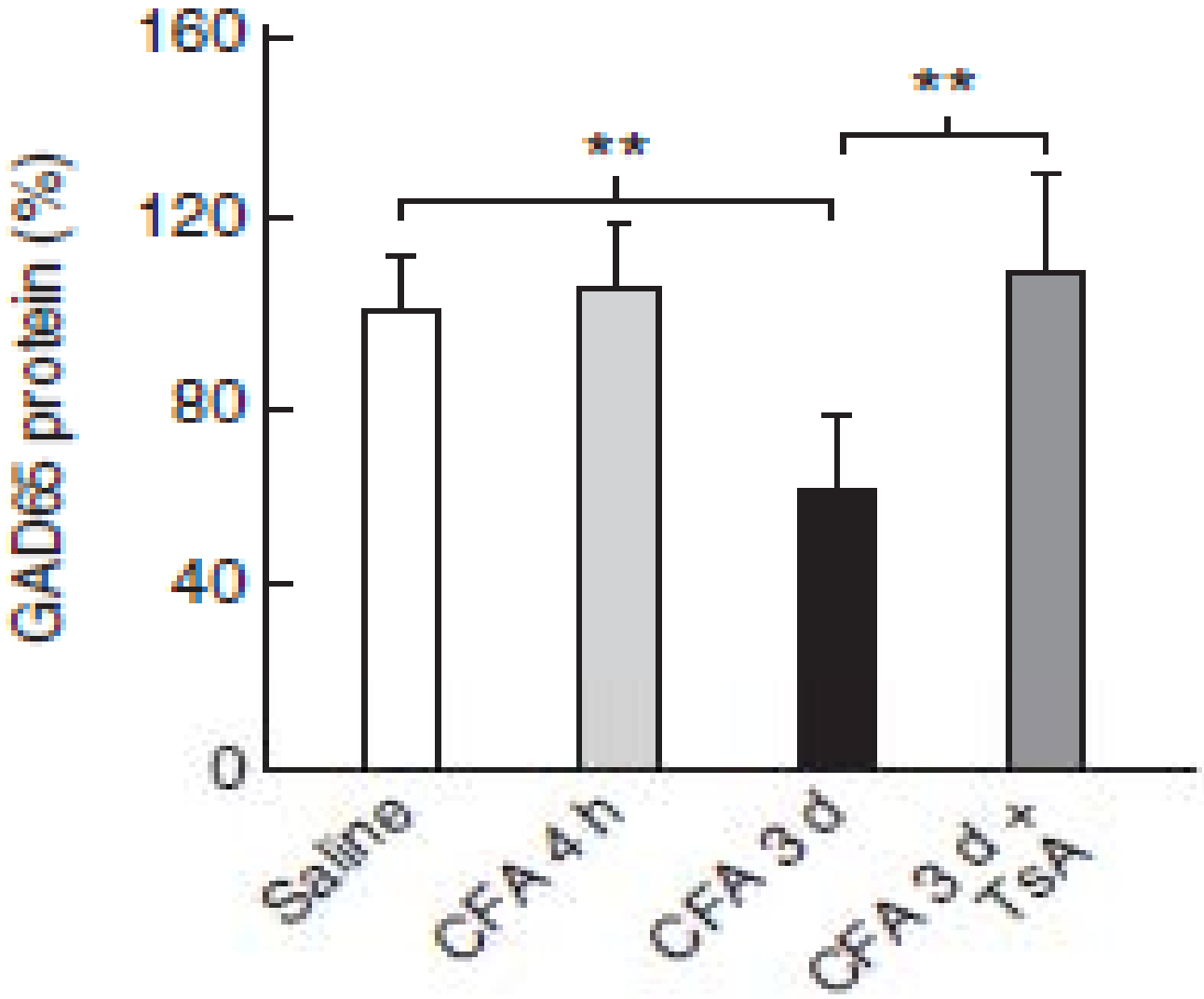
Zhang et al (2011) Nature Medicine

Chronic nerve injury reduces AcH3, Gad2 (message) and GAD65 (protein)



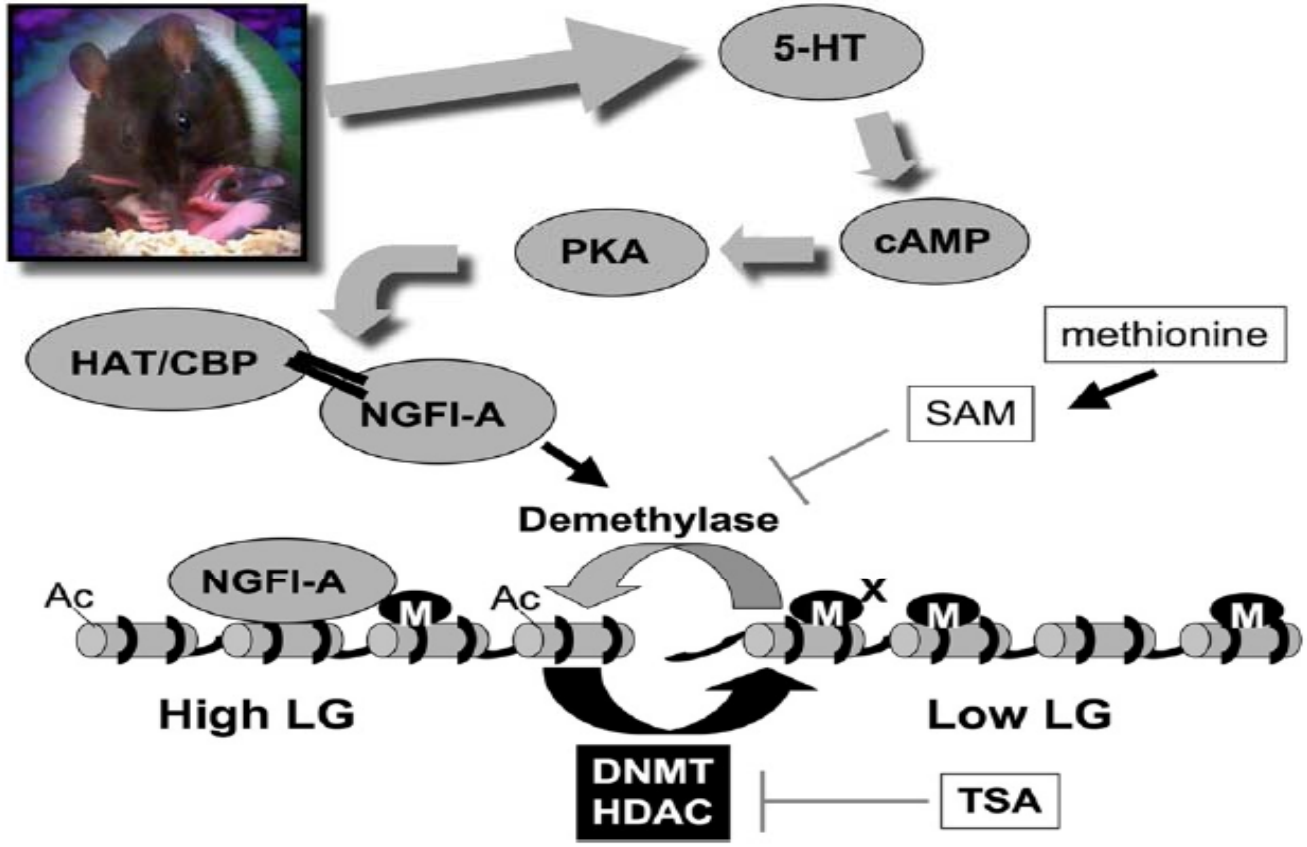
Zhang et al (2011) Nature Medicine

HDAC inhibitor reverses CFA induced decrease in GAD65



Zhang et al (2011) Nature Medicine

Maternal care, increases GR expression and dampens stress response



• Maternal care increases TF NGFI-A and histone acetylation, decreases DNA methylation and increases GR expression

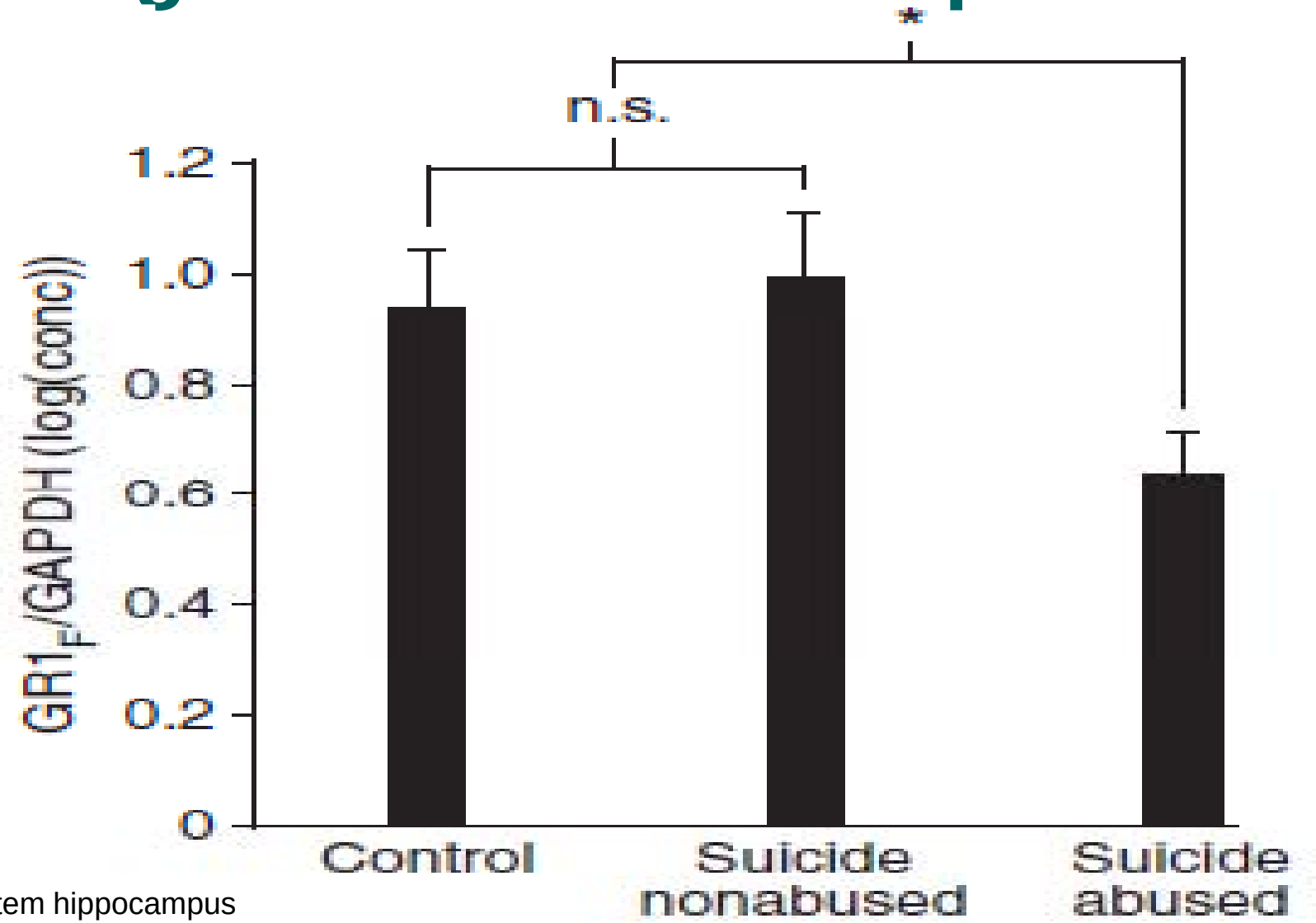
• Methionine promotes methylation and Low LG phenotype

• HDAC inhibs increase acetylation and High LG phenotype

TSA – Trichostatin A (HDAC inhib), SAM – S adenosyl methionine

McGowan et al 08

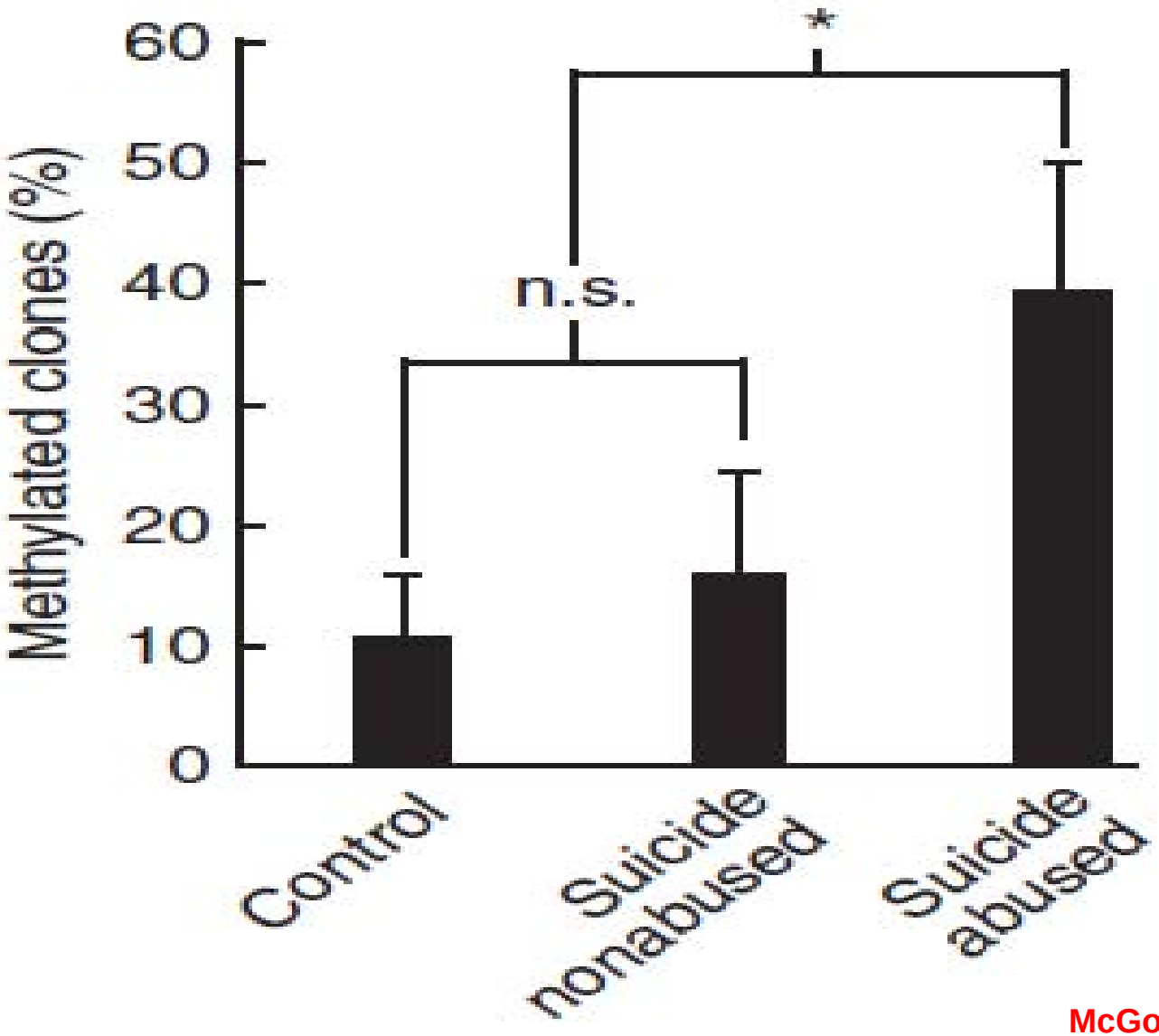
Childhood abuse decreases glucocorticoid receptor



Post mortem hippocampus
Decreased GR, leads to increased stress response
Also decreased NGFI-A

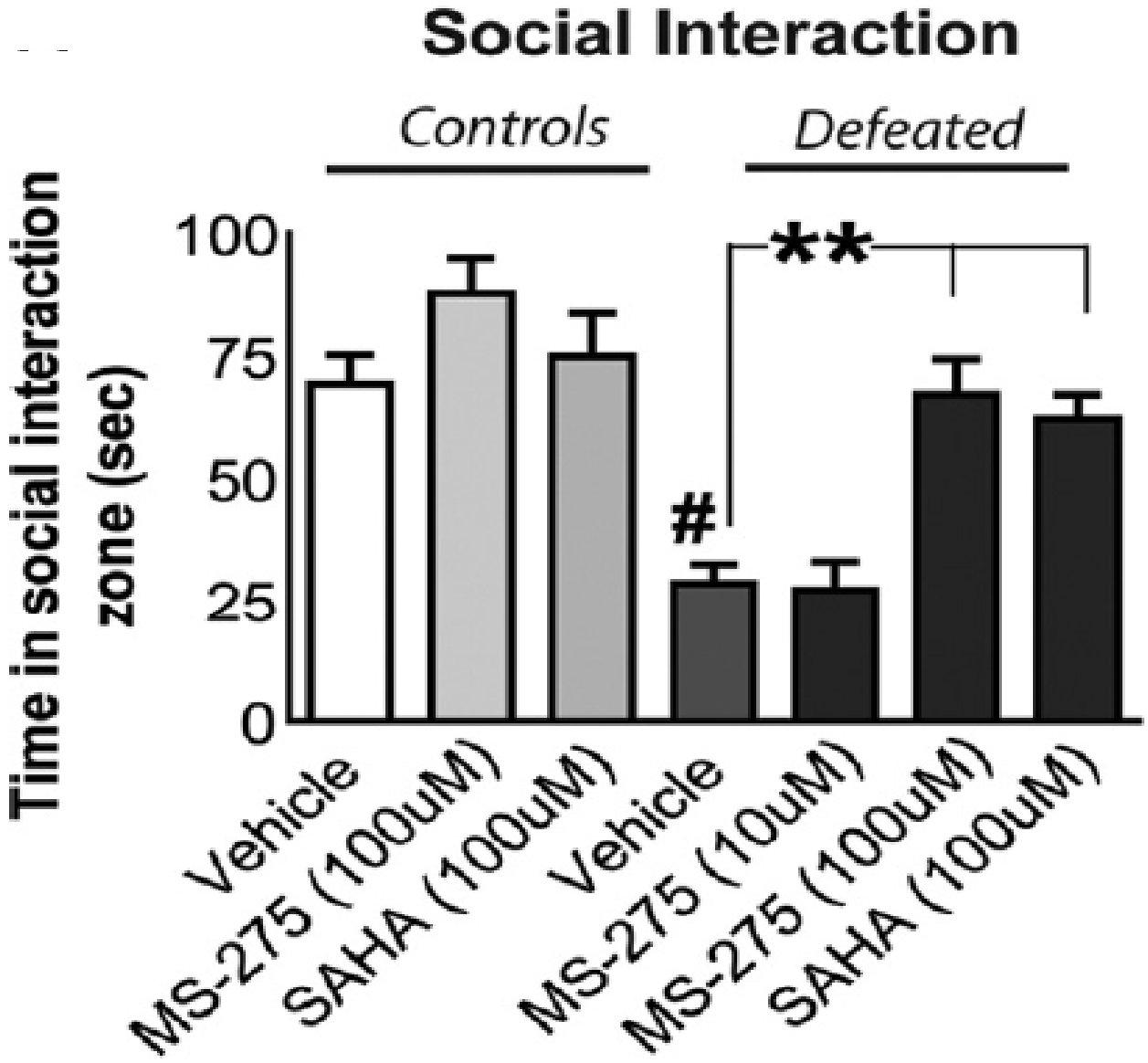
McGowan et al 09

Childhood abuse increases methylation of glucocorticoid receptor



McGowan et al 09

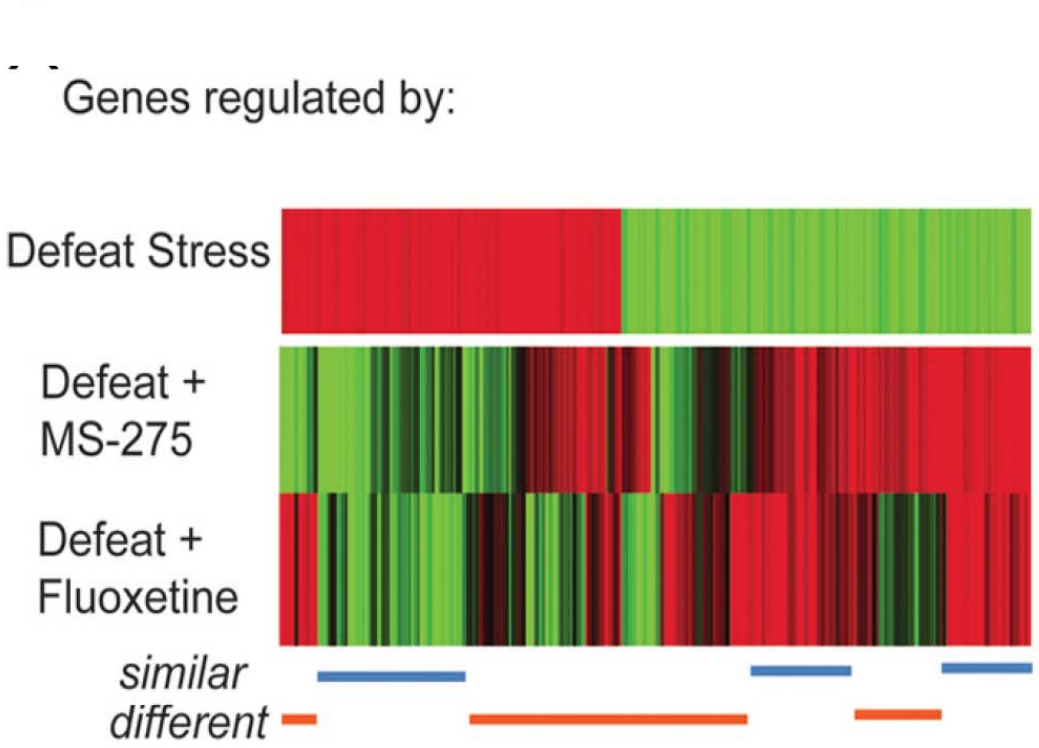
HDAC inhibs have anti-depressant like effects

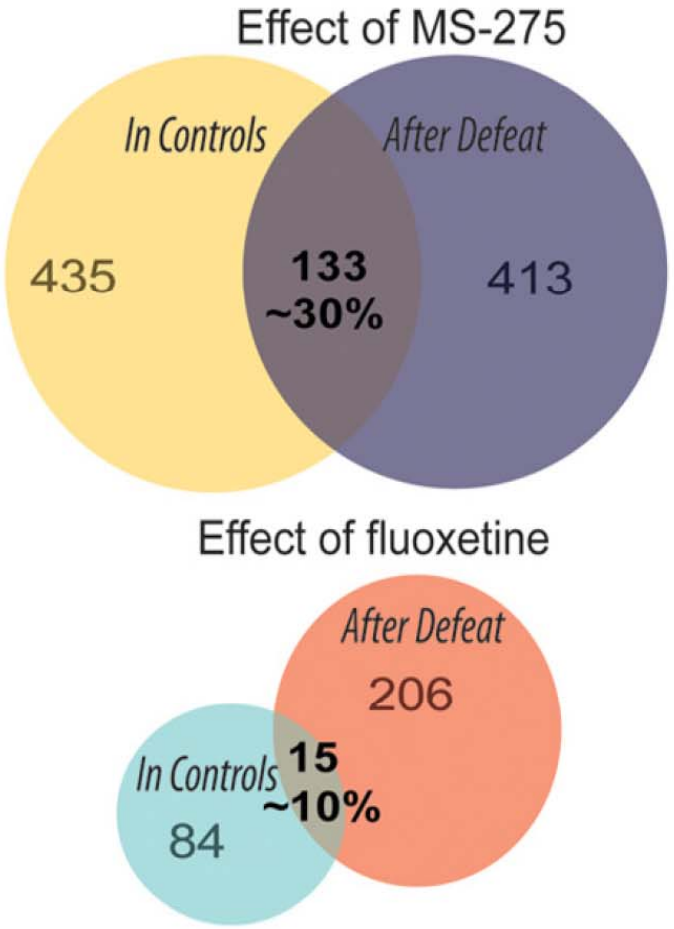


After 10 days chronic social defeat stress
Infused MS275 or SAHA 100μM

Covington et al 2009

Social defeat stress induced changes in gene expression are partially reversed by MS275 or fluoxetine

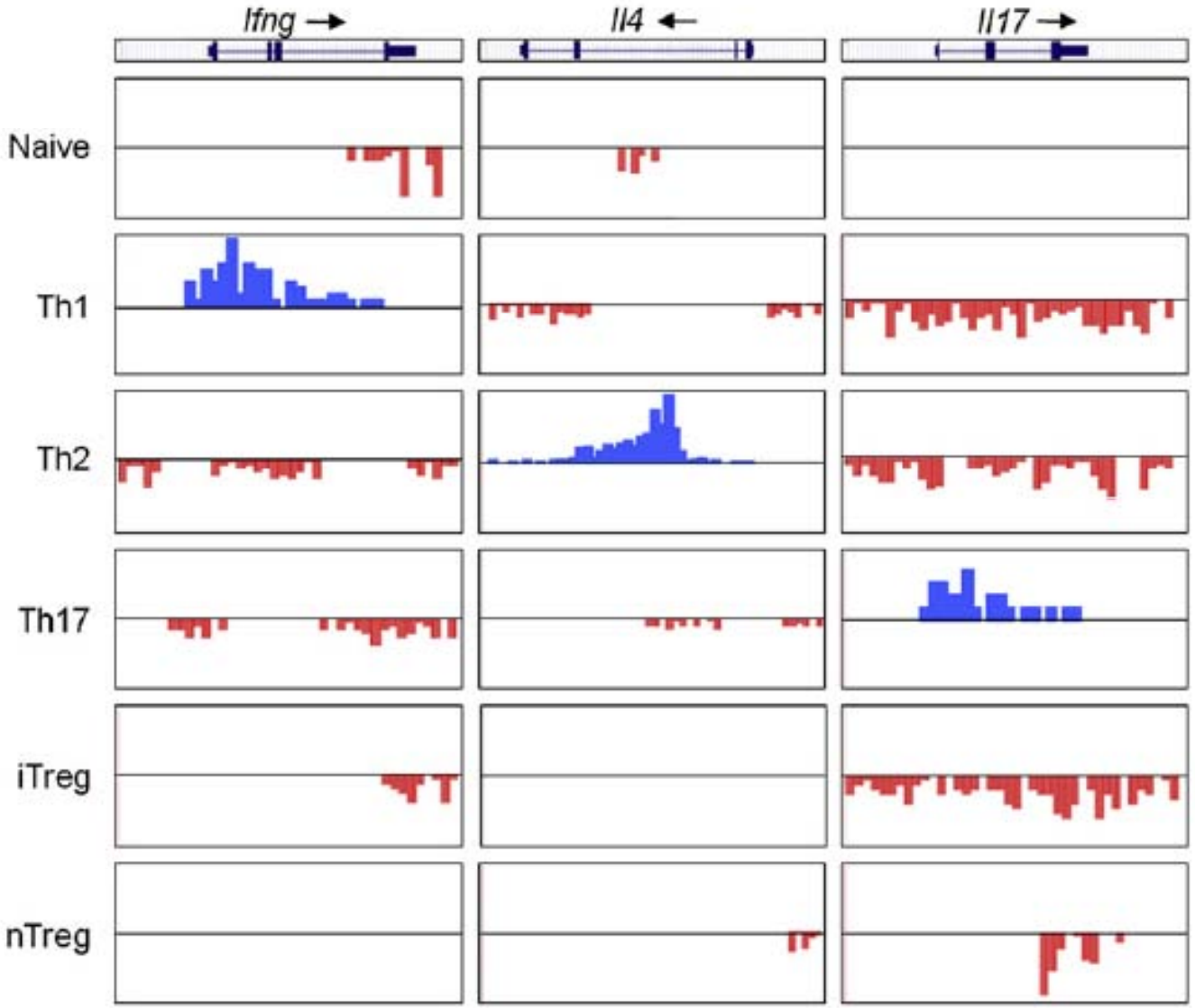




MS275: 100μM infusion into NAc
Fluoxetine: 20mg/kg/day
For 10 days after chronic (10days) social defeat stress

Covington et al 2009

T cell differentiation is associated with modifications of signature cytokines



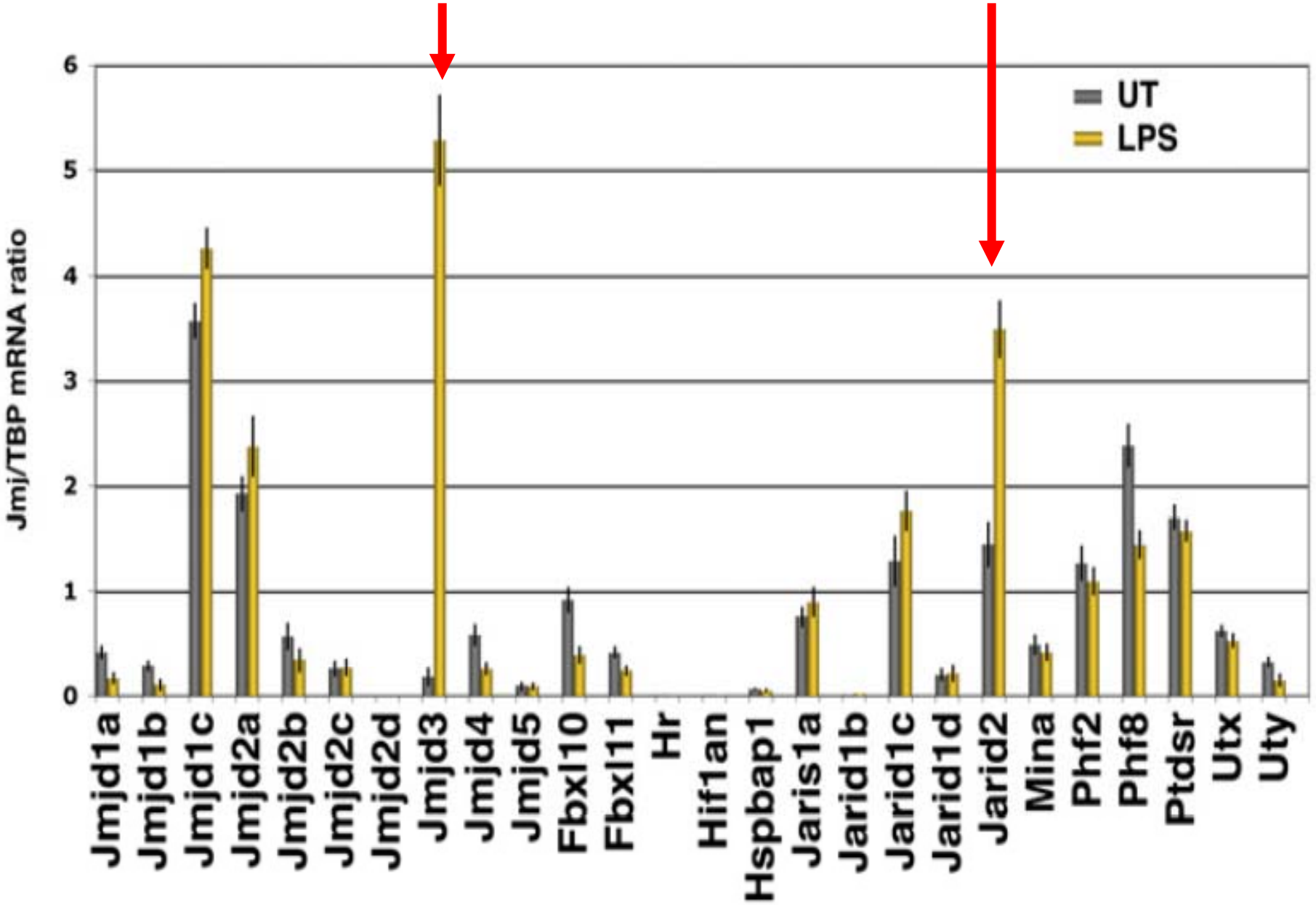
- Genome wide maps - ChIP Seq
- Signature cytokines as expected

H3K4me3 - activating

H3K27me3 - repressing

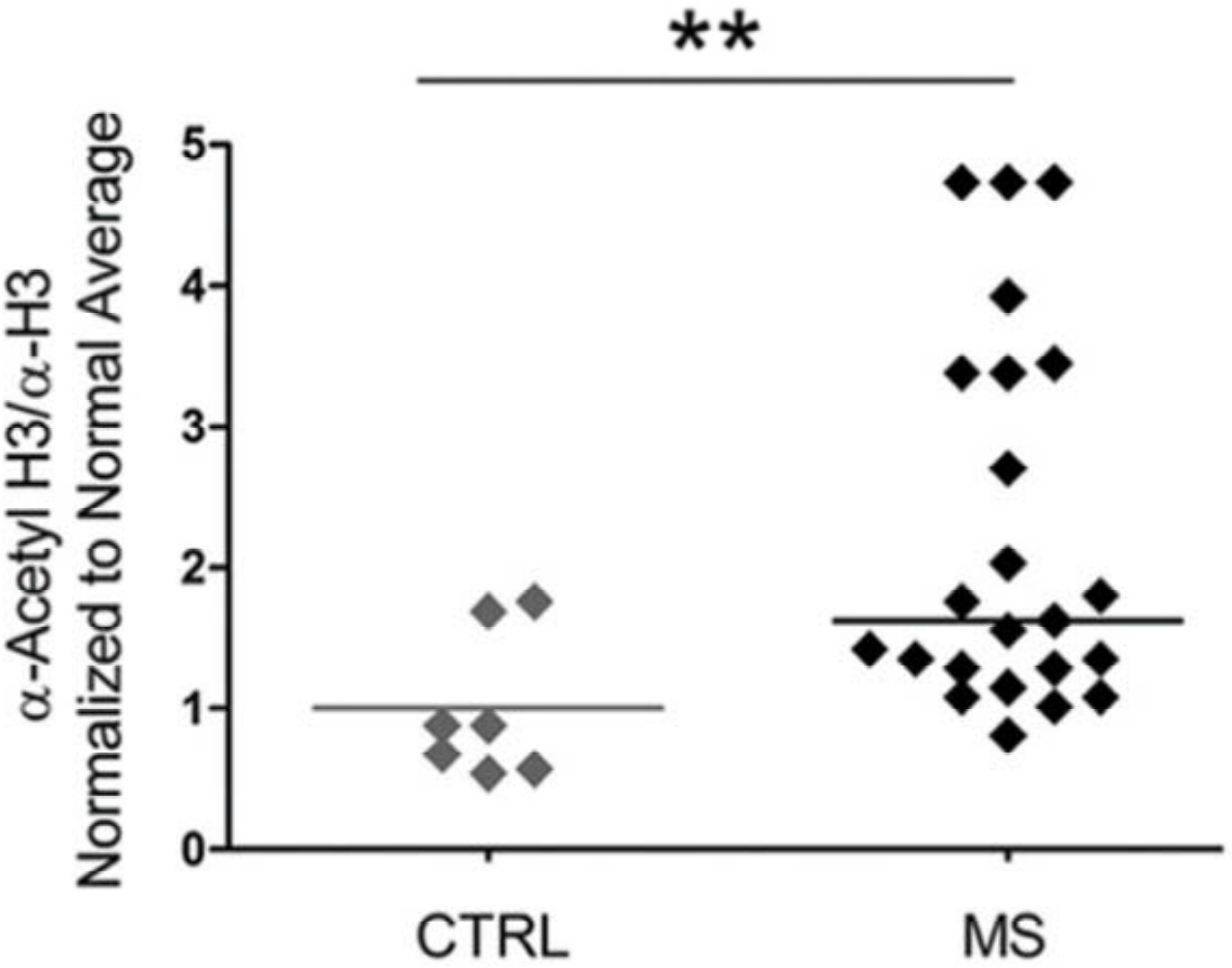
Wei et al 09

JmjD3 is increased in activated macrophages



De Santa et al 07

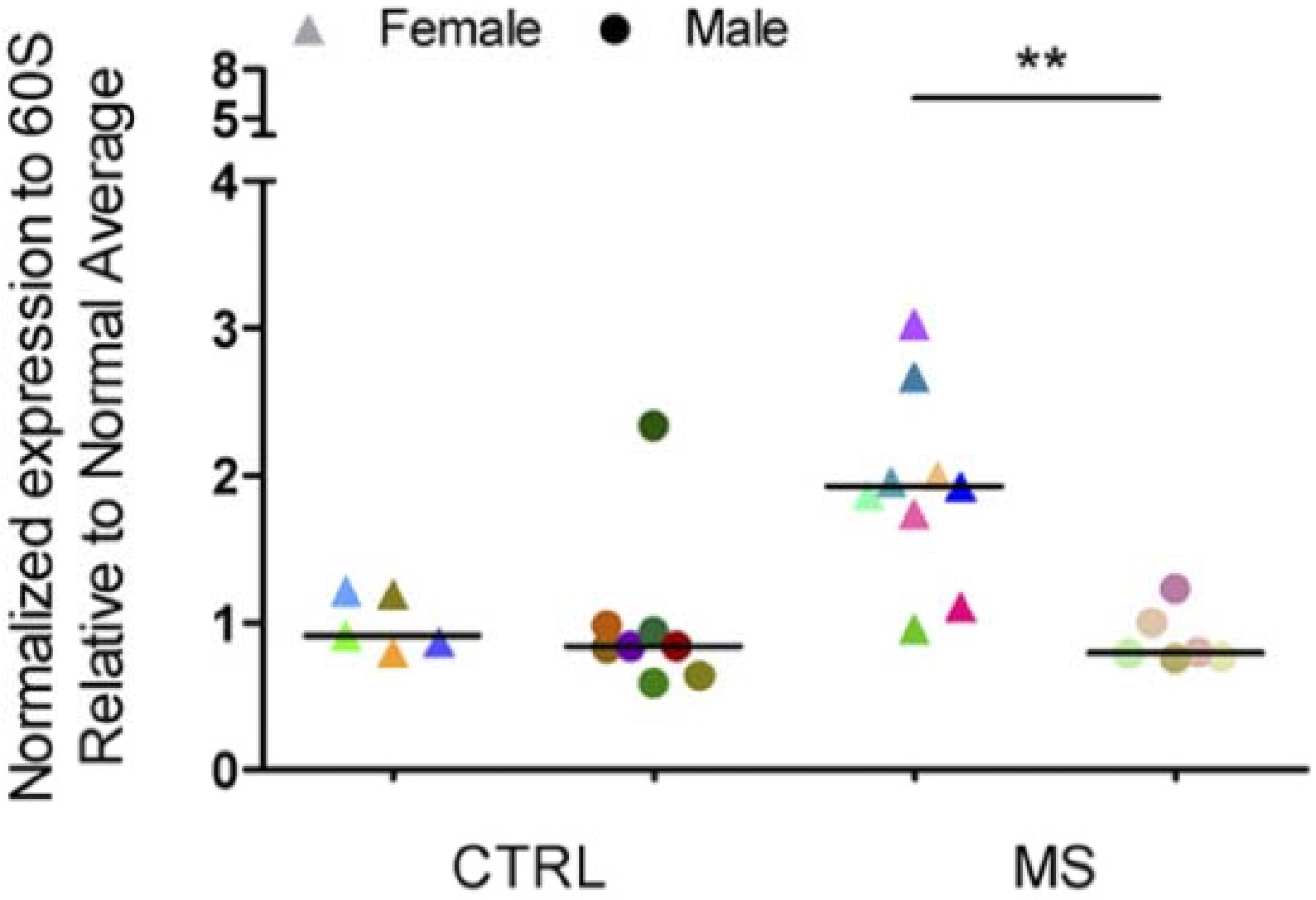
Increased acH3 in MS patients



Frontal lobes, normal appearing white matter

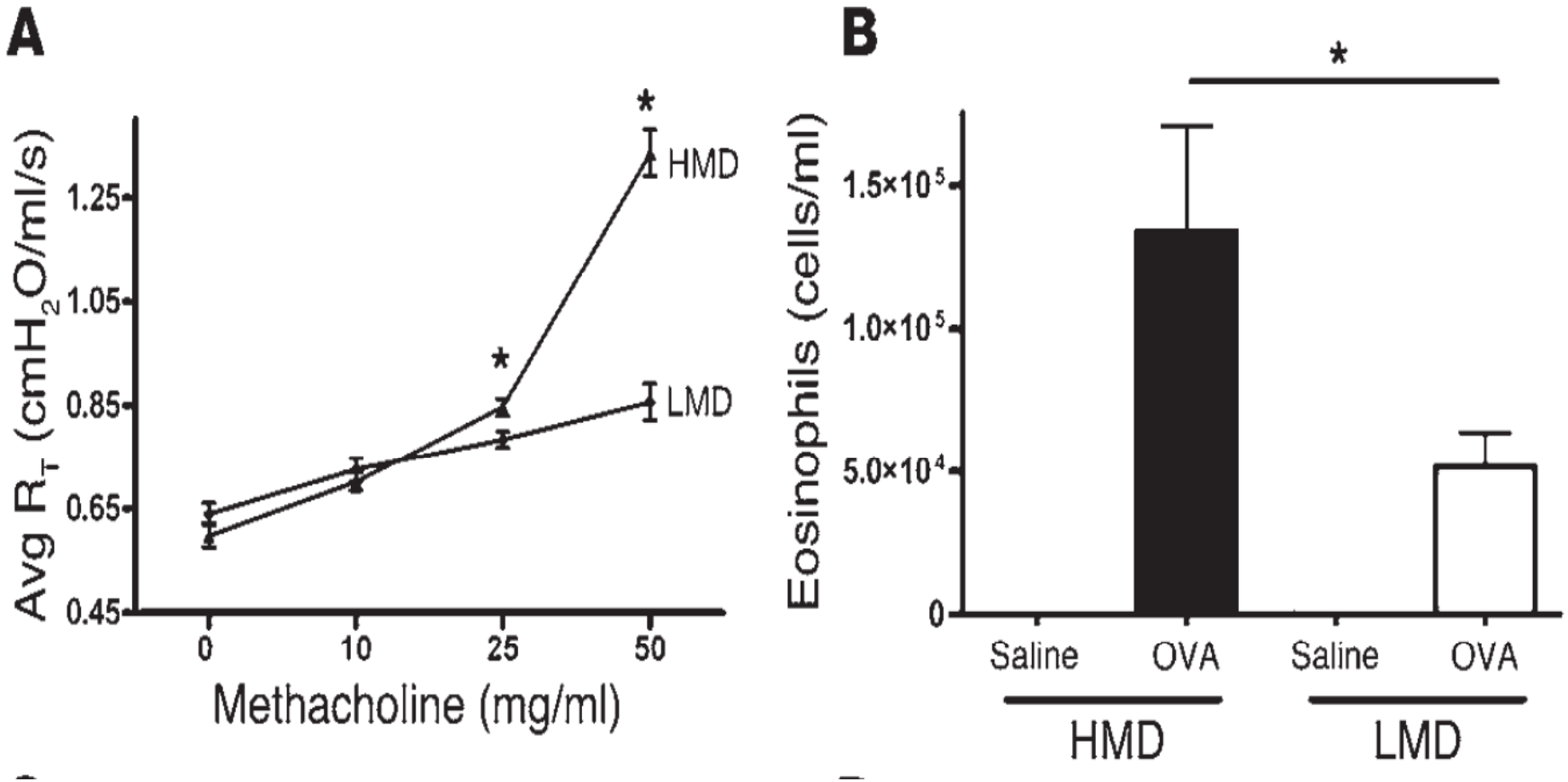
Pedre et al (March 2011) J Neuroscience 3435

Increased HAT (P300) in female MS patients



Pedre et al (March 2011) J Neuroscience 3435

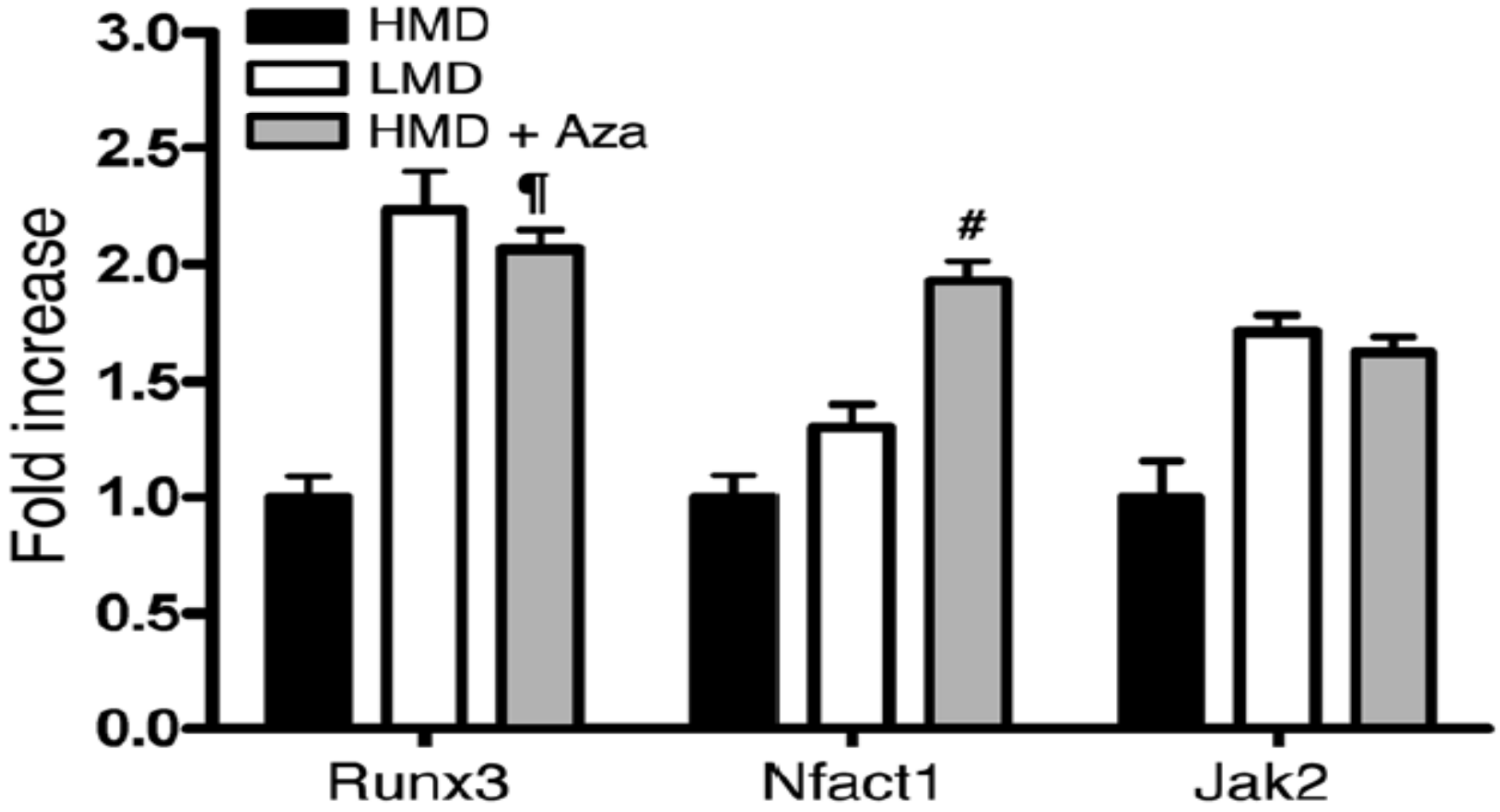
High Methyl Diet (HMD) increases allergic inflammation



Diet: -2w and pregnancy
Ovalbumen challenge (6-10w)
Lung lavage

Hollingsworth et al 08

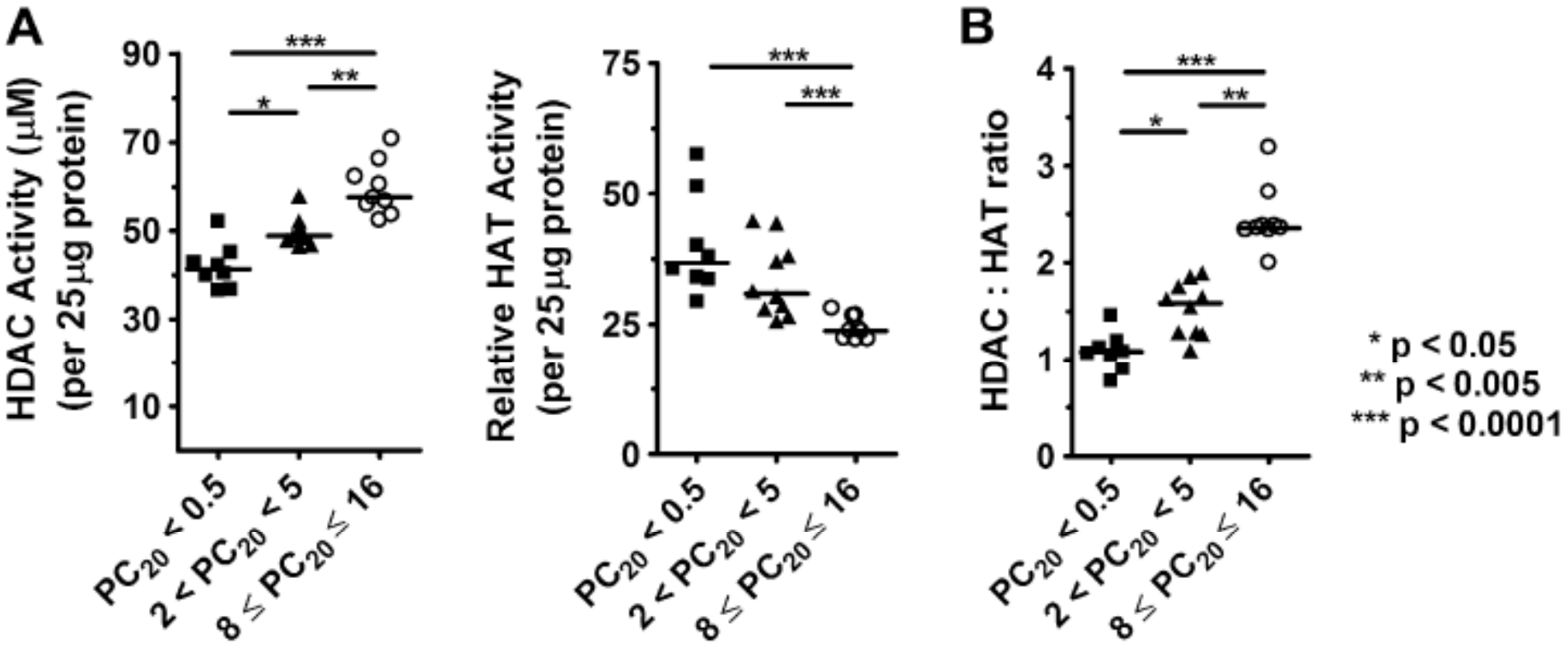
HMD induced decrease in gene expression is reversed by azacytidine (demethylating agent)



Nfatc1: nuclear factor of activated T cells
Jak2: Janus kinase 2
Azacytidine – in vitro

Hollingsworth et al 08

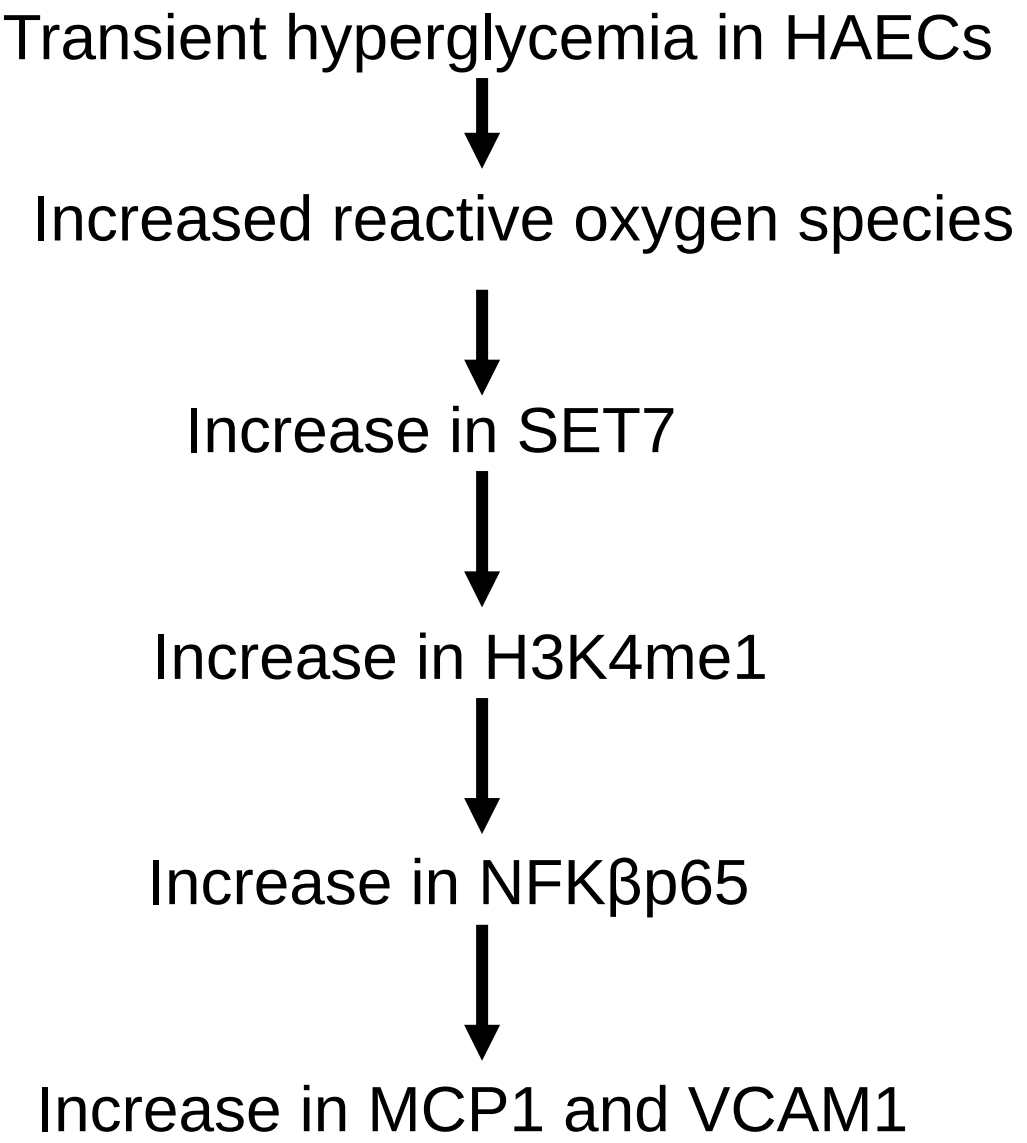
HDAC decreases and HAT increases with broncho hyper-responsiveness



Severe <0.5, mild <5, non asthmatic >8mg/mL
Activity measured ex vivo in nuclear PBMC lysates

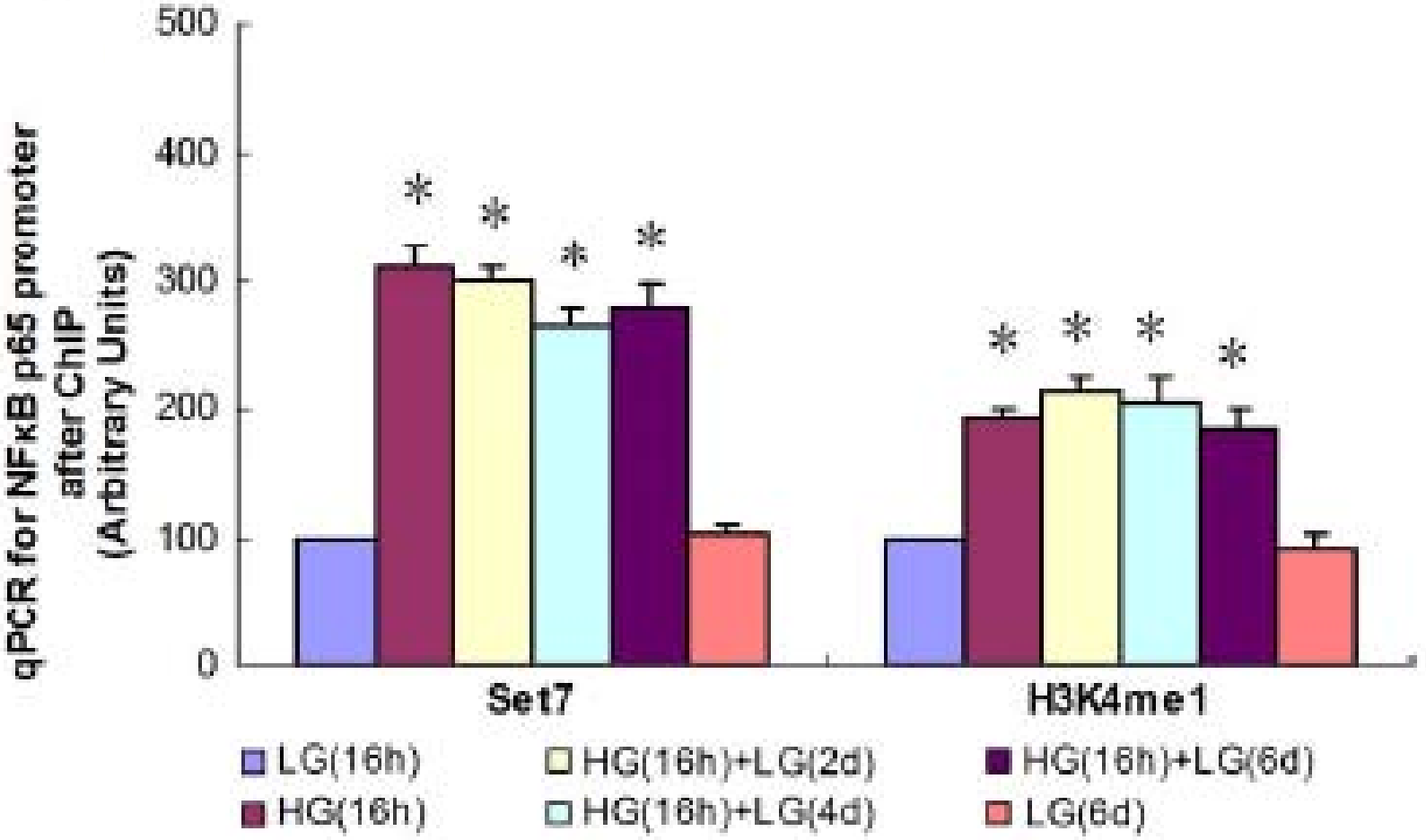
Su et al 09

Transient hyperglycemia produces long lasting changes in human AECs



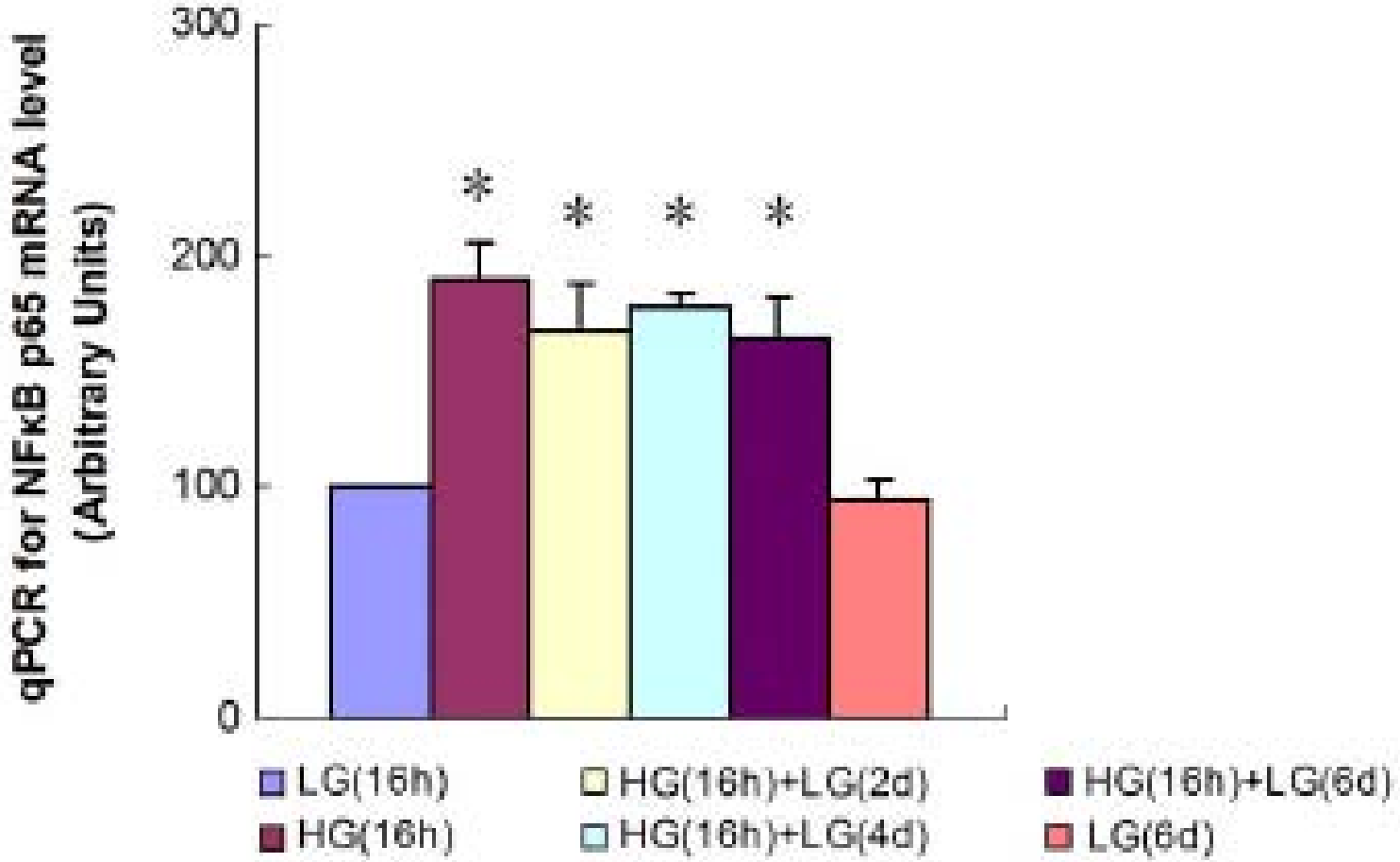
El-Osta 2008

Transient hyperglycemia produces sustained elevation of SET7 binding and H3K4me1



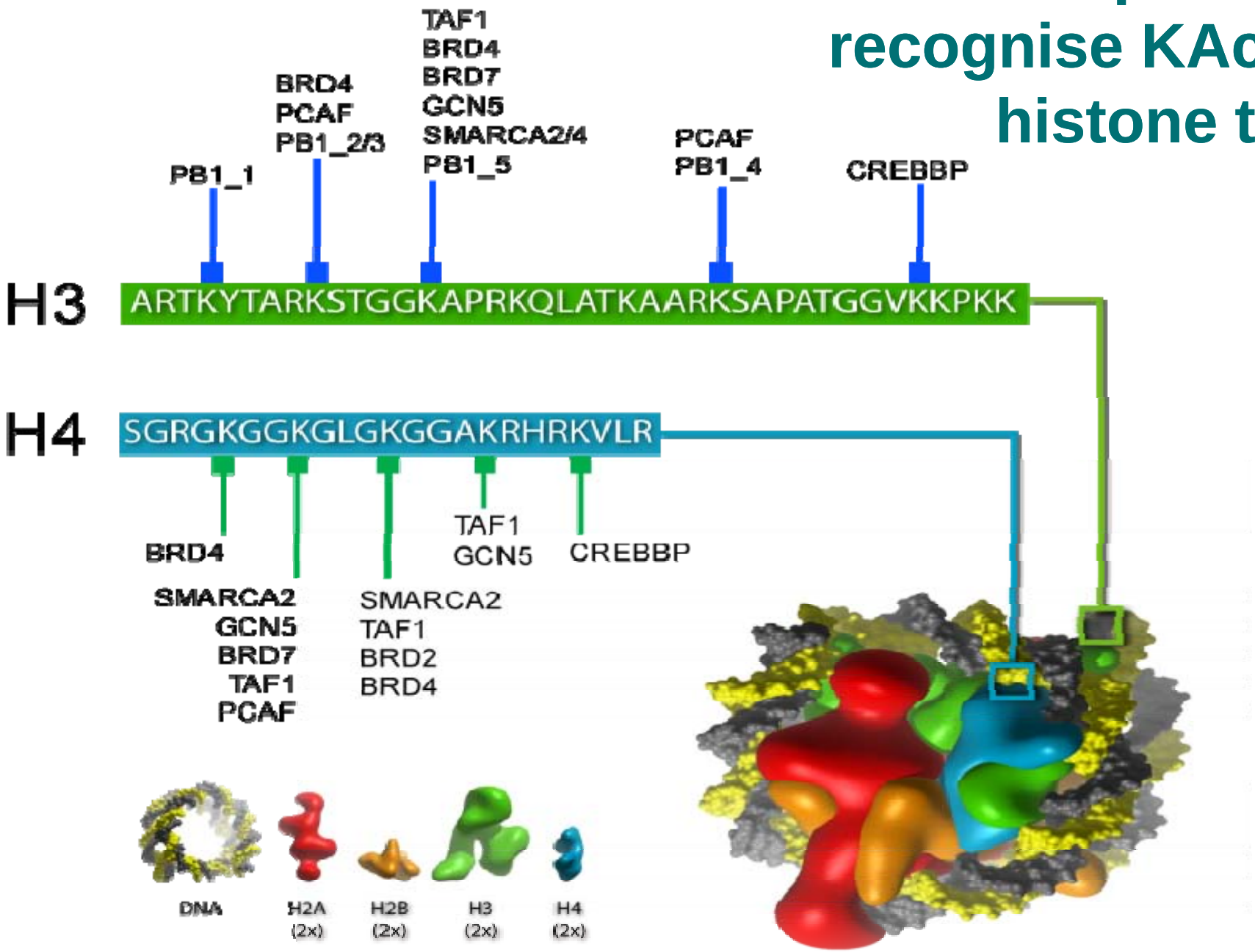
El-Osta 2008

Transient hyperglycemia produces sustained elevation of p65 mRNA



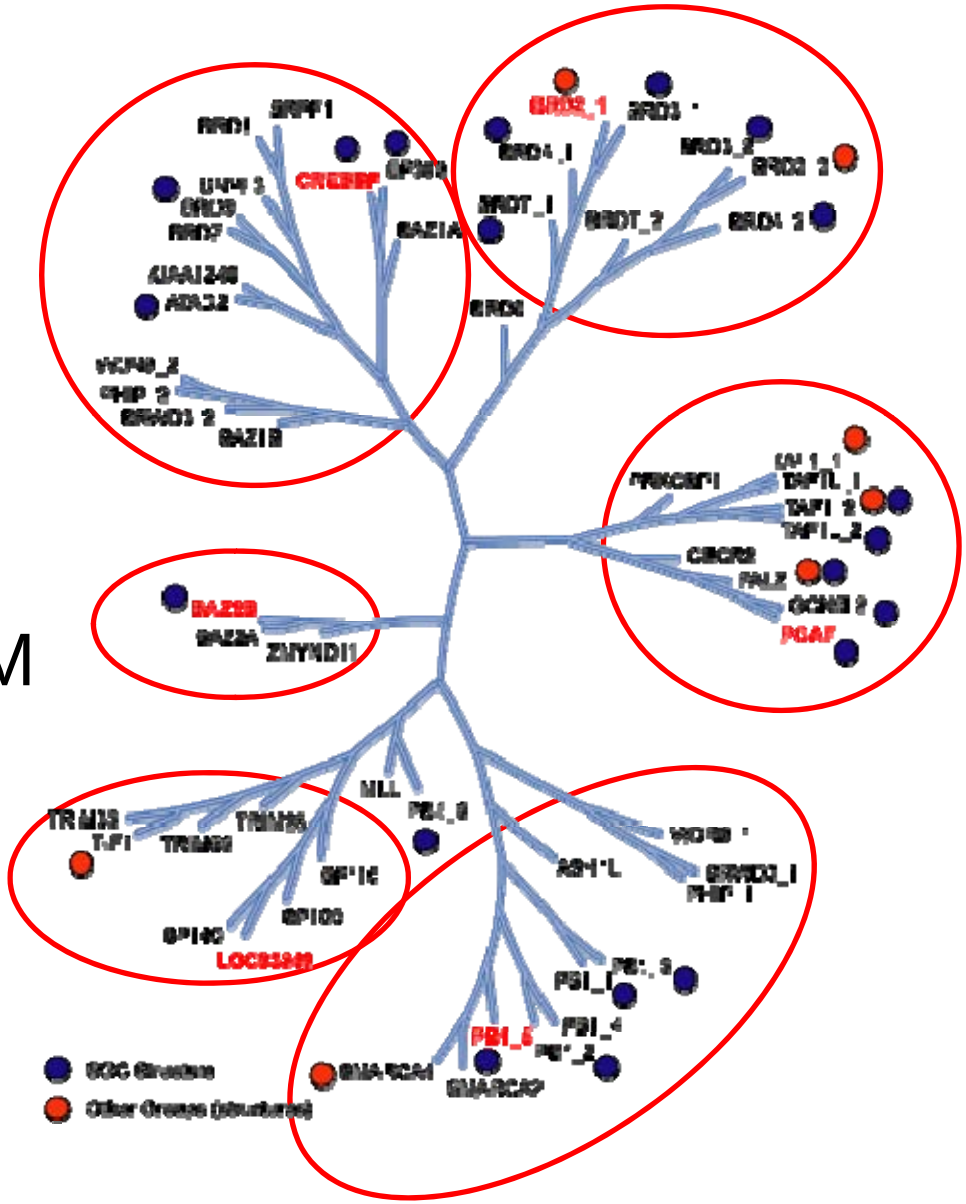
El-Osta 2008

Bromodomain proteins recognise KAc on histone tails

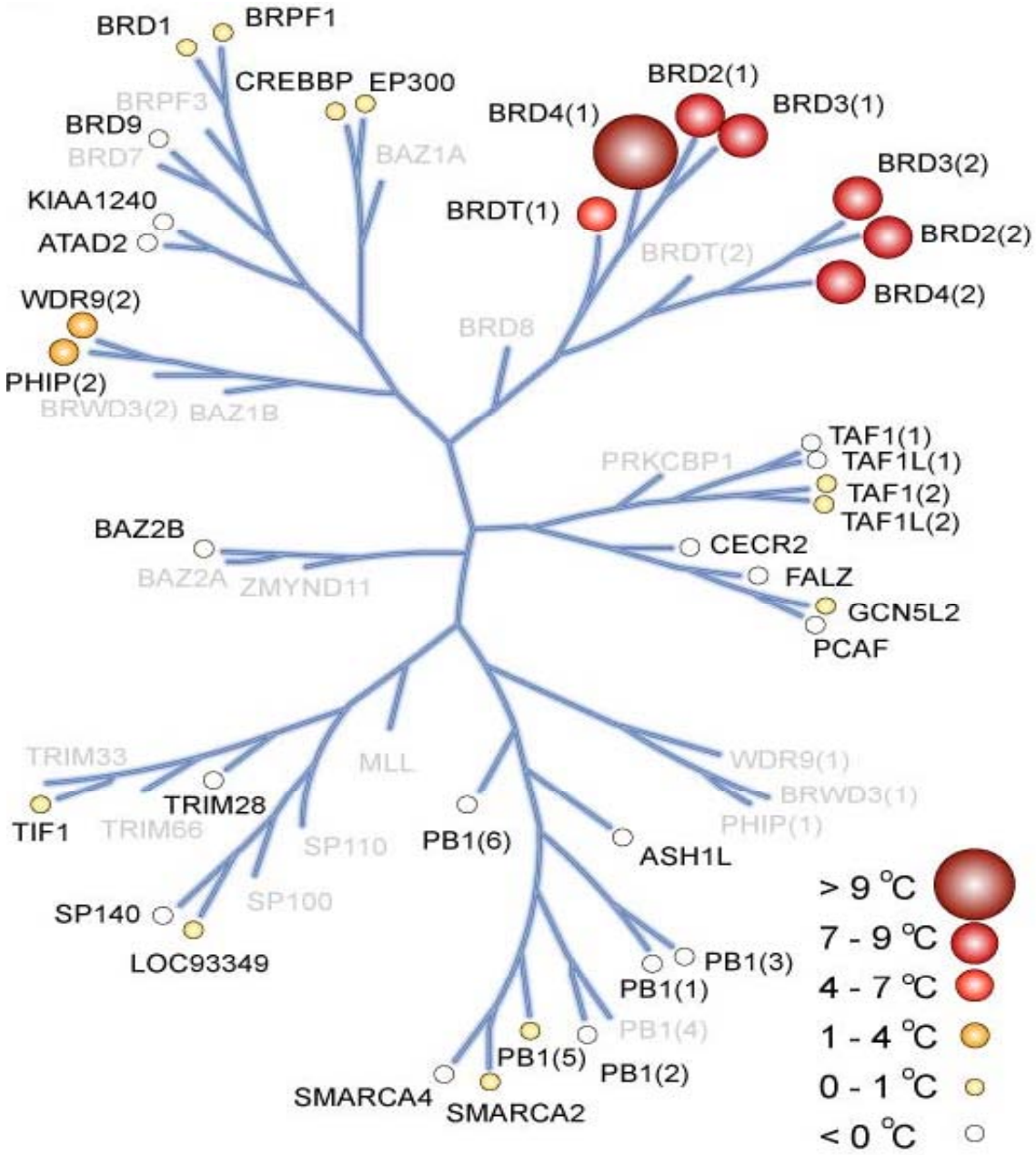


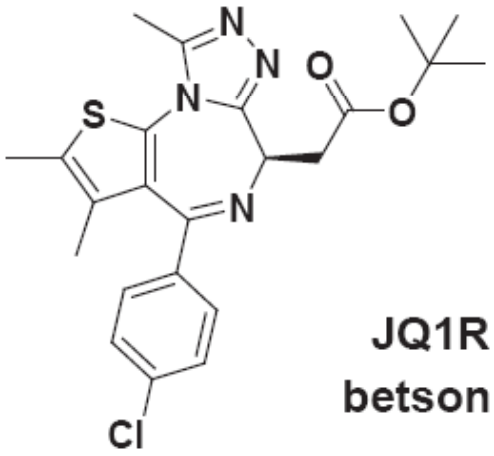
Bromodomain Probes - Target Profile

- <100 nM
- >30-fold selectivity *vs* other sub-families
- Cellular potency <1µM

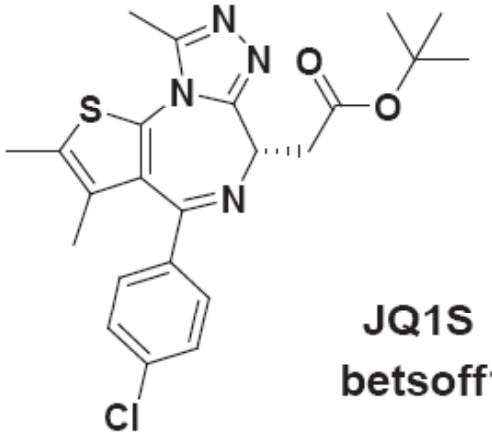


A selective inhibitor for BET sub-family





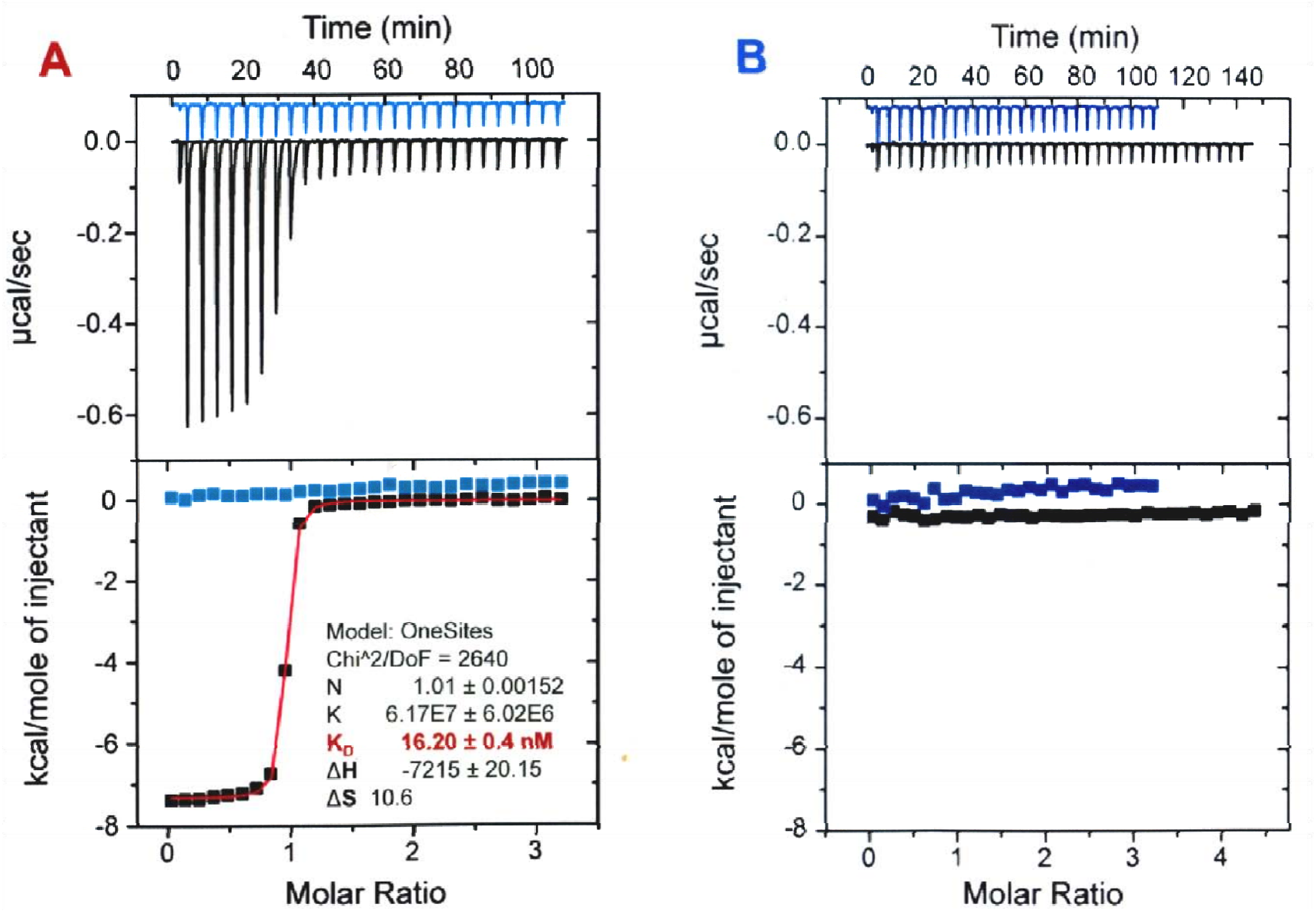
JQ1R
betson1



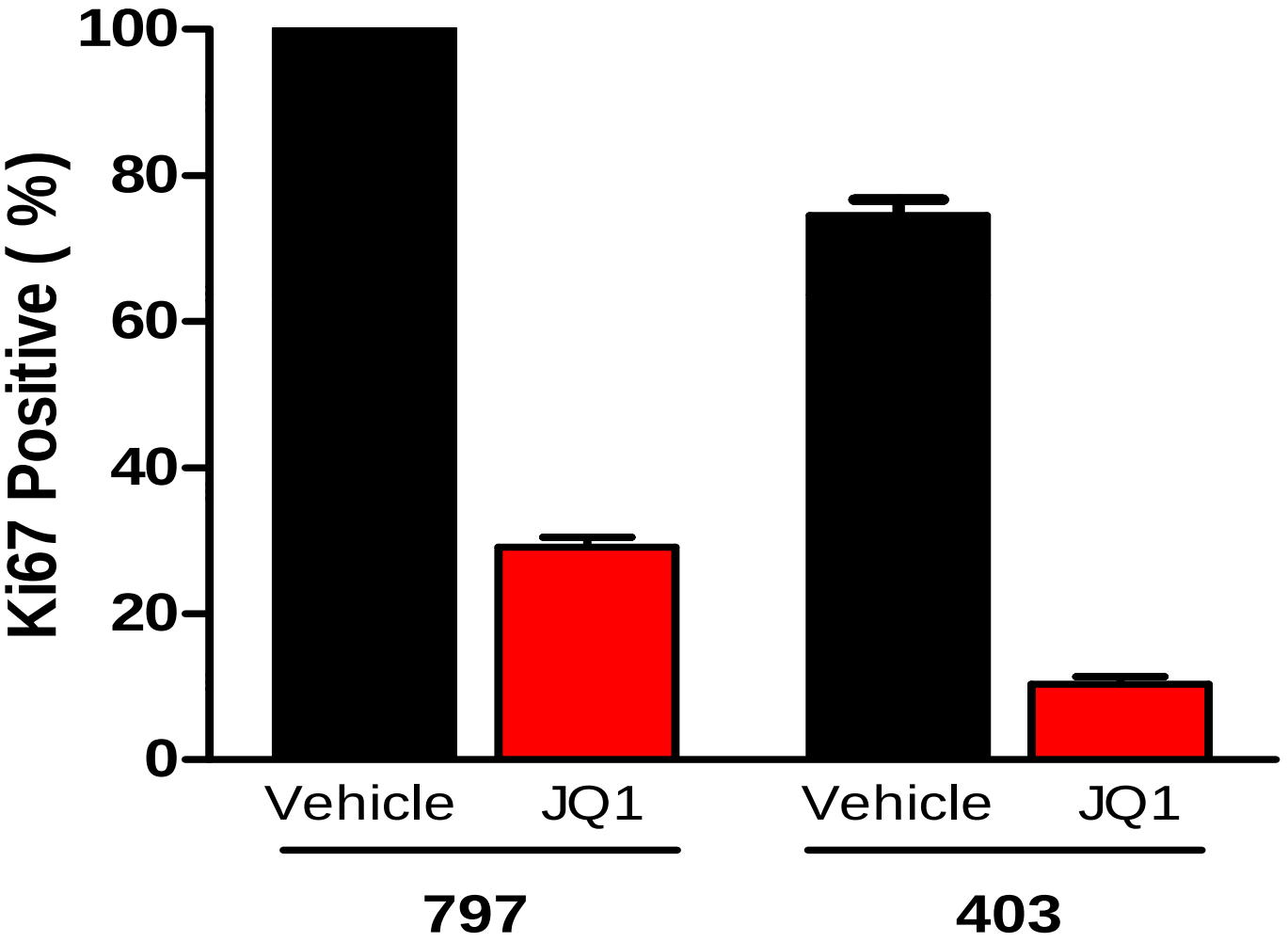
JQ1S
betsoff1

Nature, Dec 23, 2010

BRD4 probe shows enantiomeric specificity

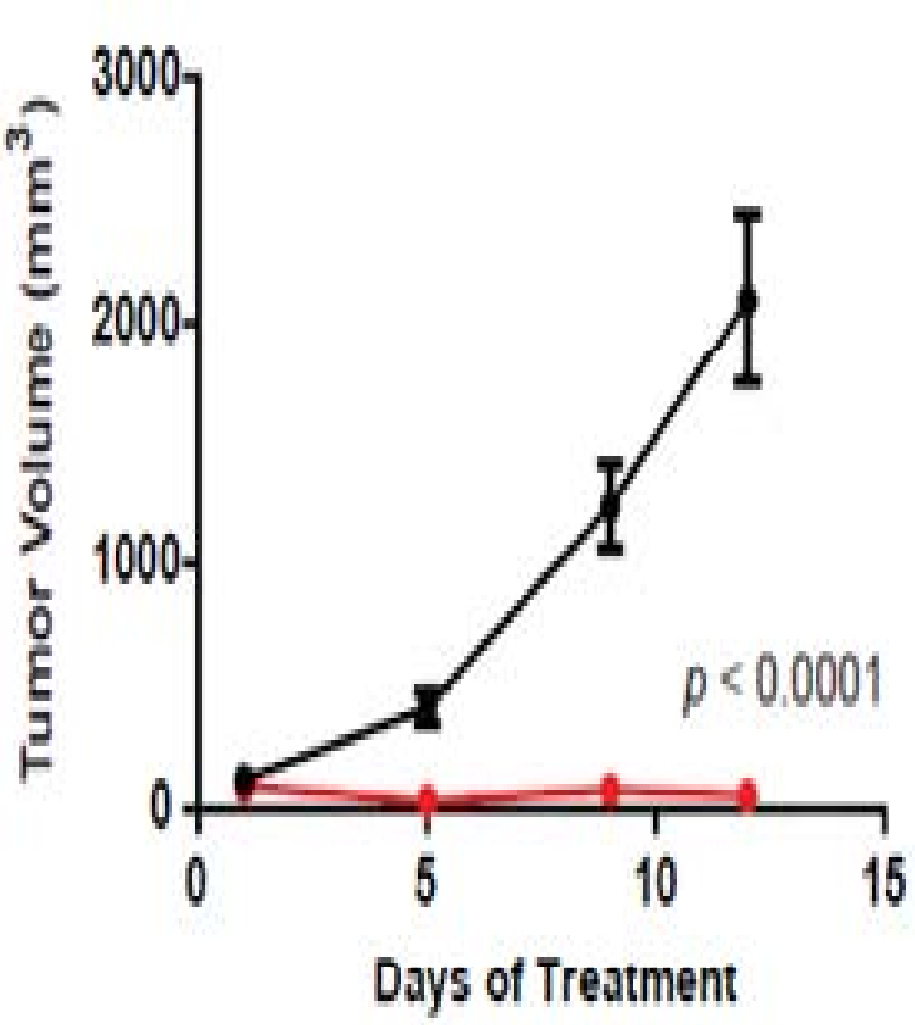


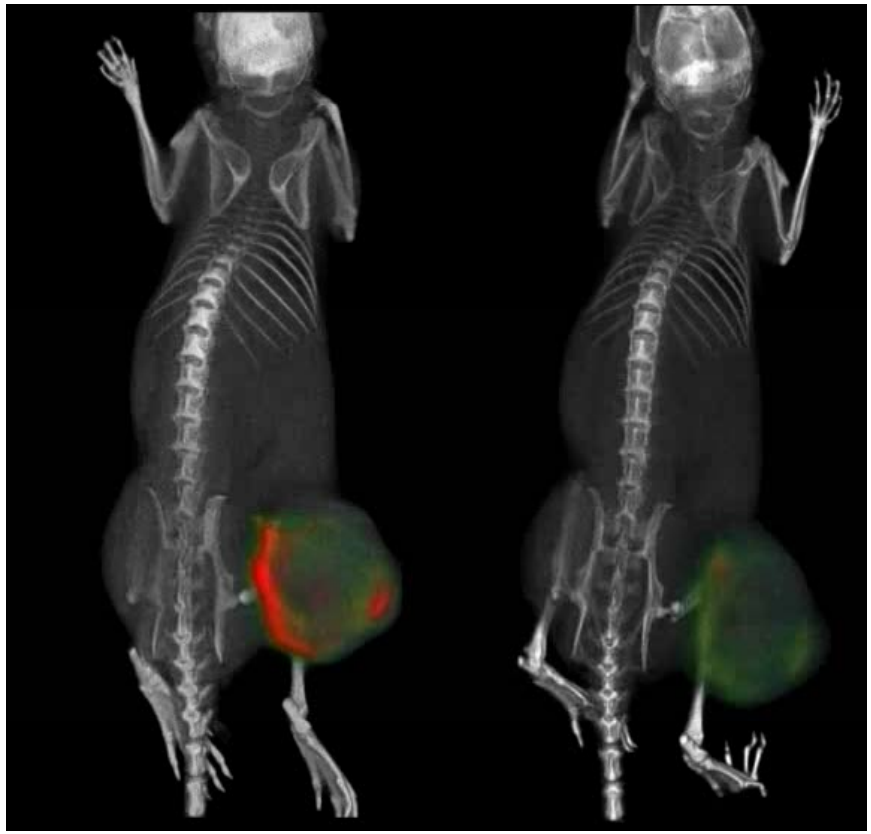
First probe: JQ1 reduces proliferation in two patient derived cell lines



KI67 positive = proliferating

…and reduces tumour size



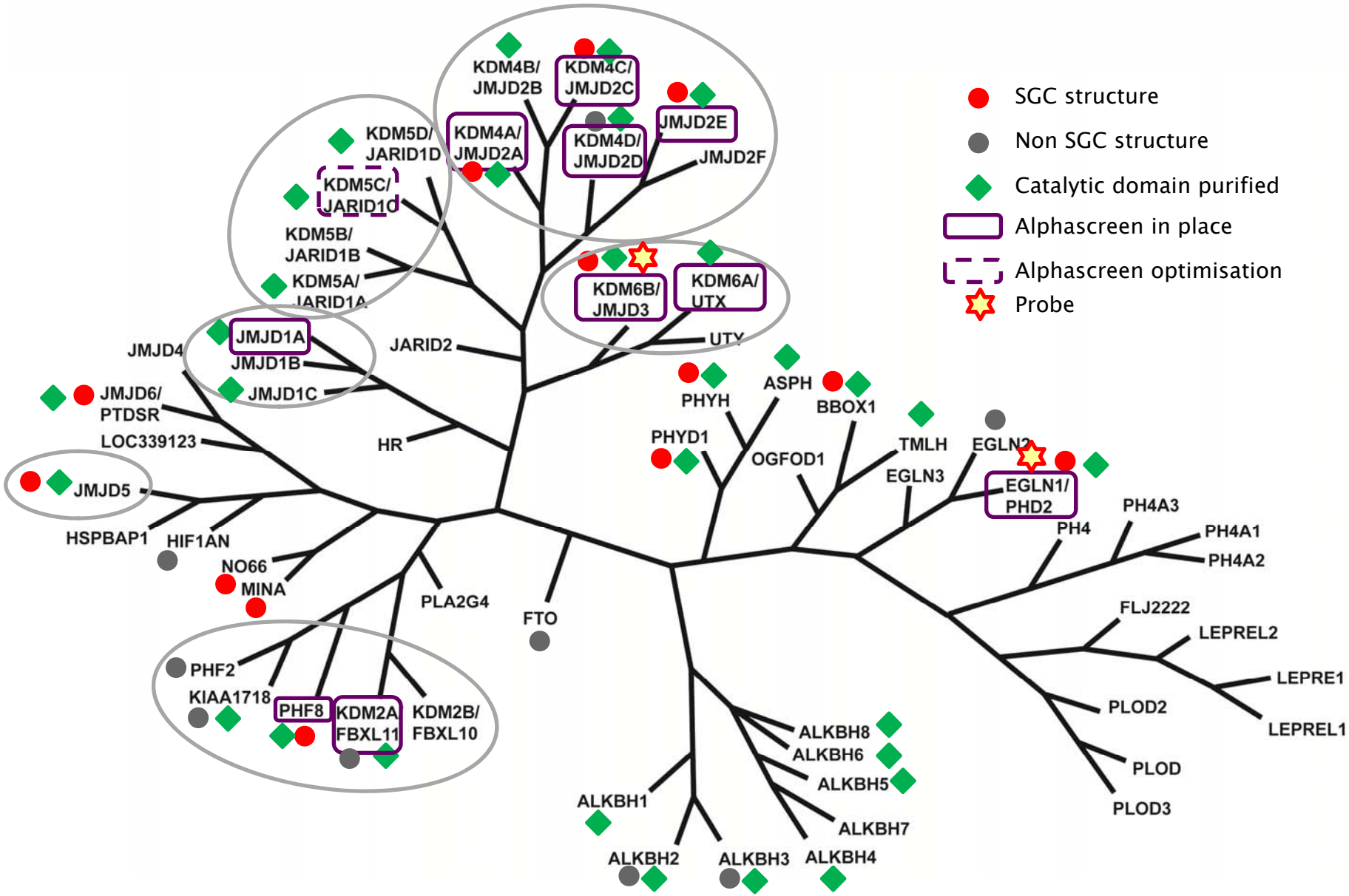


Impact of first probe

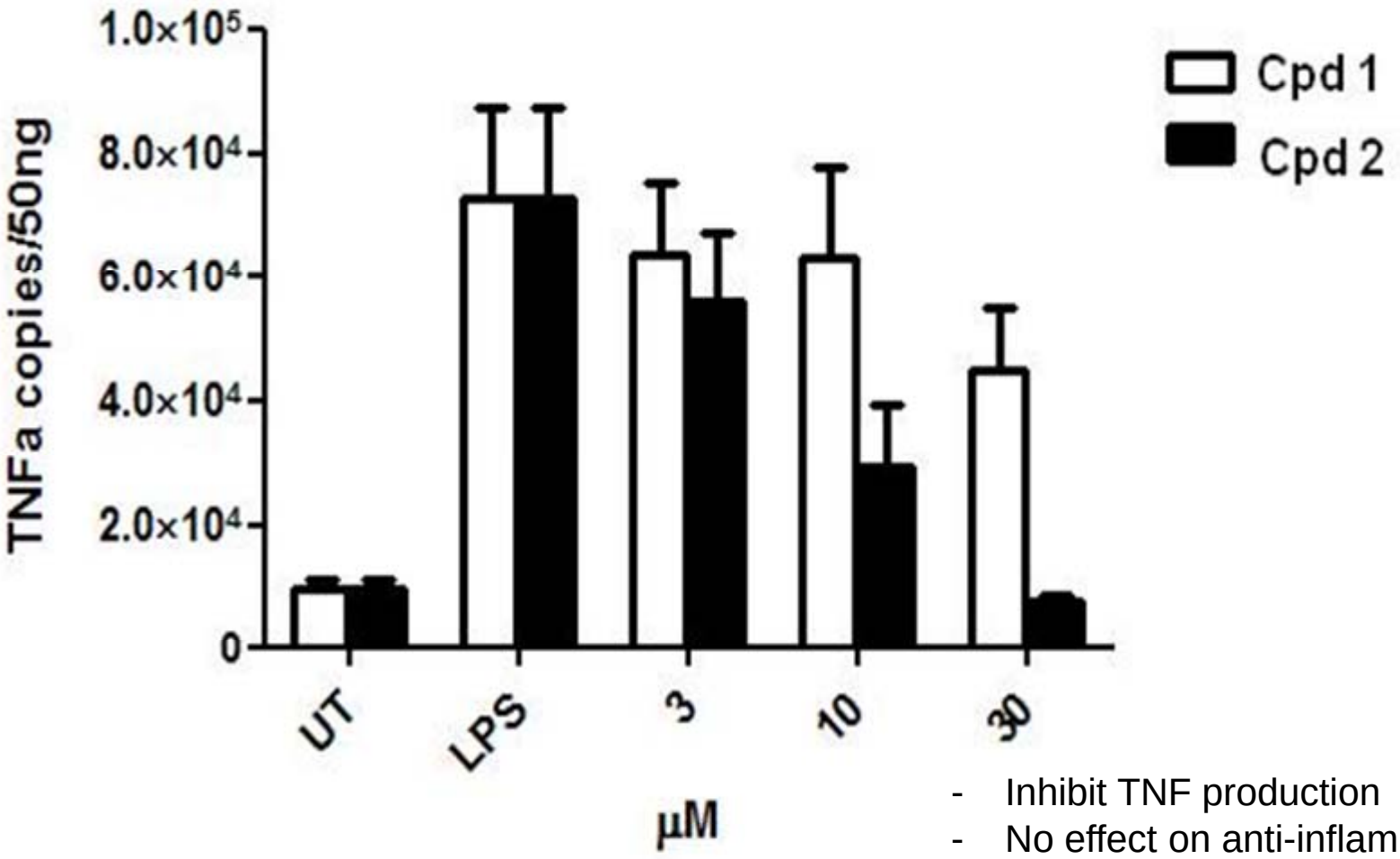
- Cited 60+ times
- Distributed to >200 labs/companies
- Partners started proprietary efforts
- Collaborator secured $15 M VC funding
- Opened new area of science:

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

Lysine demethylases



JMJD3 inhibitor reduces TNF transcripts in RA primary macrophages

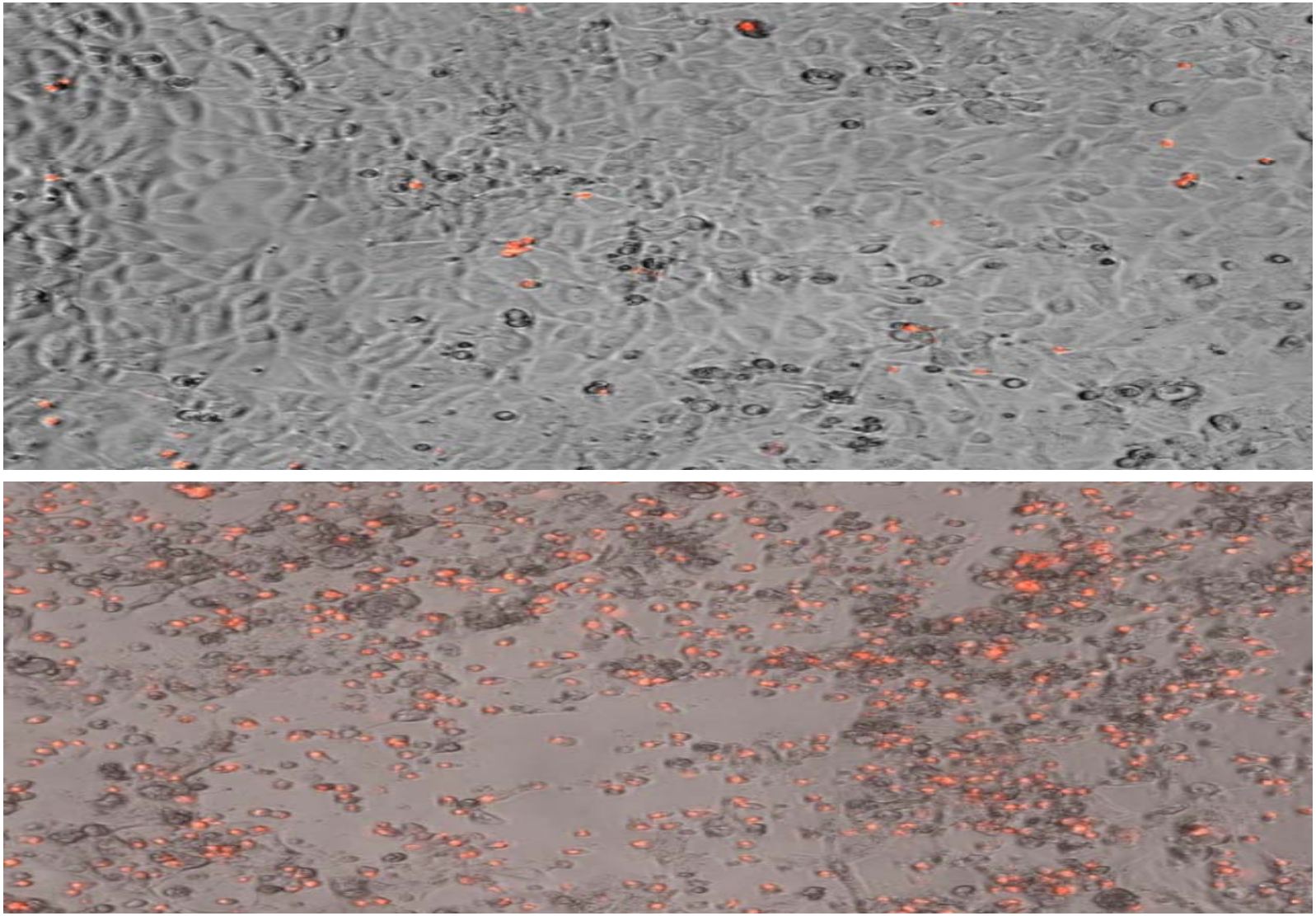


- Inhibit TNF production
- No effect on anti-inflam cytokine - IL10
- Inhibit loss of H3K27me3 (CHIP)
- Block recruitment of RNA polymerase II
- No cell toxicity

JMJD3 inhibitor increases apoptosis in human breast cancer cells (MCF7)

Vehicle

D3 inhib

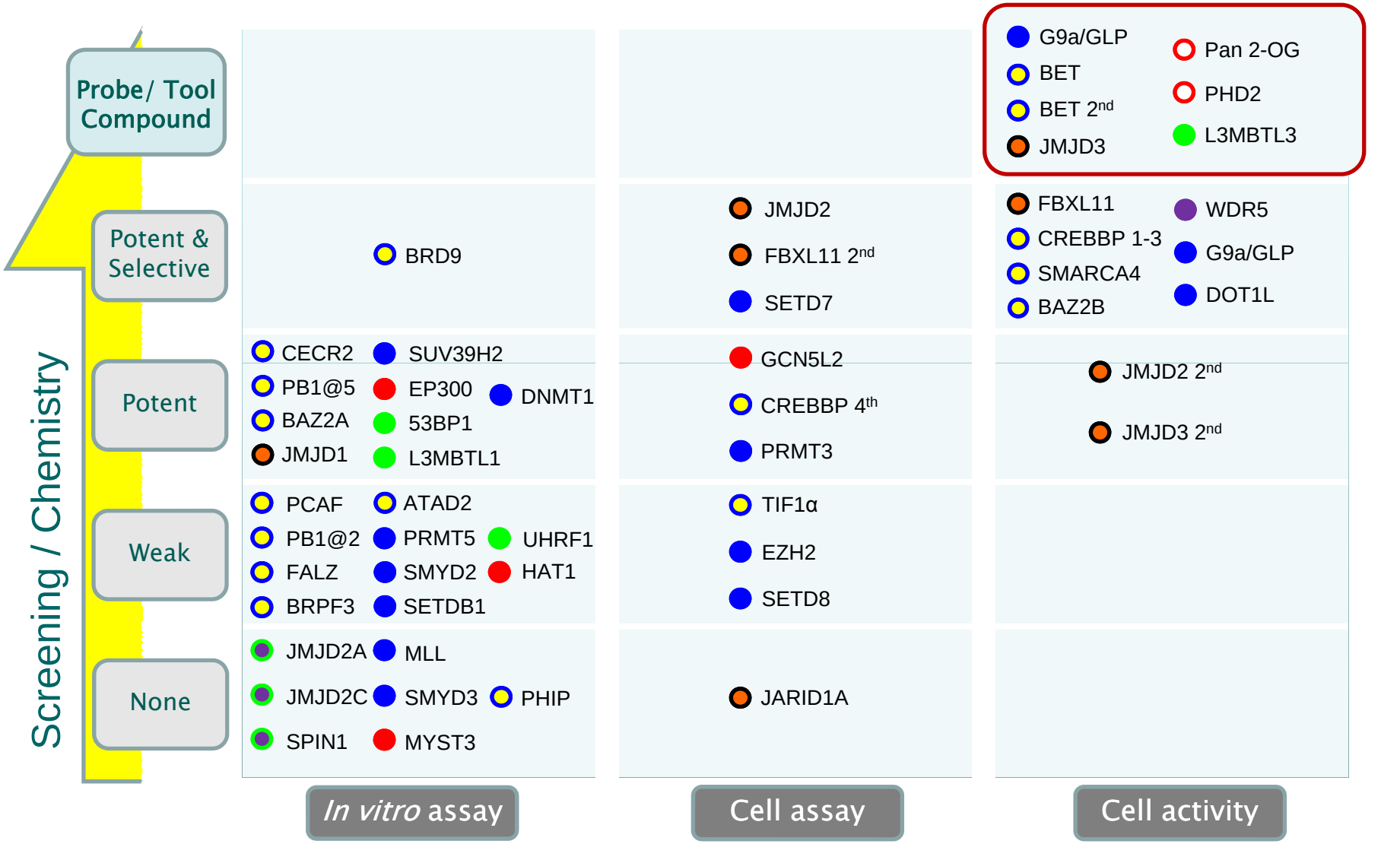


Red dots: propidium iodide stained apoptotic cells
D3/UTX traditionally believed to be tumour suppressors

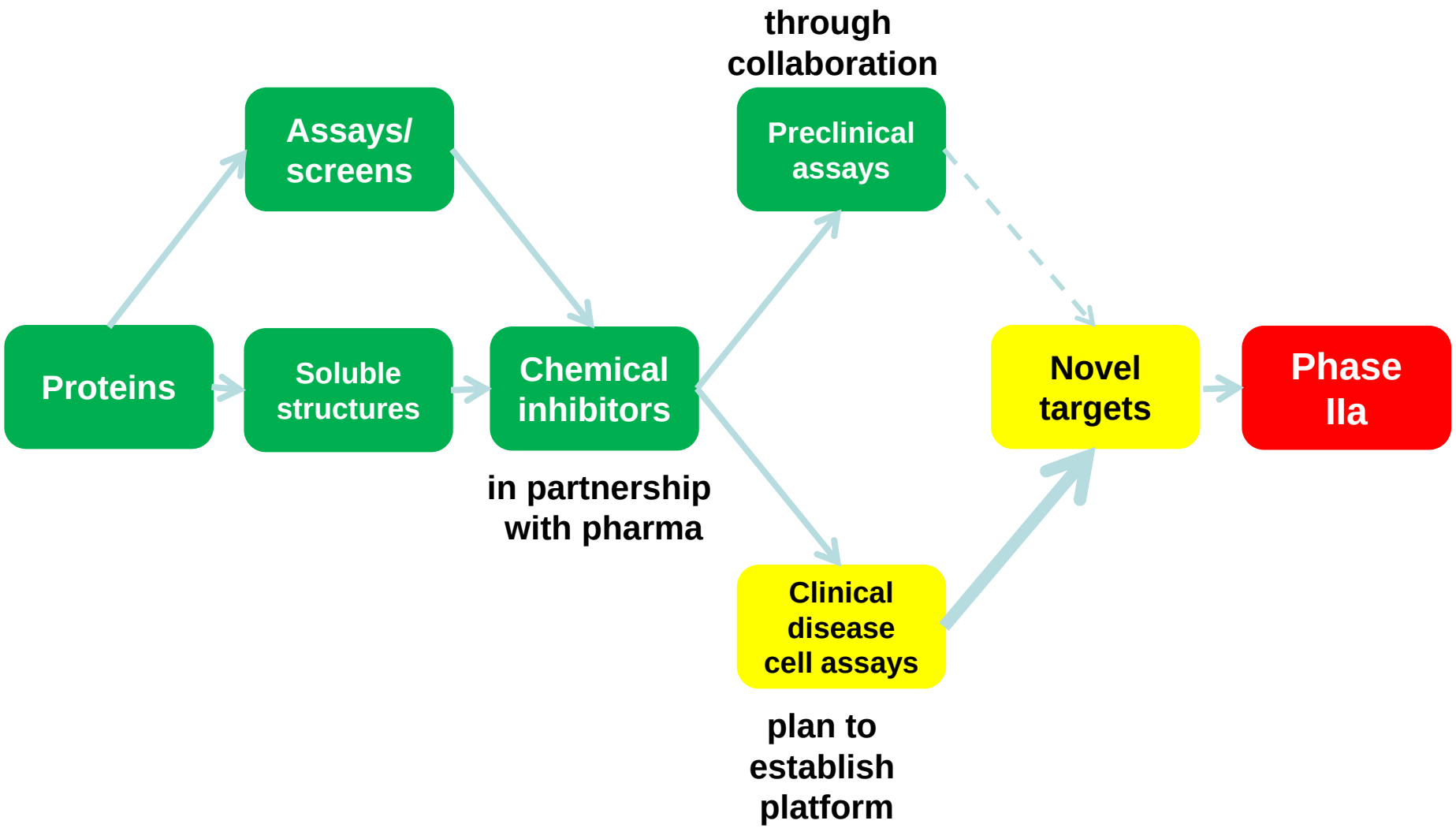
We are ahead for most families

	Purified	Assay	Structure	
			SGC	Others
HMT	42	21	16	8
BRD	40	41	29	5
KDM	18	16	8	3
MBT	25	2	16	3
Tudor	36	5	8	14
Chromo	35	9	9	5
PHD	35	3	1	25
PARP	13	12	9	1
MACRO	11	8	5	2
HAT	8	7	5	3
PWWP	15	0	7	6

Pipeline (Mar 2012)



Plans



….everything pre-competitively

Acknowledgements

- SGC
  - Stefan Knapp
  - Udo Oppermann
  - Brian Marsden
  - Susanne Muller Knapp
  - Paul Brennan
  - Nicola Burgess Brown
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