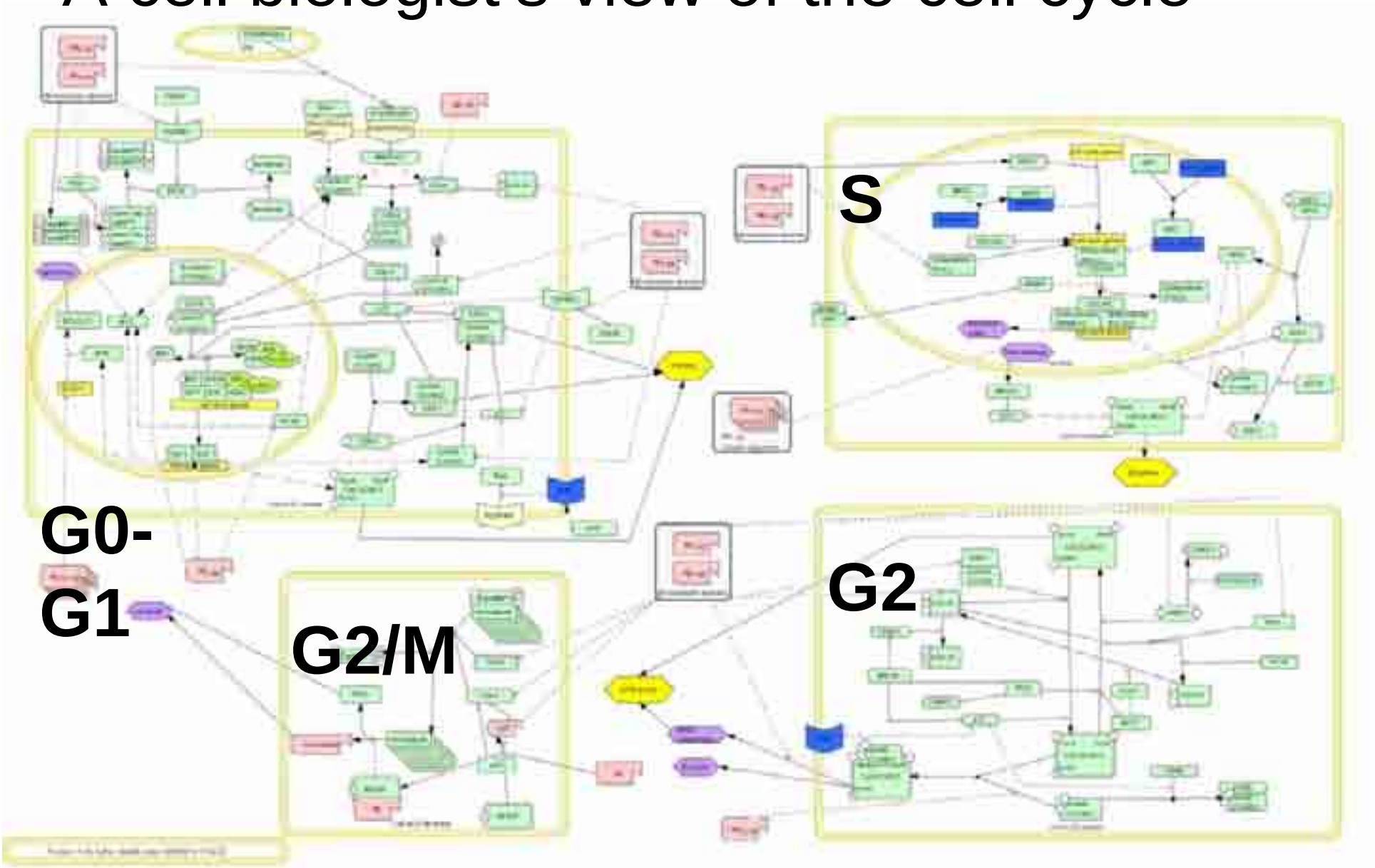
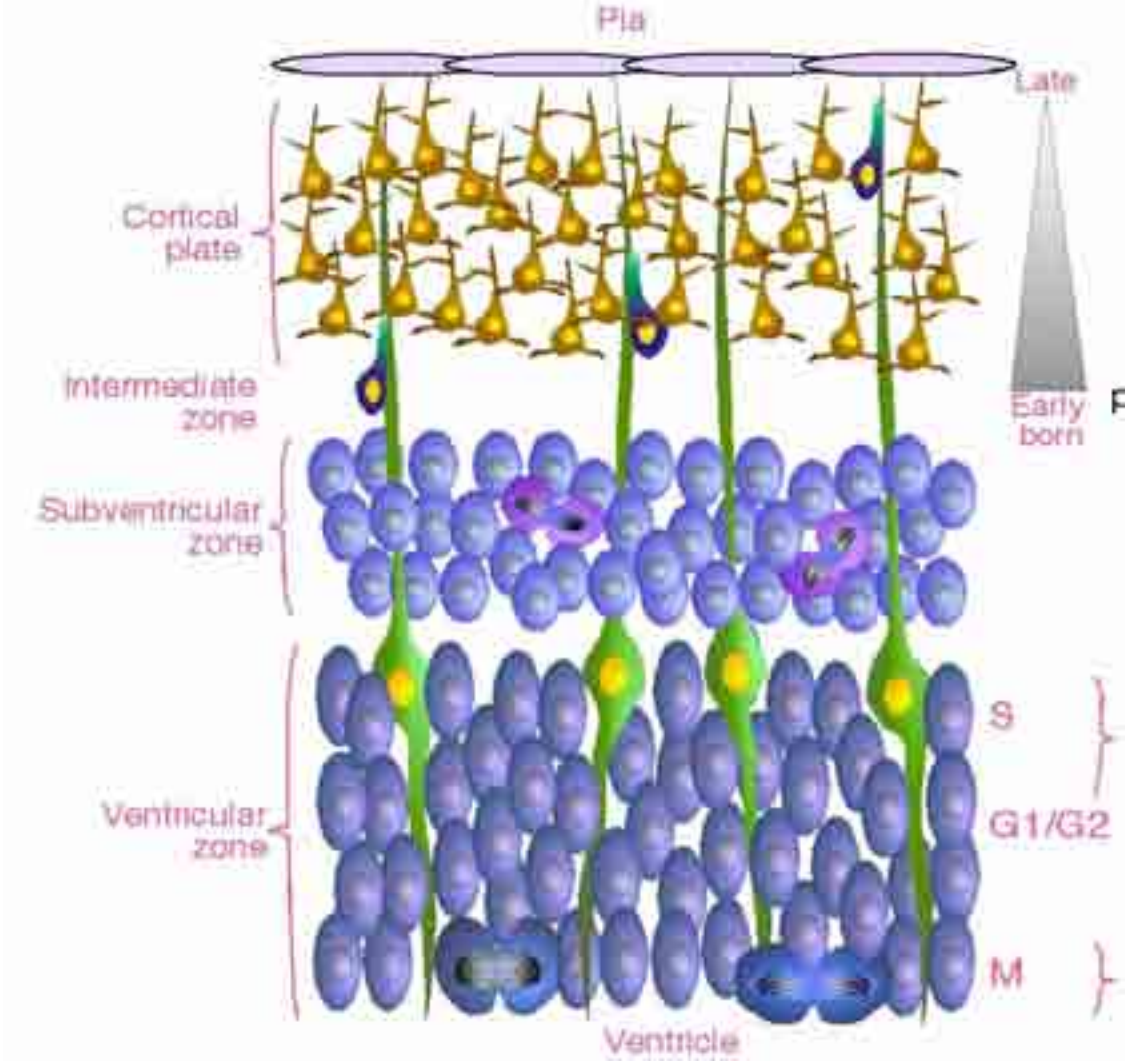
Divide and die – how cell cycle regulation plays a role in neurodegenerative disease

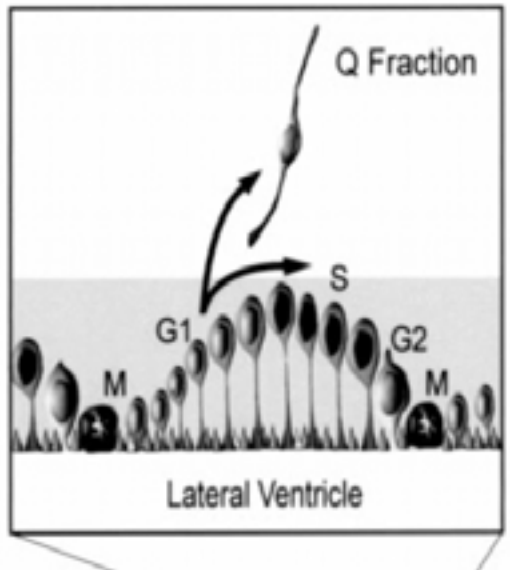
ADIT Symposium – Prague, Czech Republic
March 10, 2009

A cell biologist's view of the cell cycle



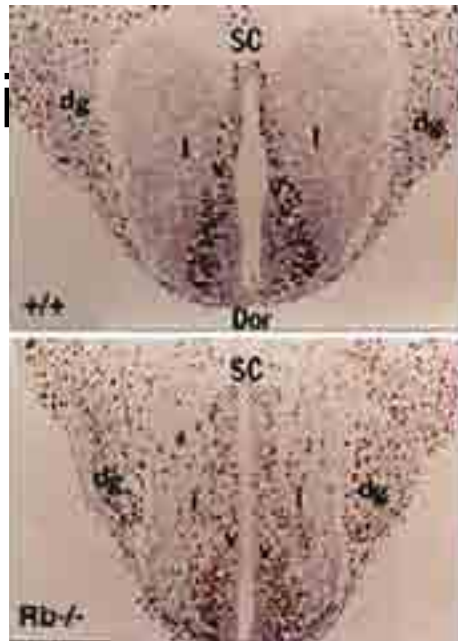
A neurobiologist's view of the cell cycle





Divide and die: Background

- Cell cycle in immature neurons
  - Force a neuron to divide, it cycles and dies
  - Remove cell cycle suppressors, it cycles and dies
  - Add certain toxins, it cycles and di
  - It is the cycling cells that die
  - Block the cycle and you block the

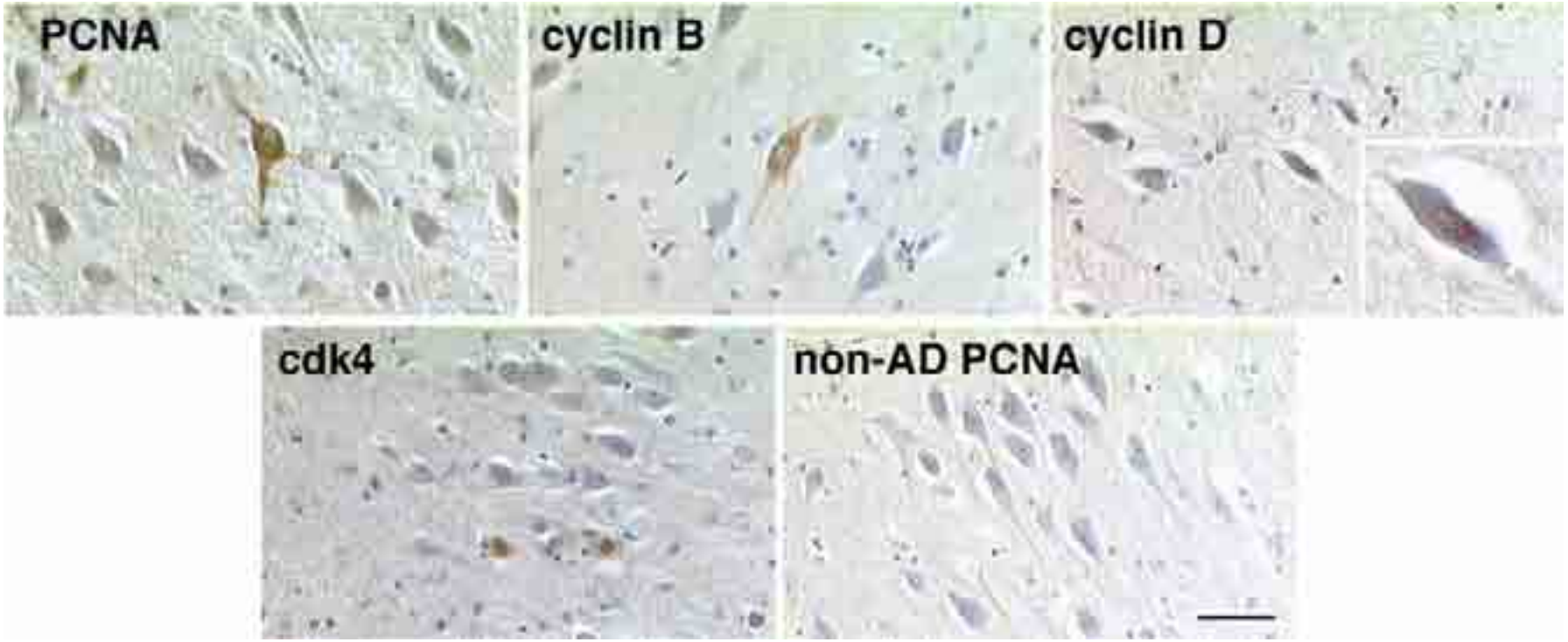


Divide and die: Background

- In mature neurons the linkage is broken
- Neurons can cycle but
  - They don't divide
  - They don't die
- Cycling is tightly linked to disease
  - Alzheimer’s disease
  - Parkinson’s disease
  - ALS
  - Stroke …

Divide and die: Alzheimer's disease

- Neurons at risk for death are ‘cycling’

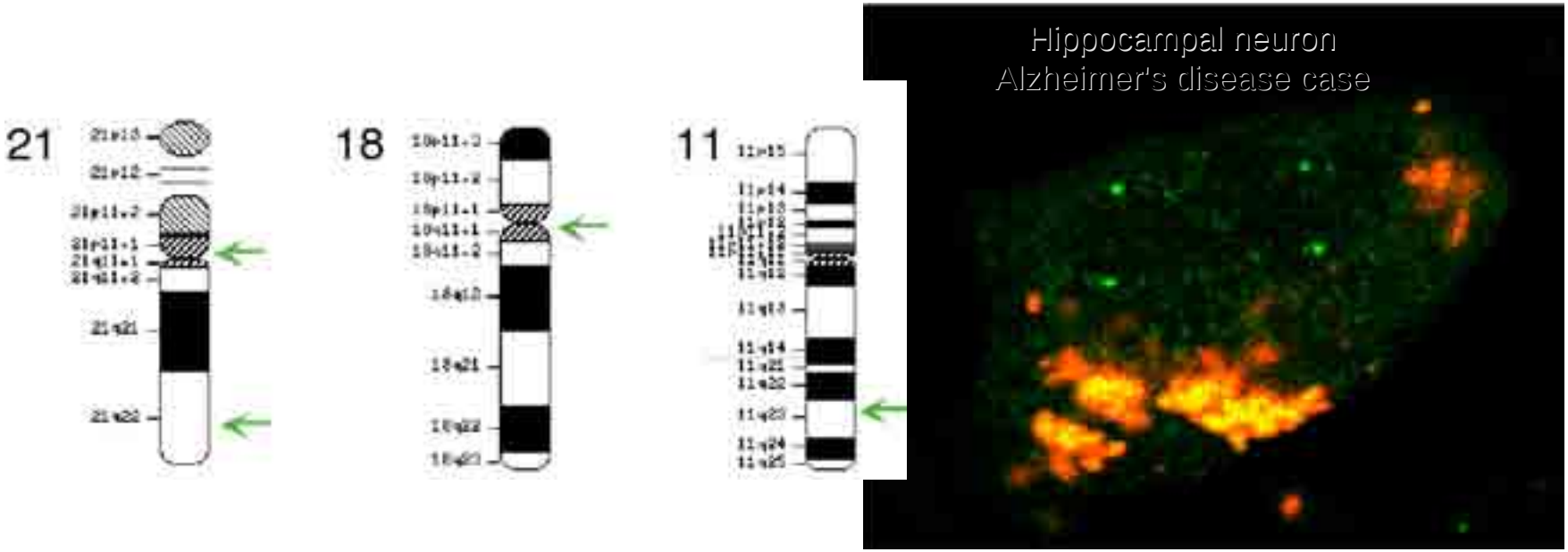


AD hippocampal pyramidal cells

Busser et al (1998)

Divide and die: Alzheimer's disease

- Neurons at risk for death show DNA replication
- Stops short of M-phase



Yang et al (2001)

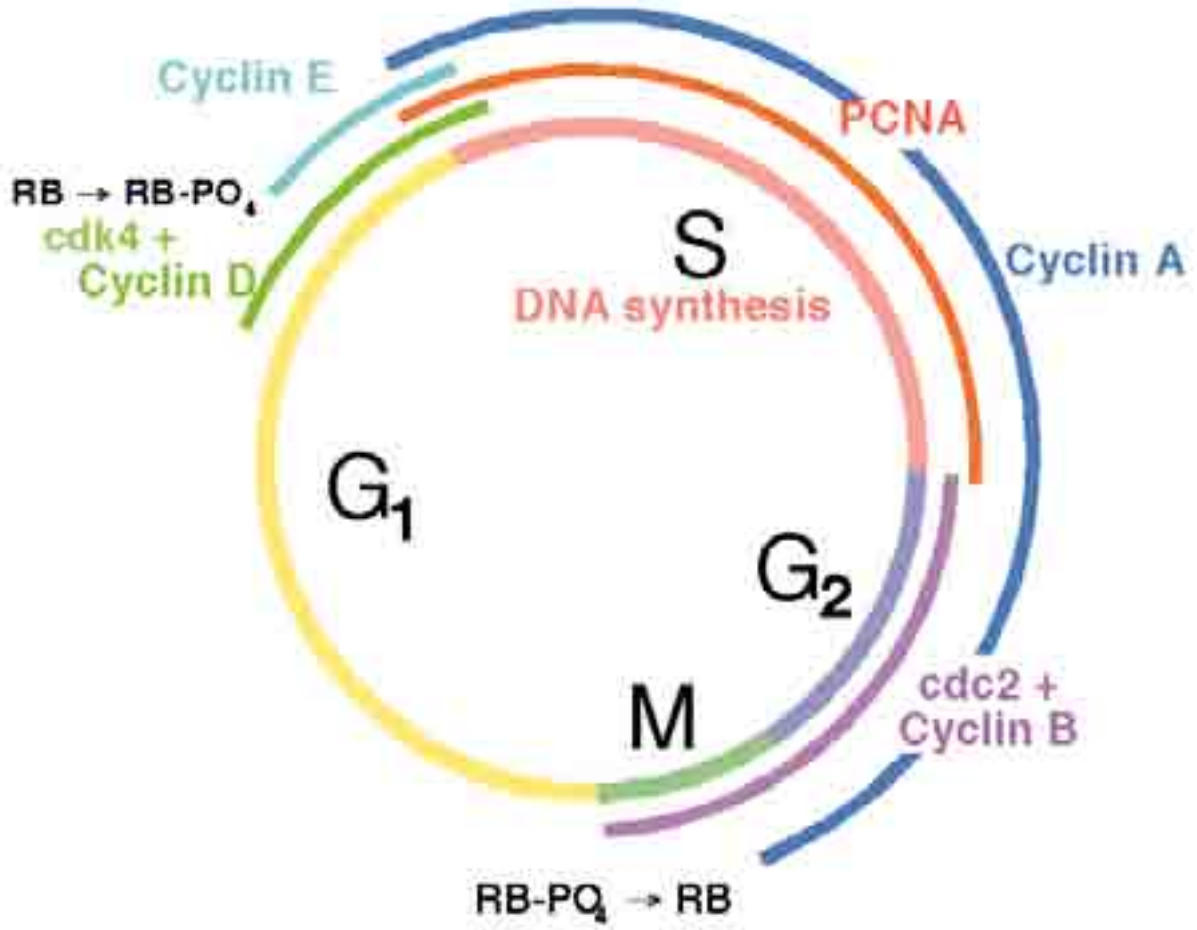
Divide and die: Alzheimer's disease

- Death by cycle must be slow

FISH spots per nucleus

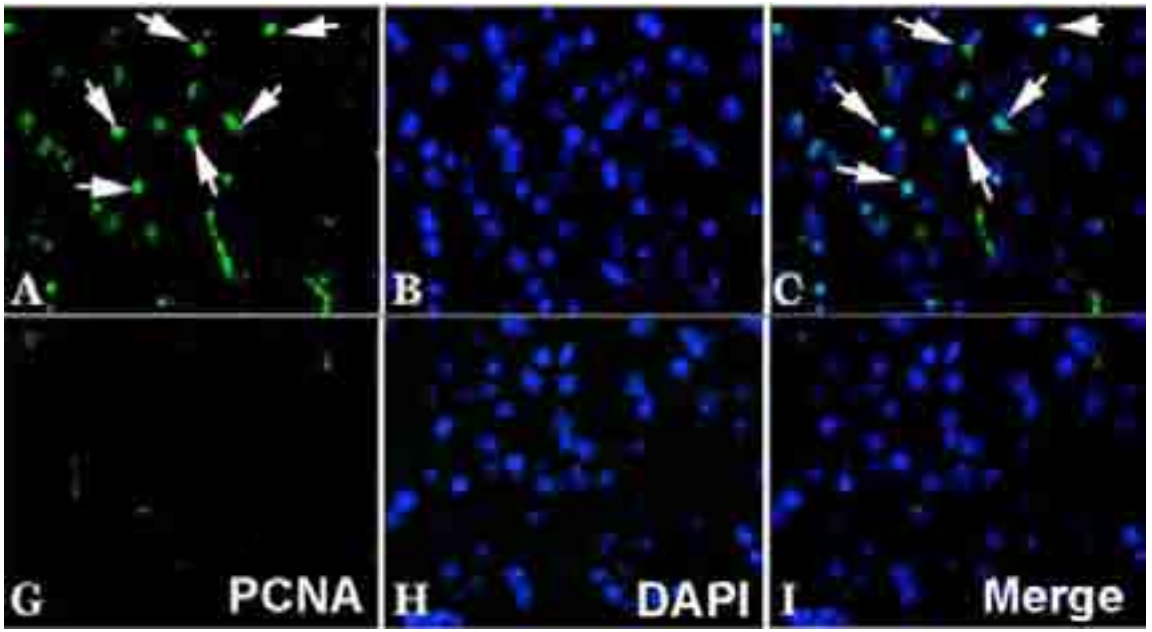
	0	1-2	3-4
Control (n = 4)	36.4% ± 6.2	63.6% ± 6.2	0
Alzheimer's disease (n = 6)	25.1% ± 3.9	71.1% ± 3.3	3.7% ± .9

Cell cycle markers



Mouse genomic models mimic human AD

- Neurons show clear cycling
- But these are mature neurons
- There is no death.

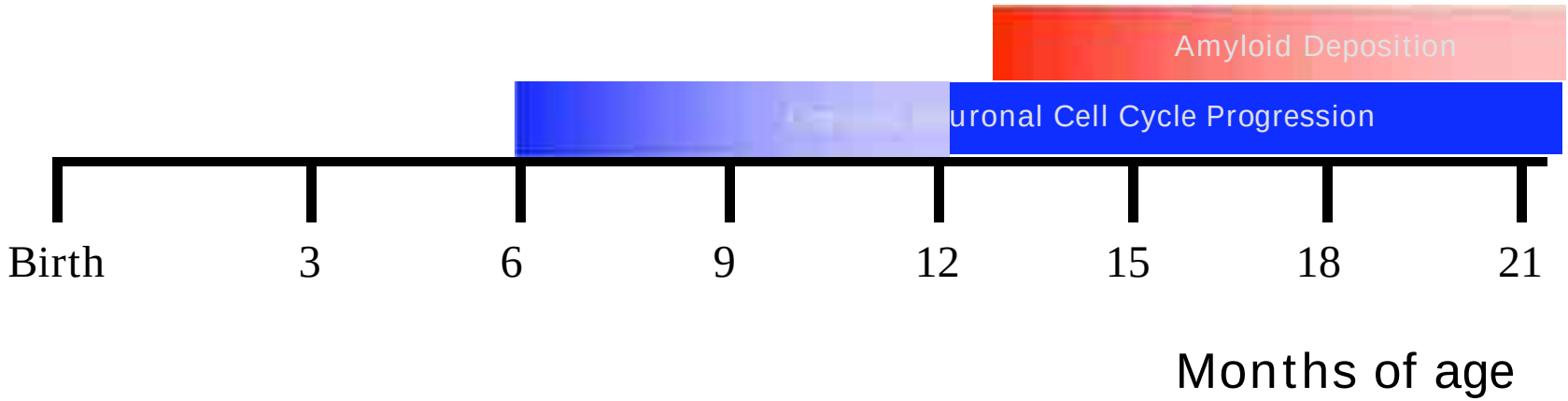


Frontal cortex - 22 months

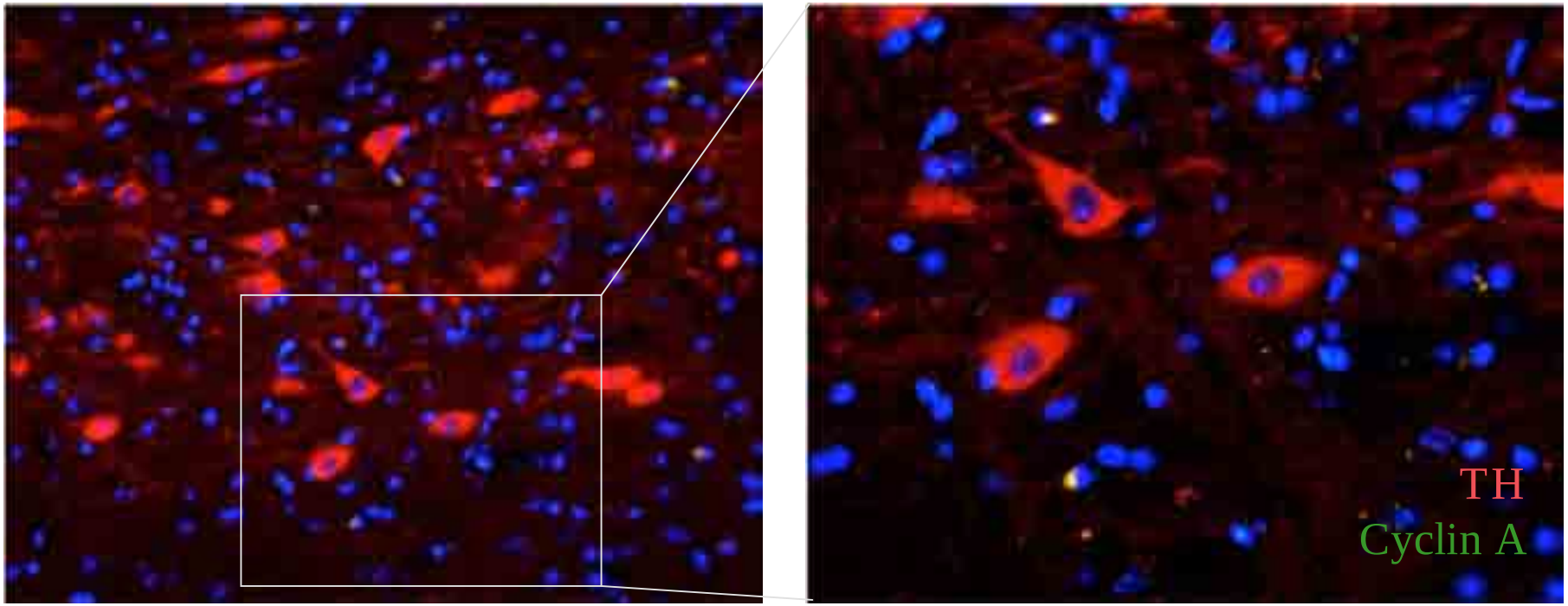
Yang, Varvel et al, 2005

Cell cycle is an early 'stress' signal

- Cell cycle events precede plaques



Cell cycle in the R1.40 mouse

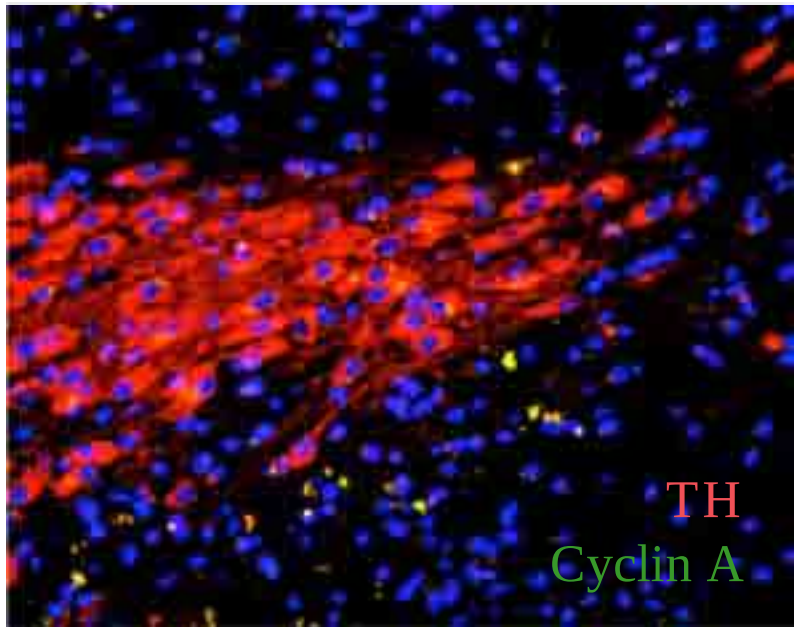


Substantia nigra

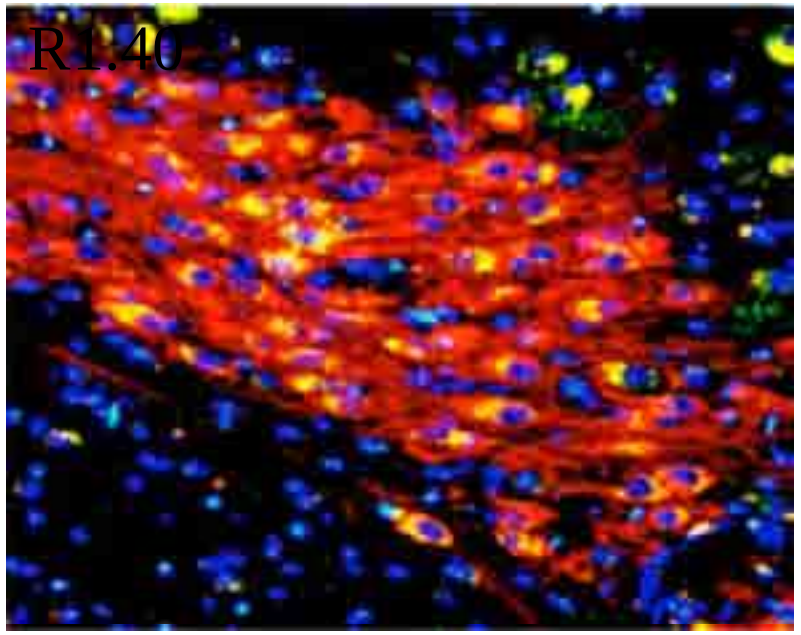
Yang, Varvel et al, 2005

Cell cycle in the R1.40 mouse

Wild type



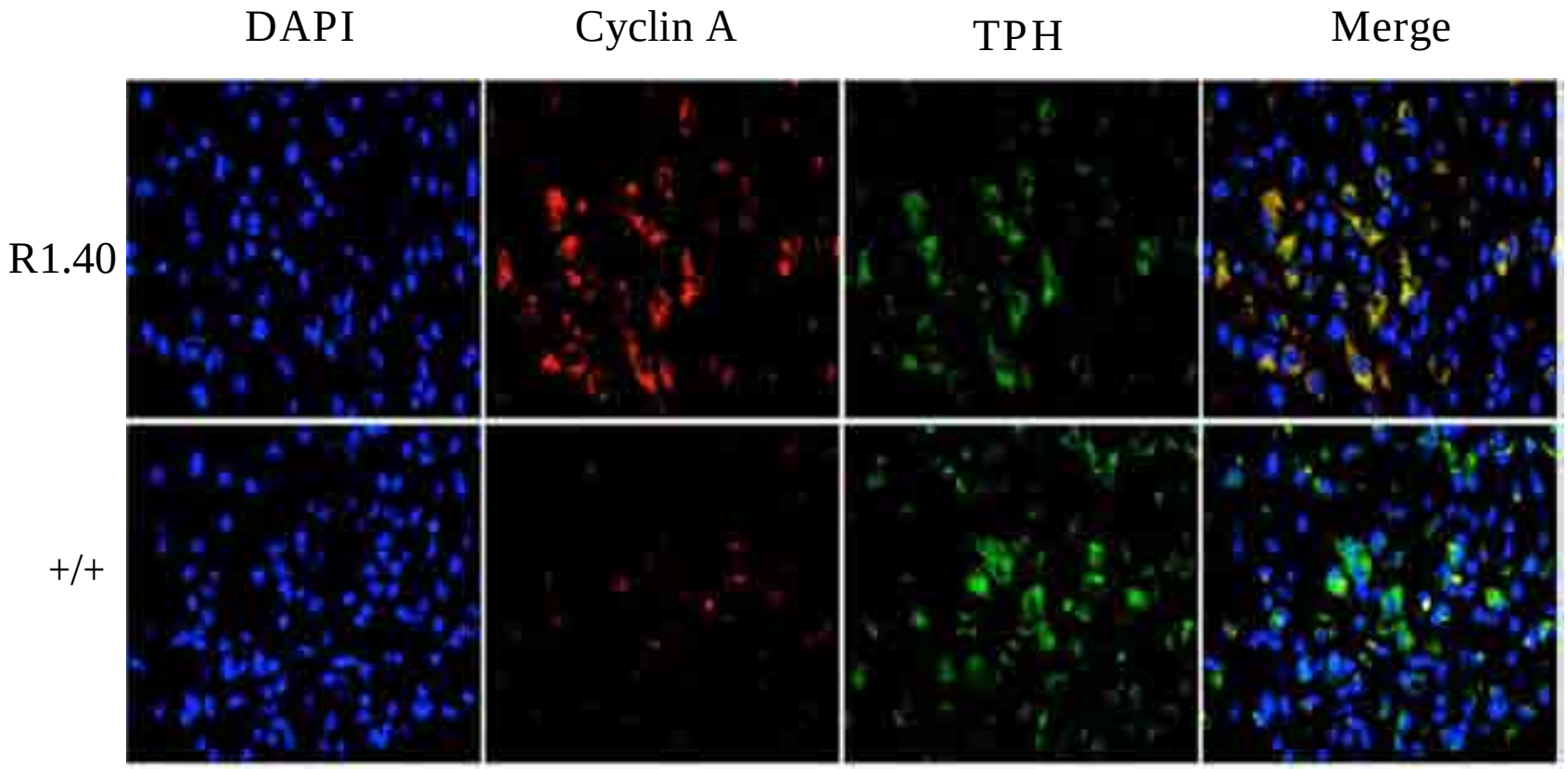
R1.40



Locus coeruleus

Yang, Varvel et al, 2005

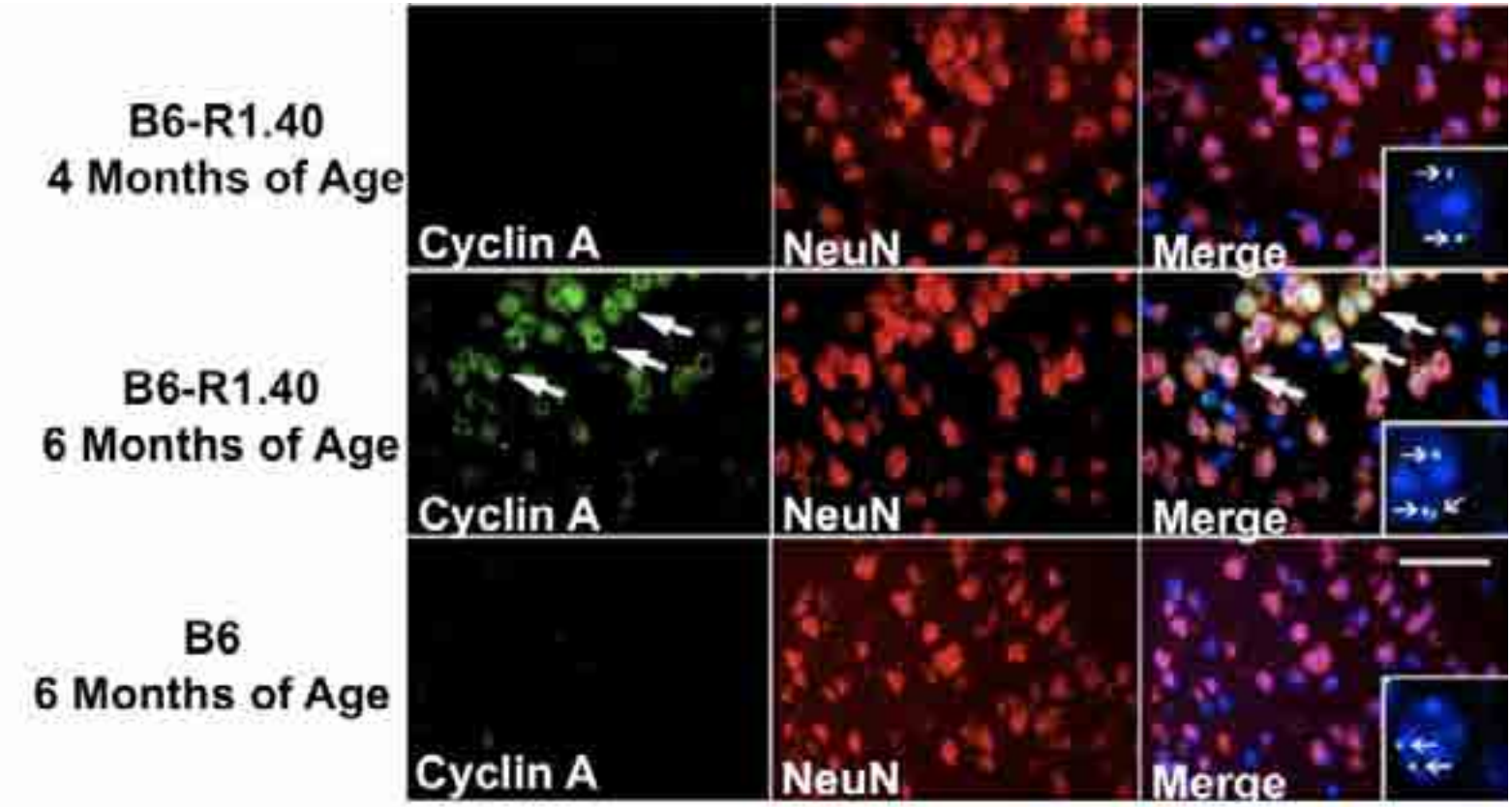
Cell cycle in the R1.40 mouse



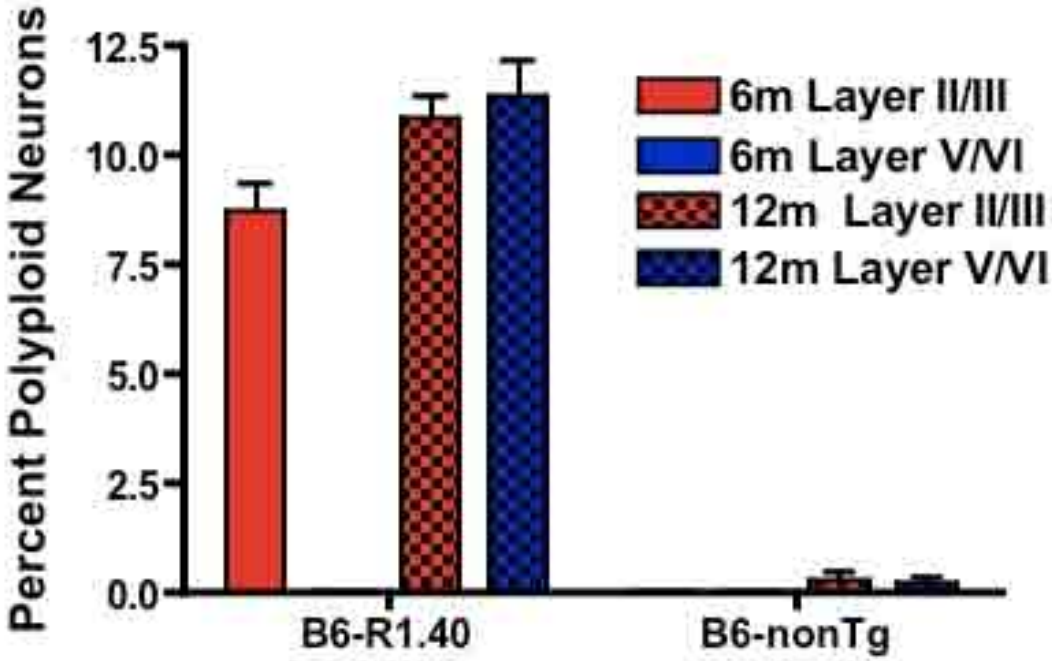
Dorsal raphe

Yang, Varvel et al, 2005

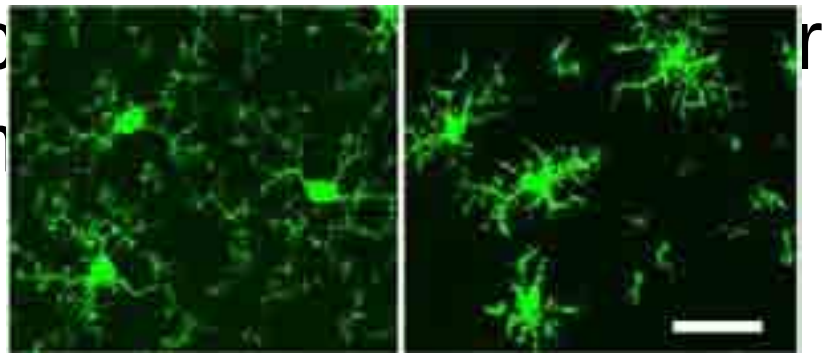
Mouse genomic models mimic human AD

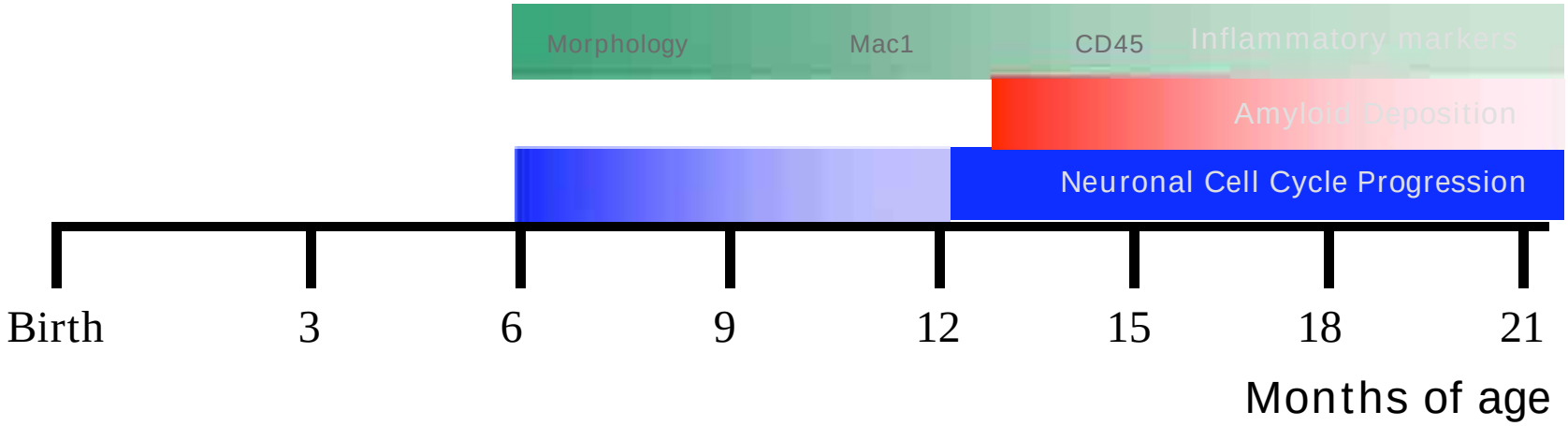


Mouse genomic models mimic human AD



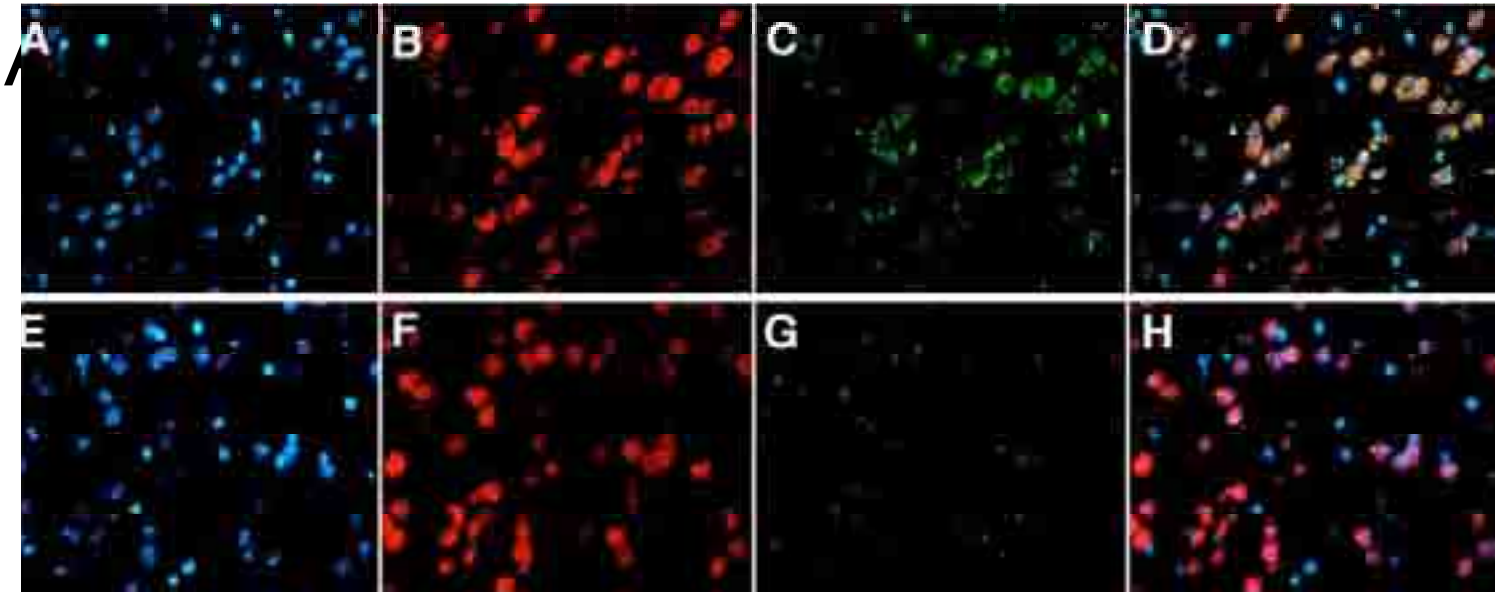
Cell cycle initiation may be immune mediated

- Cell cycle events precede plaques
- Mic  r at about the sar



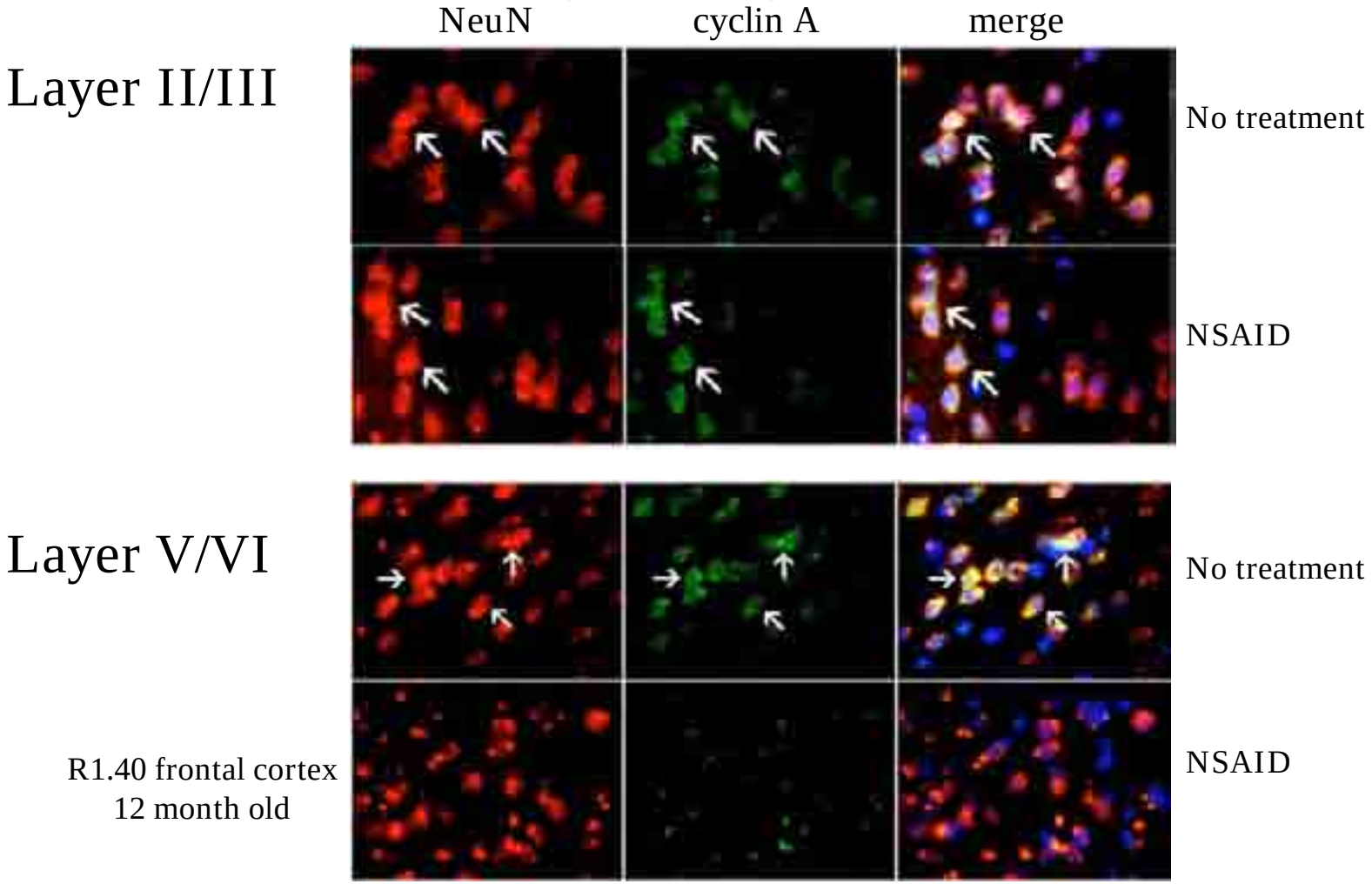
NSAIDs prevent cycling

- LPS injections advance the appearance of cycle
- NSA



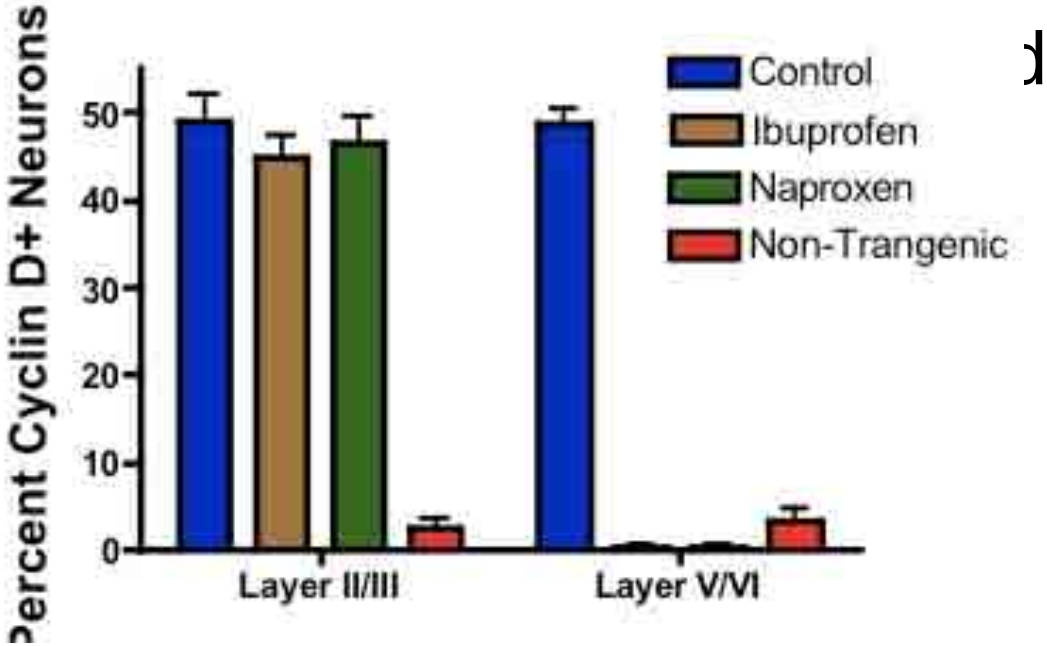
Layer II - frontal cortex
6 month R1.40 mice

NSAIDs prevent but cannot reverse cycling



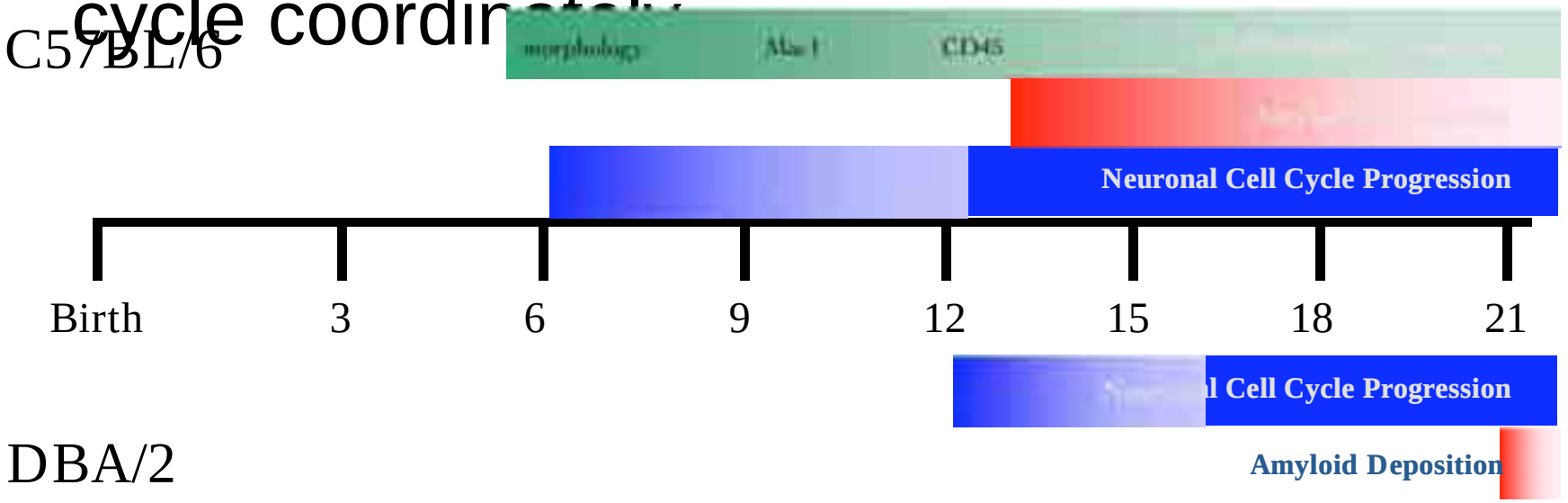
NSAIDs prevent but cannot reverse cycling

- Layer II/III started before drug treatment
  - No effect
- Layer V/VI start after drug treatment
  - These



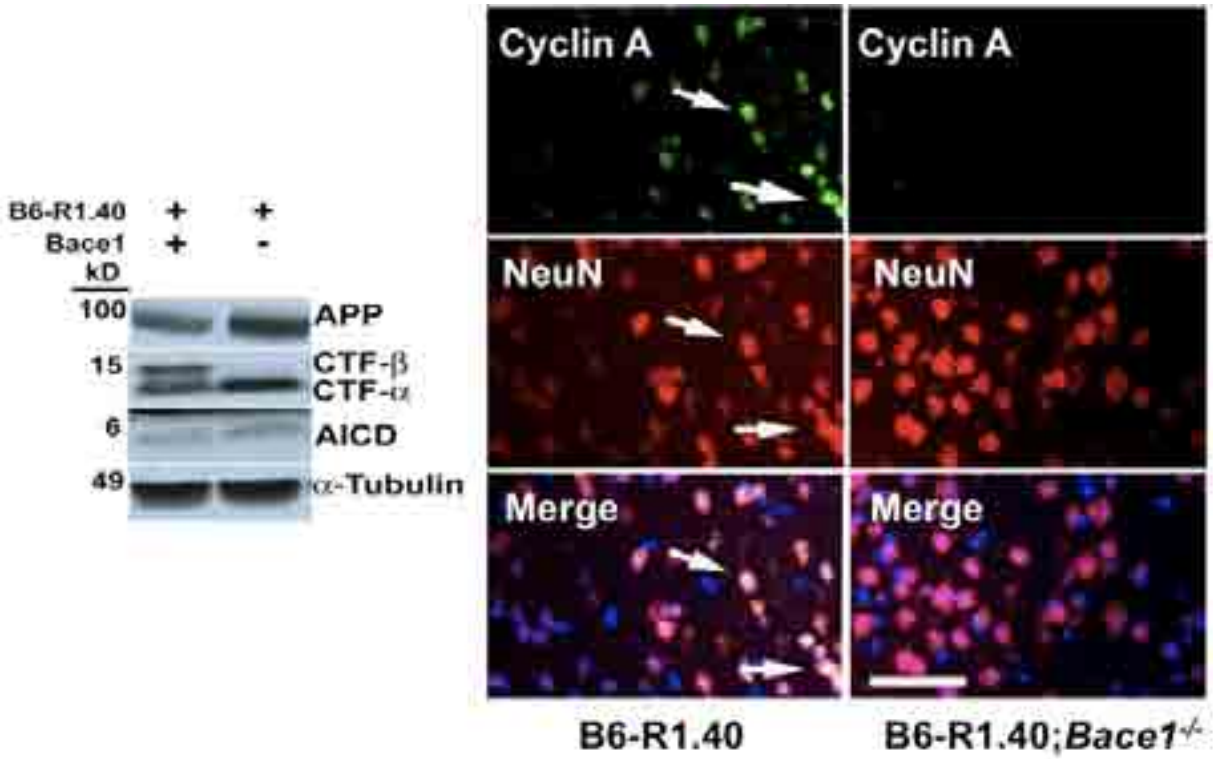
Cell cycle initiation may be Aβ mediated

- Cell cycle events precede plaques
- Microglial changes precede cycle
- Genetic background changes deposition & cycle coordinately



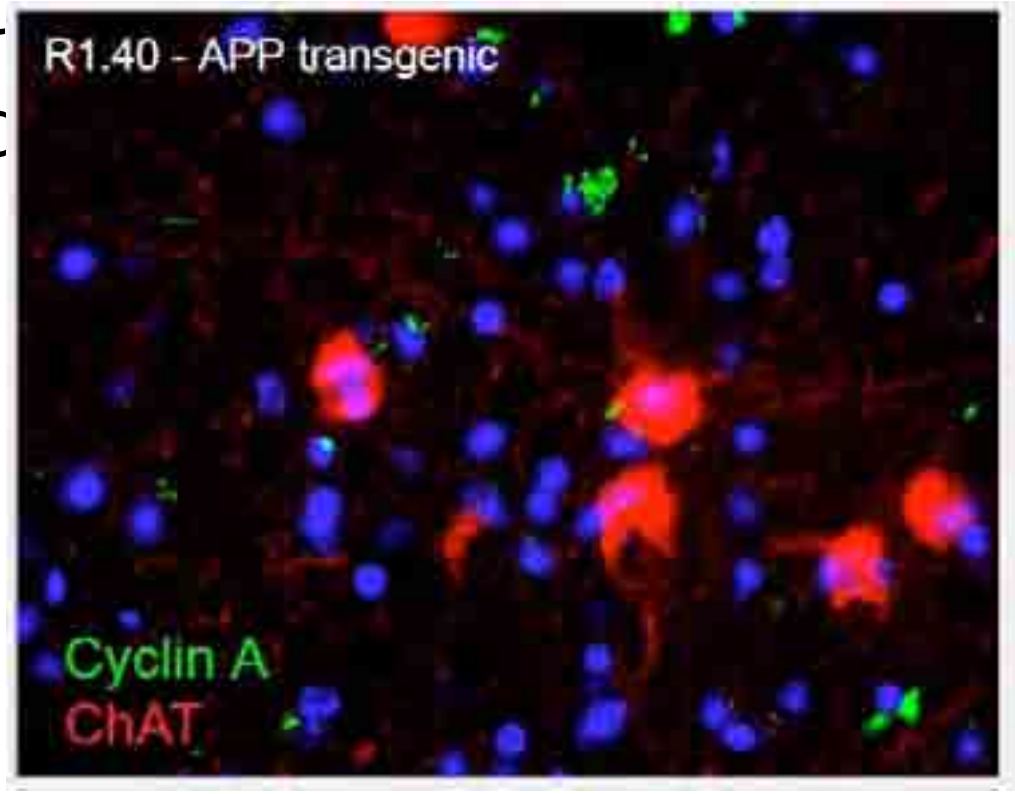
Cell cycle initiation may be Aβ mediated

- Bace1 - deficiency prevents cell cycle events



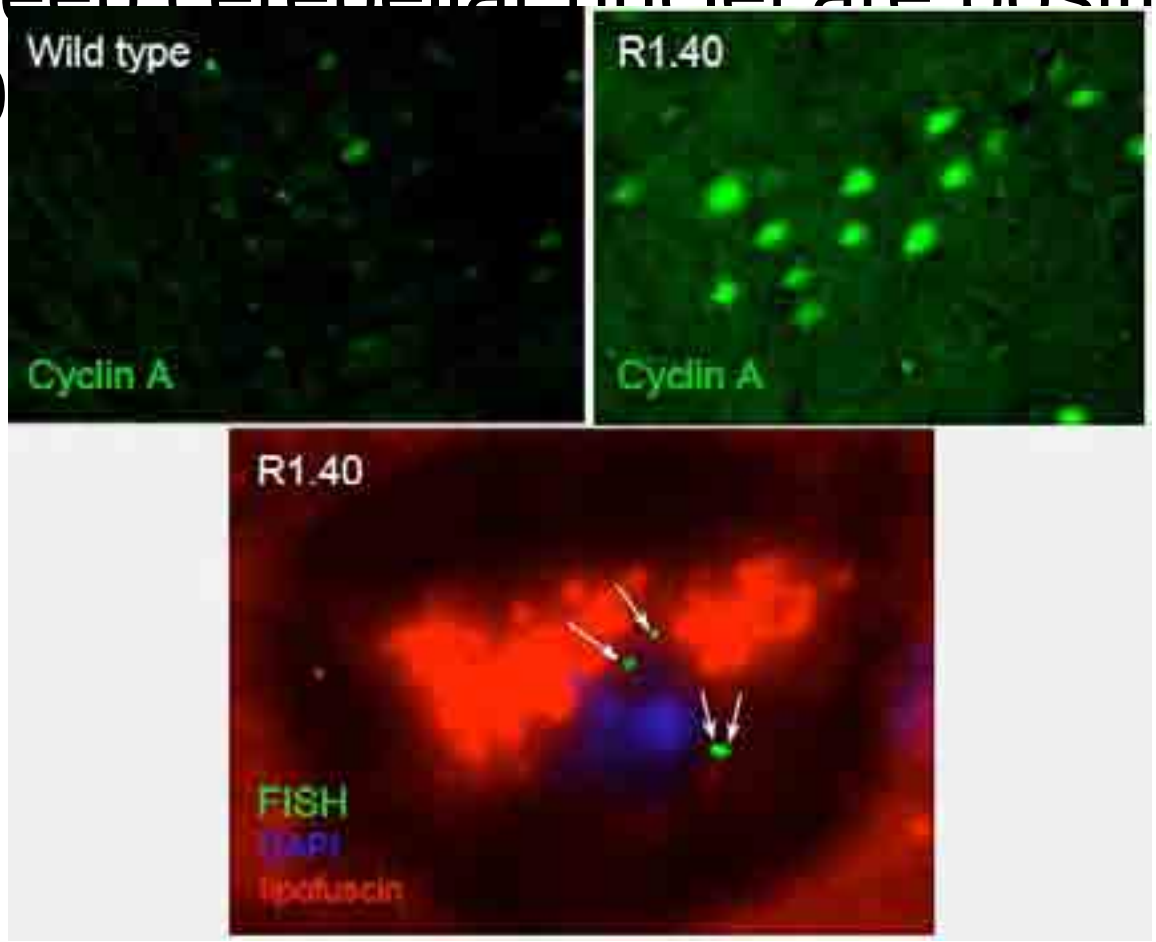
The model talks back

- Cell deaths in the basal nucleus may be indirect
- Consec mpus



The model talks back

- The deep cerebellar nuclei are positive in R1.40



The model talks back

- As predicted human cerebellar dentate neurons also positive

The model t

- The correlation is stro
- Significance
  - Diagnosis
    - Cdk4: $p < 0.009$
    - Cyclin A: $p < 0.135$
  - Braak stage ≥ 5
    - Cdk4: $p < 0.008$
    - Cyclin A: $p < 0.002$

Diagnosis	Braak stage	Cdk4	CycA
AD REG	5.5	1	-
AD REG	5.5	2	1
AD REG	5.5	2	3
AD REG	5.5	2	1
AD REG	6	3	1
AD REG	5	3	-
AD REG	6	3	-
AD REG	5.5	4	1
AD REG	5.5	4	1
AD REG	6	4	1
AD REG	6	5	-
AD REG	6	5	2
AD REG	6	-	-
AD/INFARCTS/HEM	6	5	-
AML/G5HD	0	-	-
CHF	1.5	3	-
CYSTIC FIBROSIS	0	-	-
ETOH/CARDIOMYOP	5	5	1
FTLD	1.5	3	-
GI BLEED	5	5	3
INFARCTS	0	-	-
PSP-R	Dense tangles	-	4
RESP FAILURE/ASTHMA	0	2	-
SEPSIS/CHF	0	-	-
SMA type III	0	-	-

Conclusions and implications – basic

- Cell cycle events are highly sensitive predictors of neurons at risk for death in human
- In genomic mouse models of Alzheimer's disease cell cycle events mimic cell death
  - Timing
  - Anatomy
- Cell cycling represents an additional, 'neurocentric' outcome measure for preclinical trials

Conclusions and implications – clinical

- Validation of the proposed involvement of inflammatory processes in AD
  - Appearance of activated microglial cells
  - Immune challenges speed the appearance
  - NSAIDs retard
  - Perspective on human clinical trials
- Genomic mouse model has messages for human
  - Cell loss in basal nucleus may be secondary not primary
  - Brainstem aminergic neuronal loss is primary
  - Cerebellar dentate a new proposed primary disease feature
    - Planning (executive function)

Accomplices and support

- Cleveland Clinic
  - Bruce Lamb
  - Nicholas Varvel
  - Kiran Bhasker
- Case Western Reserve
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  - Mark Cohen
  - Alan Lerner
  - Gary Landreth
- Rutgers
  - Jianmin Chen

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  - NIA (Cleveland ADRC and AG24994)
  - CART
  - Blanchette Hooker Rockefeller Fund

- *Karl Herrup has no conflict of interest to declare*