

Hormesis to Enhance Neural Progenitor Cell Viability for Regenerative Medicine

Guanghu Wang, Ph.D

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Dose-Response 2012

UMass Amherst

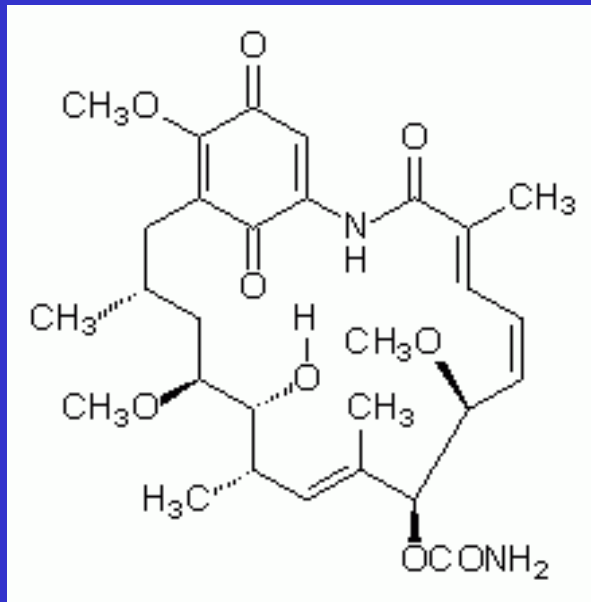
- **Regenerative Medicine:** processes of creating living, functional tissues to repair or replace tissue or organ function lost due to damage, or congenital defects
- **Two ways for neurological diseases:**
 - enhance endogenous neurogenesis,
 - neural cell transplantation using cells derived from ES cells, iPS cells or other sources
- **Cell survival and correct differentiation: bottle neck**

Heat shock protein Hsp90

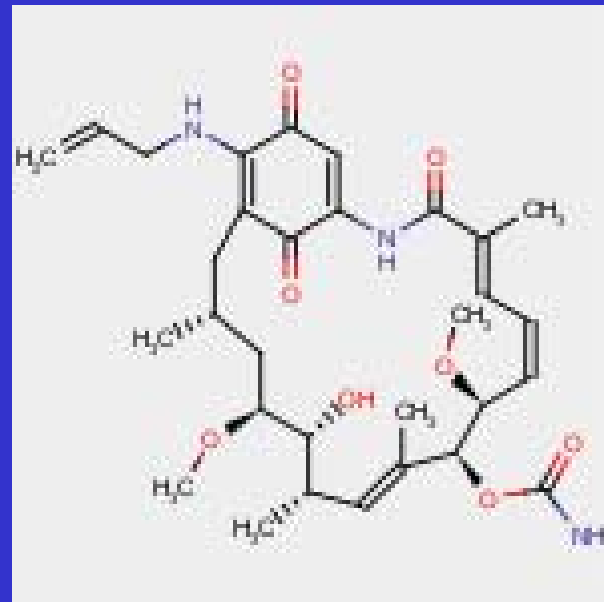
- One of the most abundant cellular chaperone proteins, functions in a wide range of cellular processes, neuroprotection and cell apoptosis.

- Hsp90 inhibitors:

GA (Geldanamycin)



17-AAG (17-allylamino-17-demethoxygeldanamycin)



Functions of Hsp90 inhibitors

- Anti-tumor, clinical trials

- GA mediates protective function in osteoclasts and ischemic brain.

Koga F, et al, PNAS, 103, 2006 (Neckers lab)

Yano A, et al, PNAS, 105, 2008 (Neckers lab)

Kwon et al., Neurol Res. 30, 2008

Wen X, et al., Neuroscience, 156, 2008

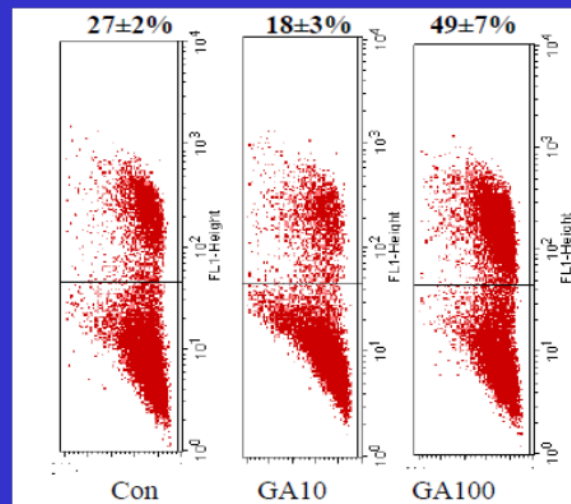
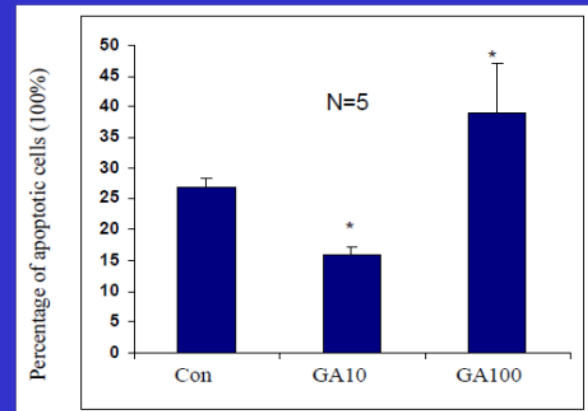
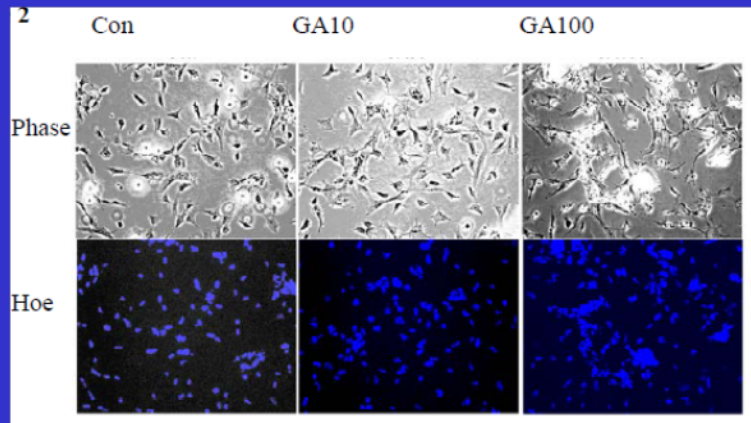
- 17-AAG ameliorates polyglutamine mediated motor neuron degeneration in spinal and bulbar muscle atrophy

- Waza M, et al, Nature Medicine, v11(10), 2005

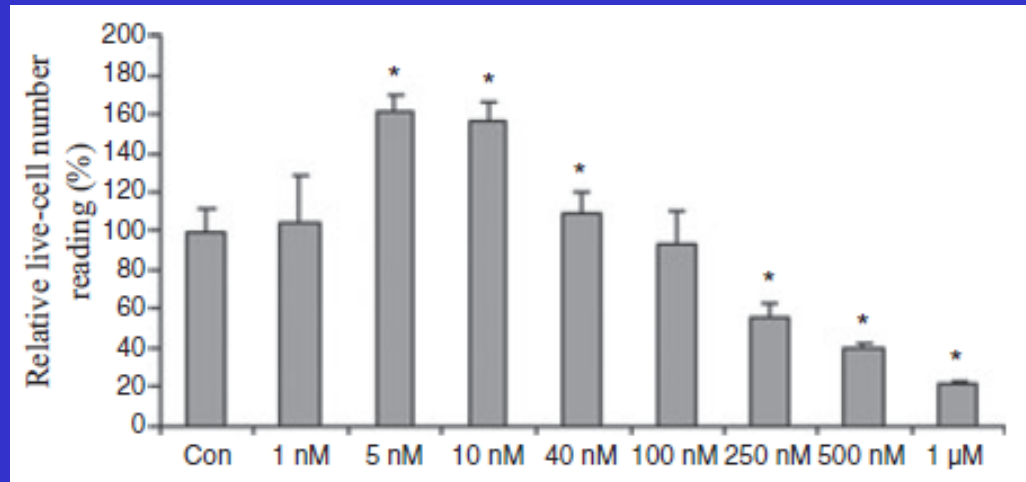
Question

How to make use of molecular chaperones for stem cell replacement therapies?

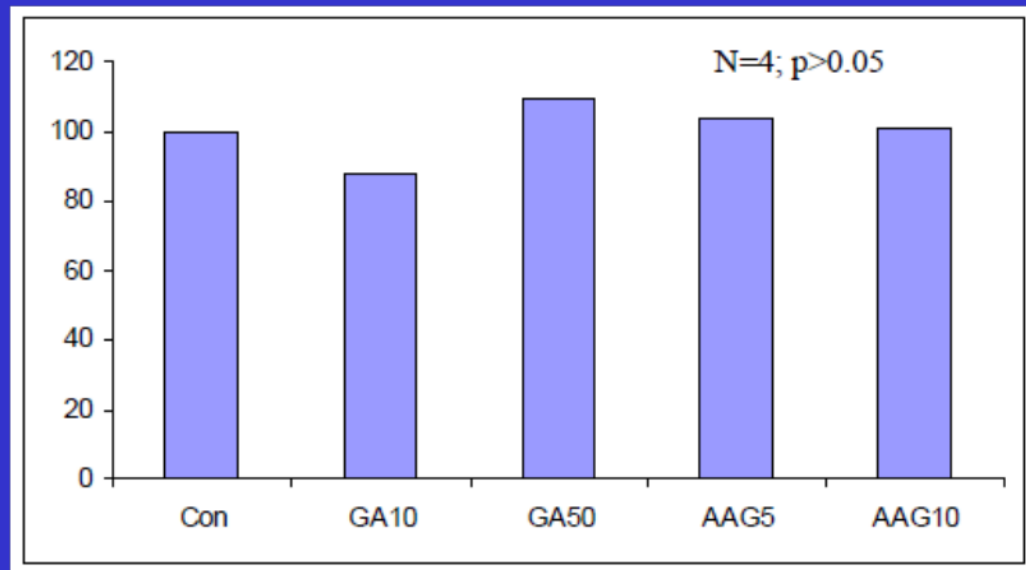
Low dose GA protects NPs from Apoptosis



Low-dose 17-AAG Enhances NPs Survival

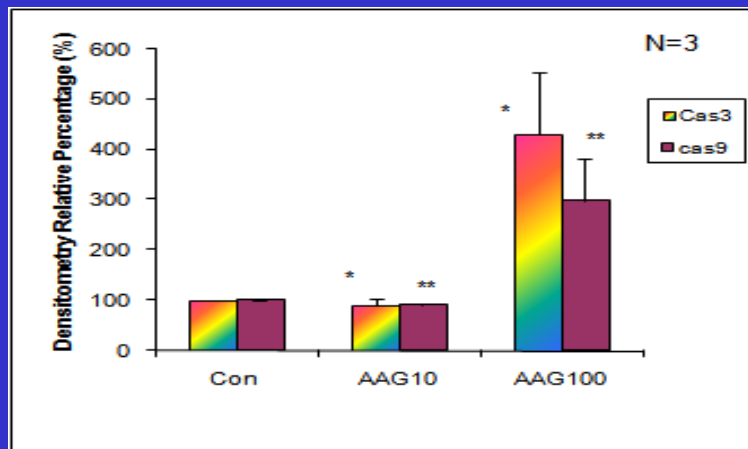
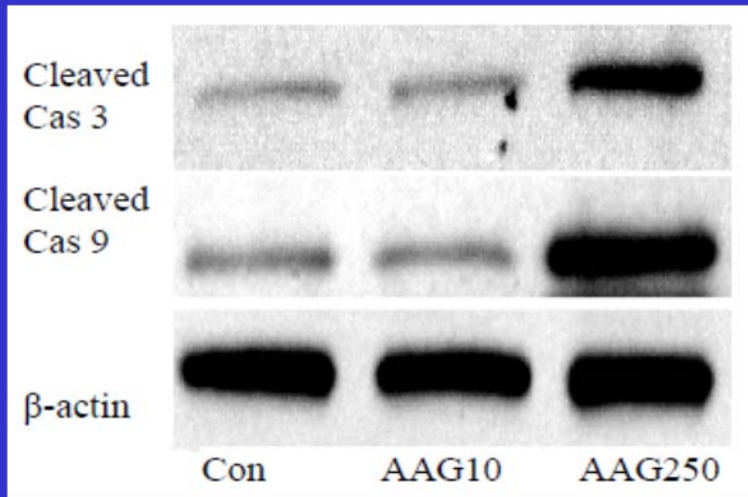


BrDU labeling

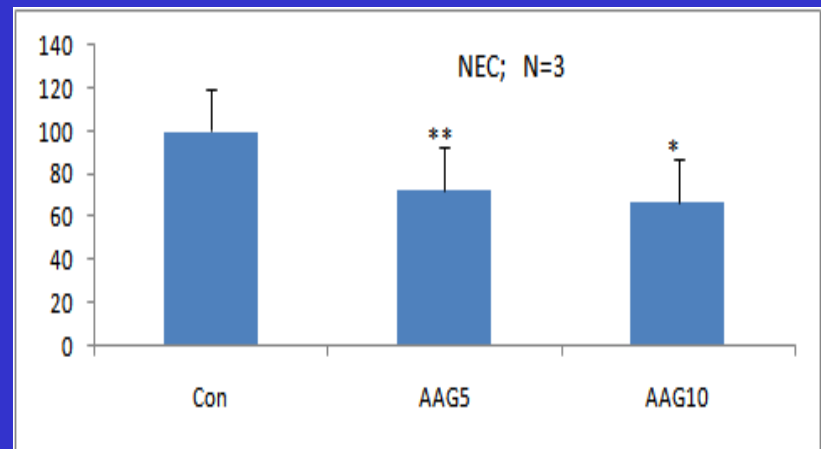
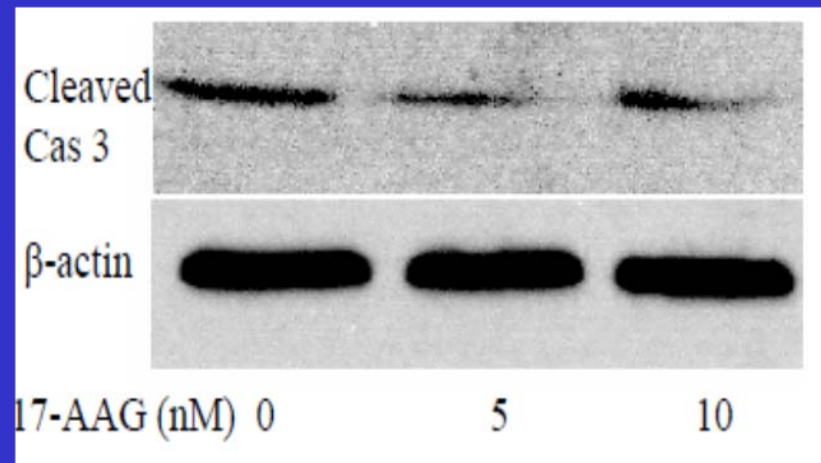


Low-dose 17-AAG Enhances NP Cell Survival (cont.)

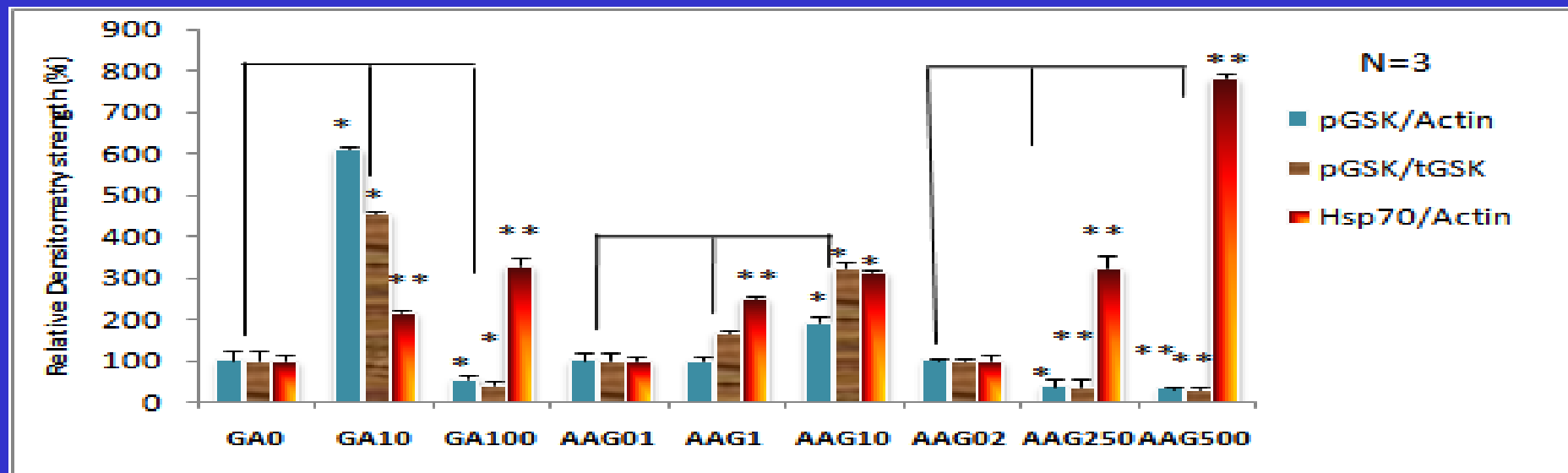
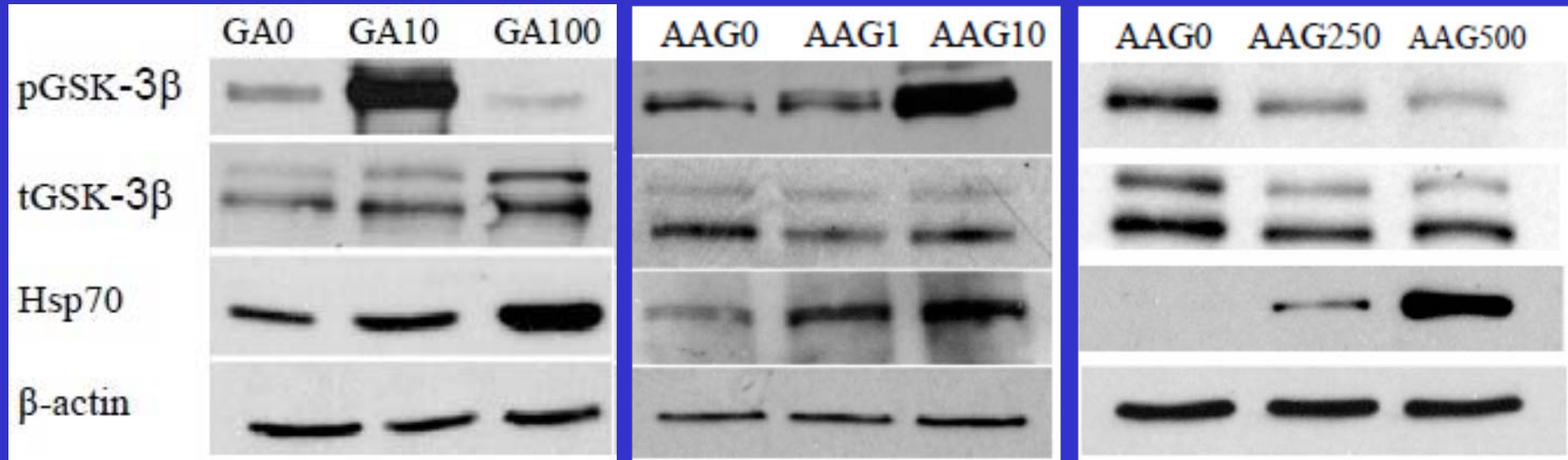
NP



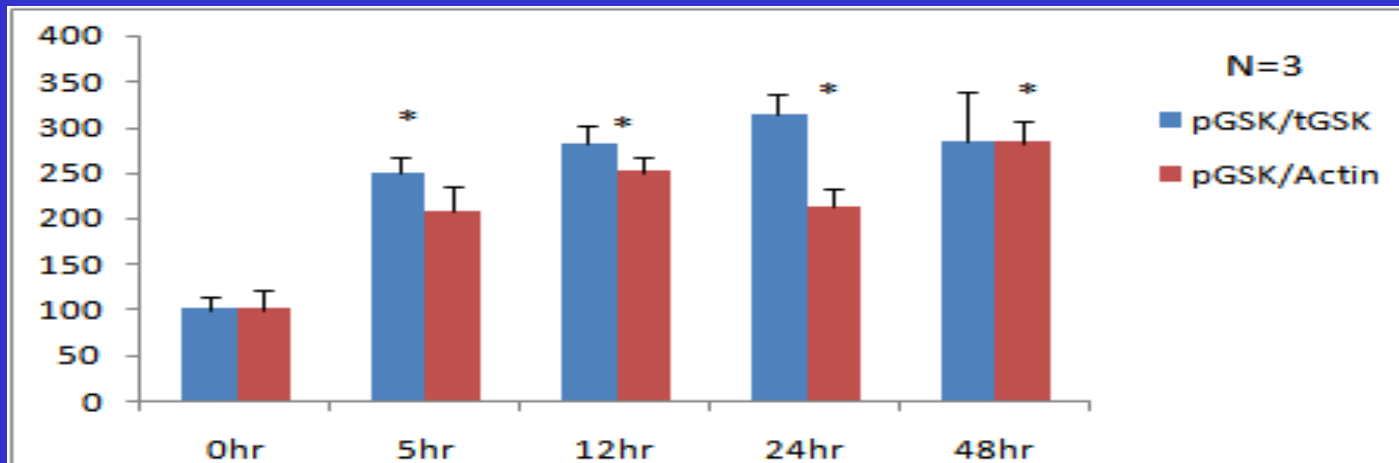
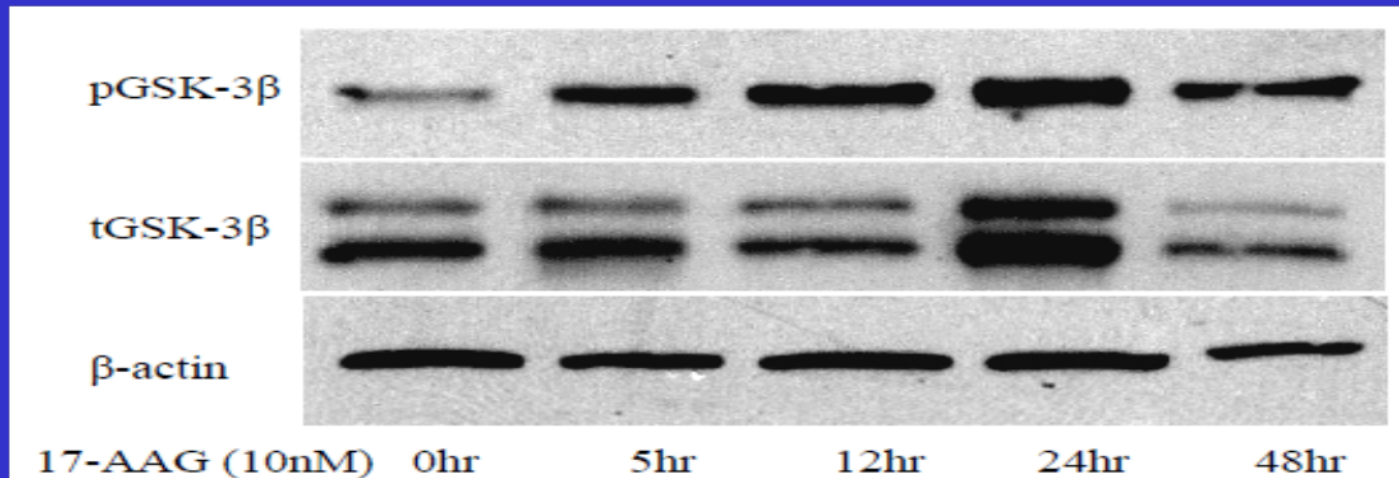
Neuroepithelium from E14.5



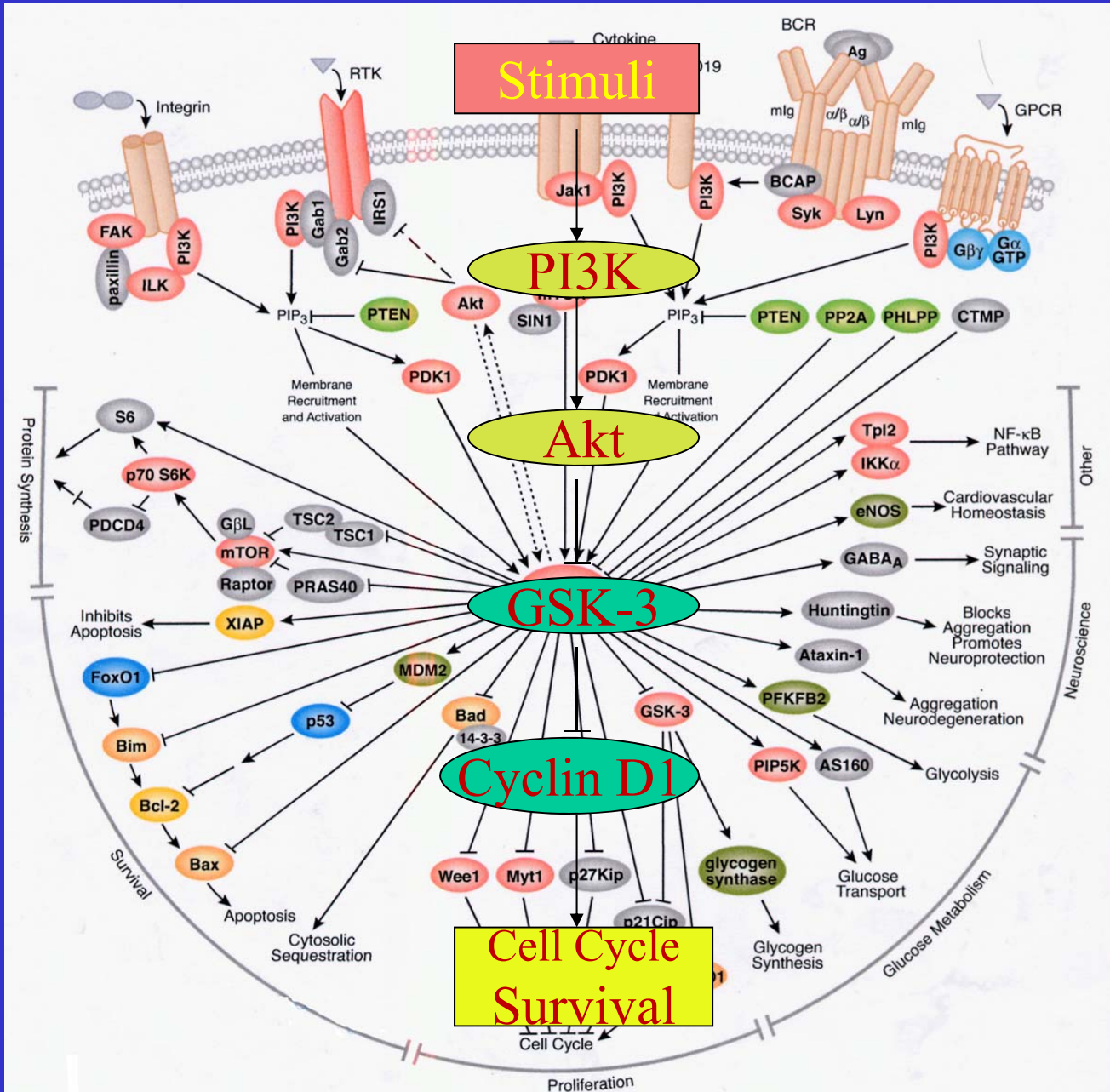
Low dose 17-AAG Induces GSK3 β Phosphorylation and Hsp70 Expression



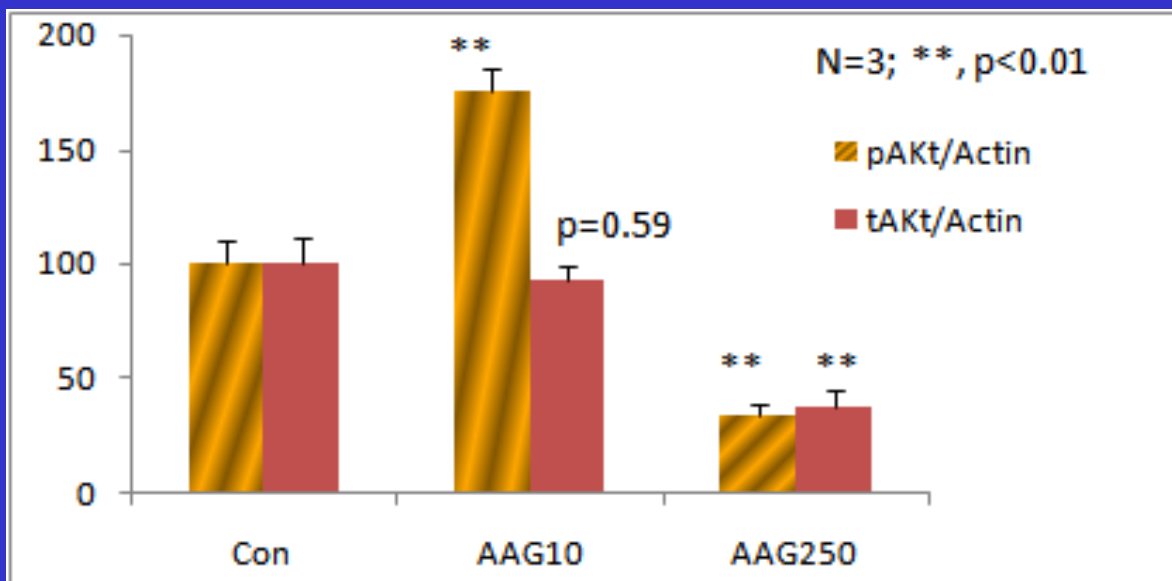
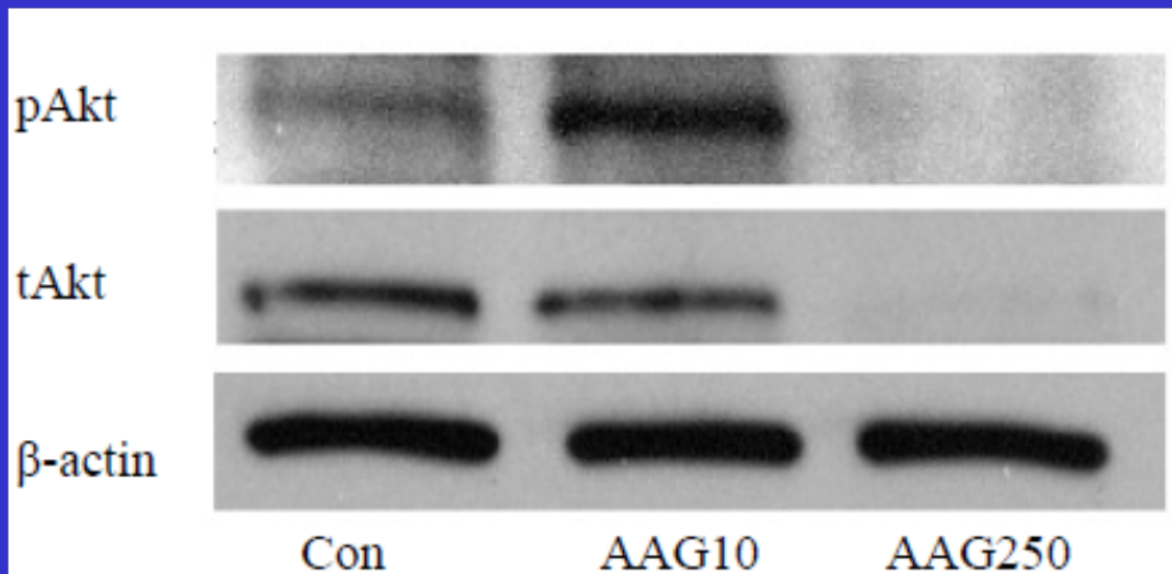
Prolonged Phosphorylation of GSK-3 β by low dose 17-AAG



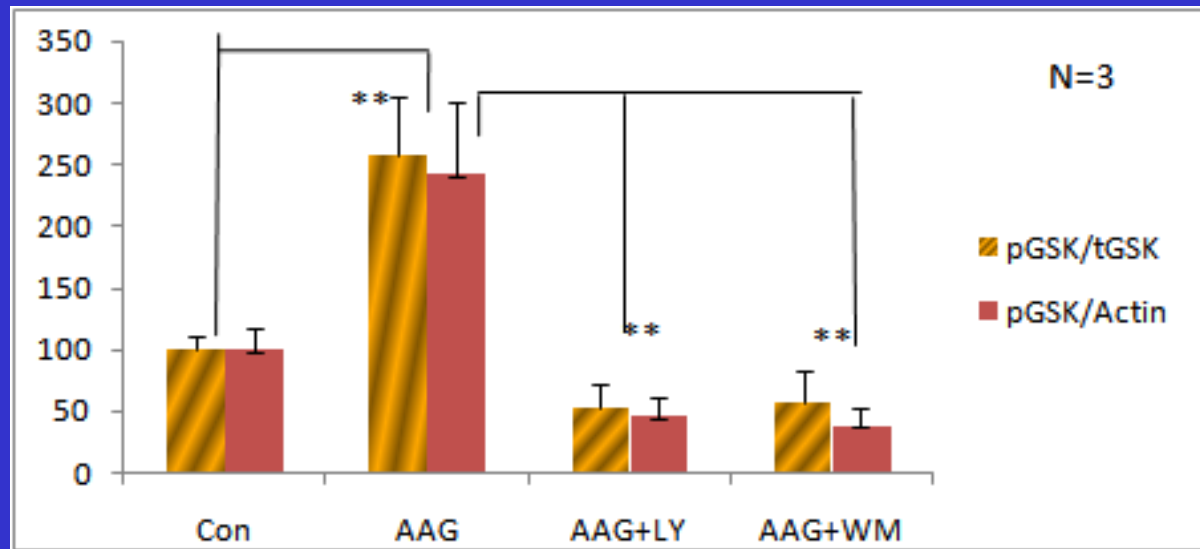
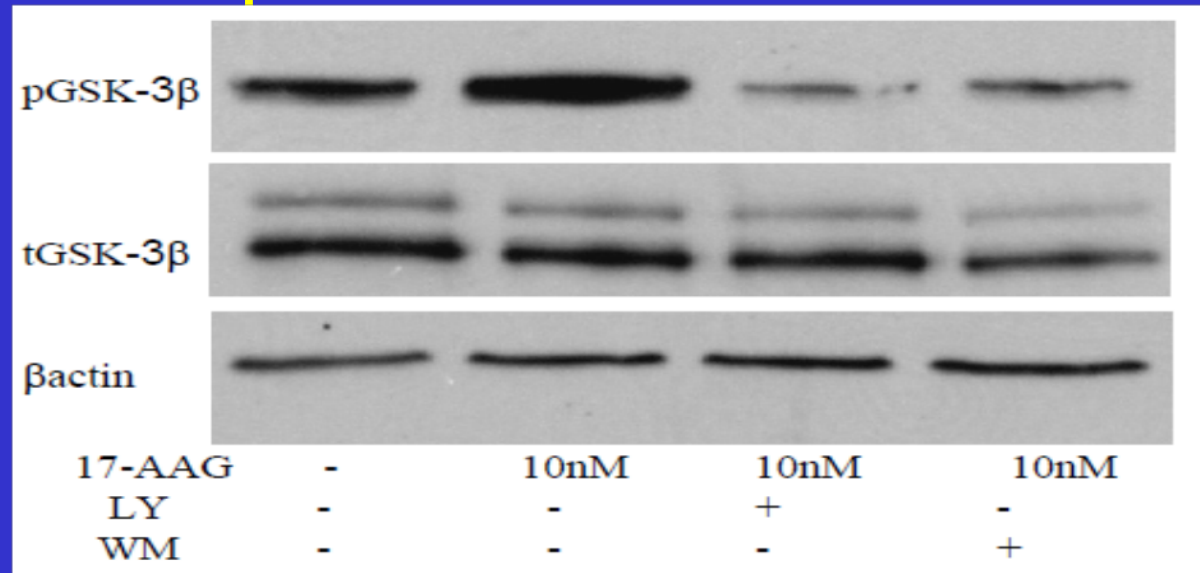
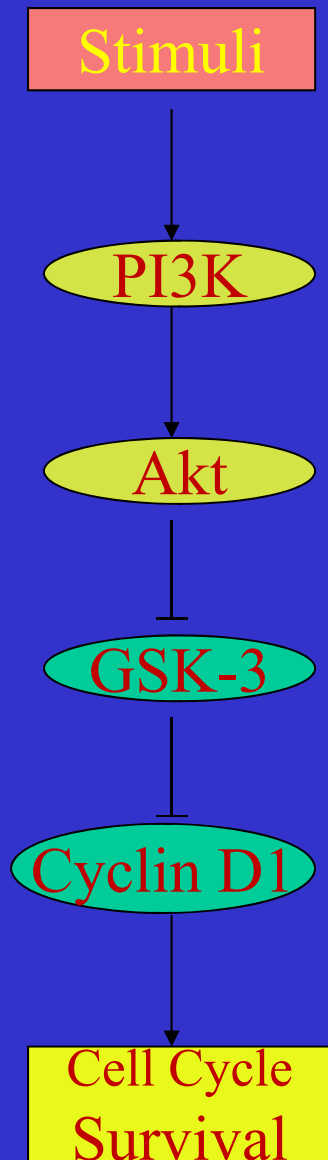
PI3K/Akt Pathway



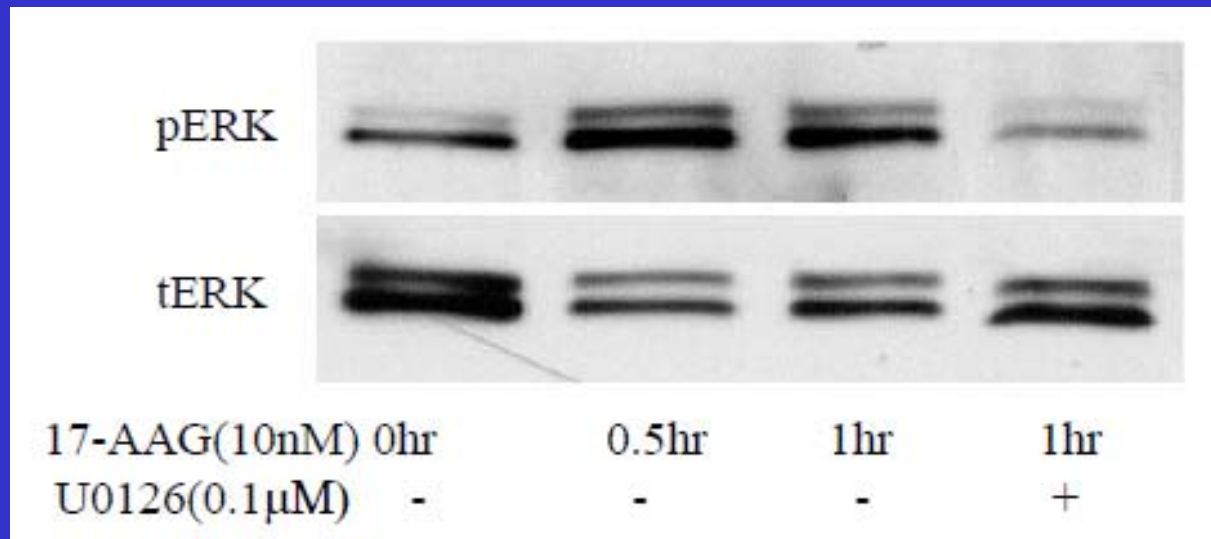
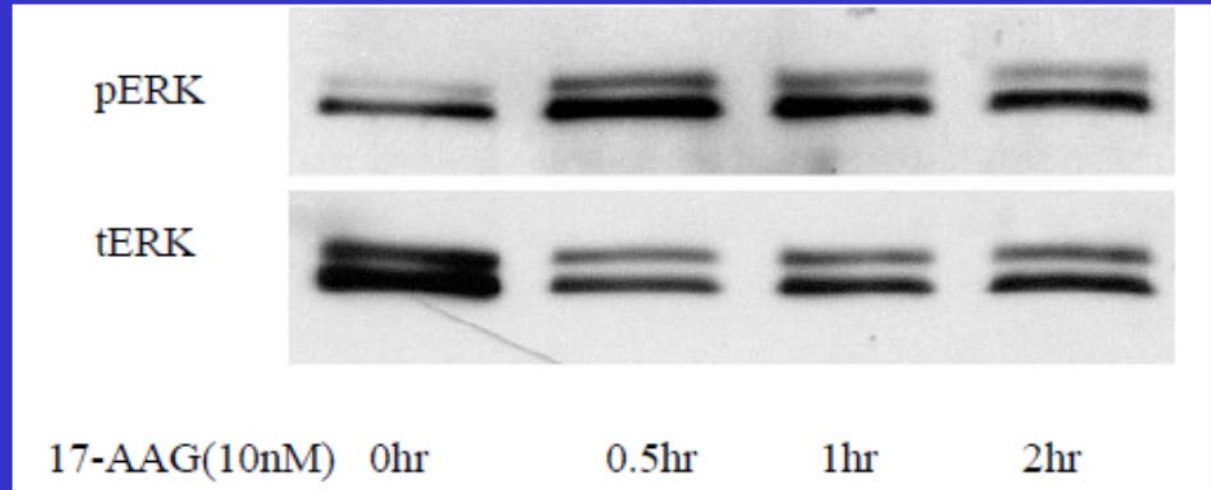
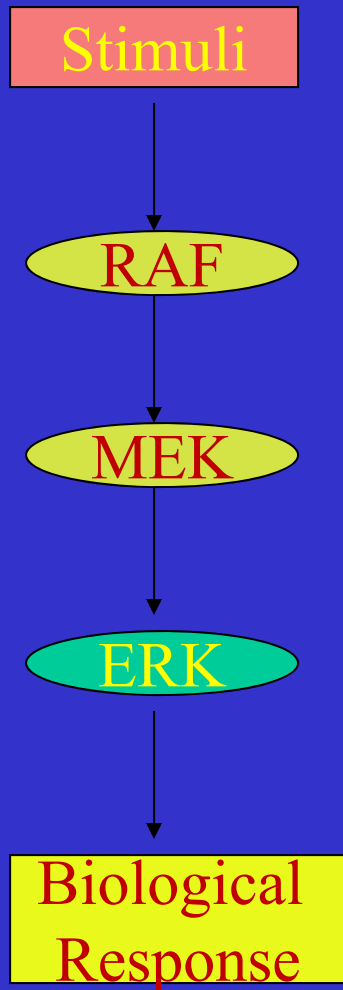
Low-dose 17-AAG Activates Akt in NPs



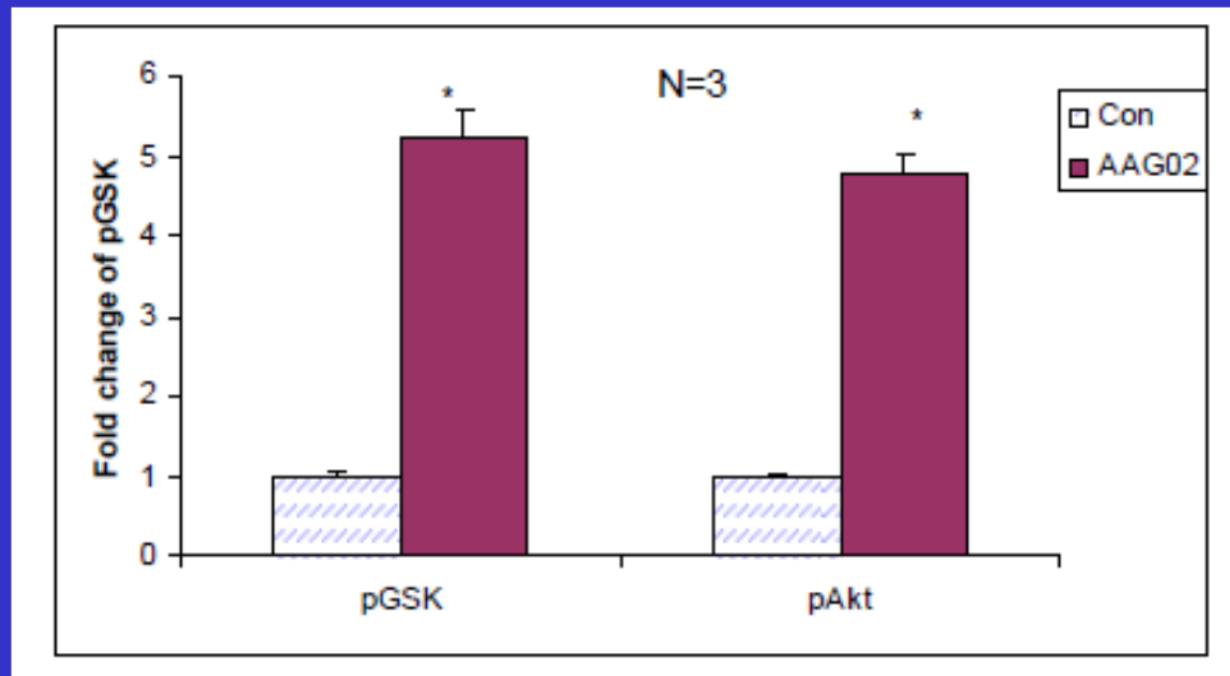
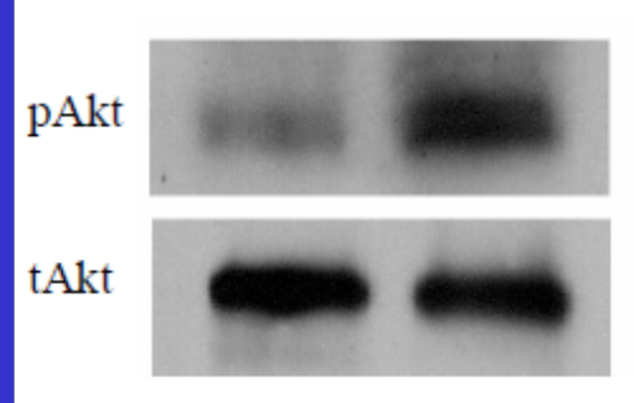
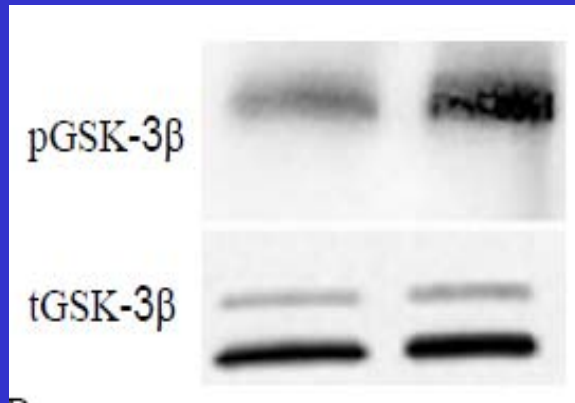
Confirmation of PI3K Pathway Mediated by Hsp90 Inhibition



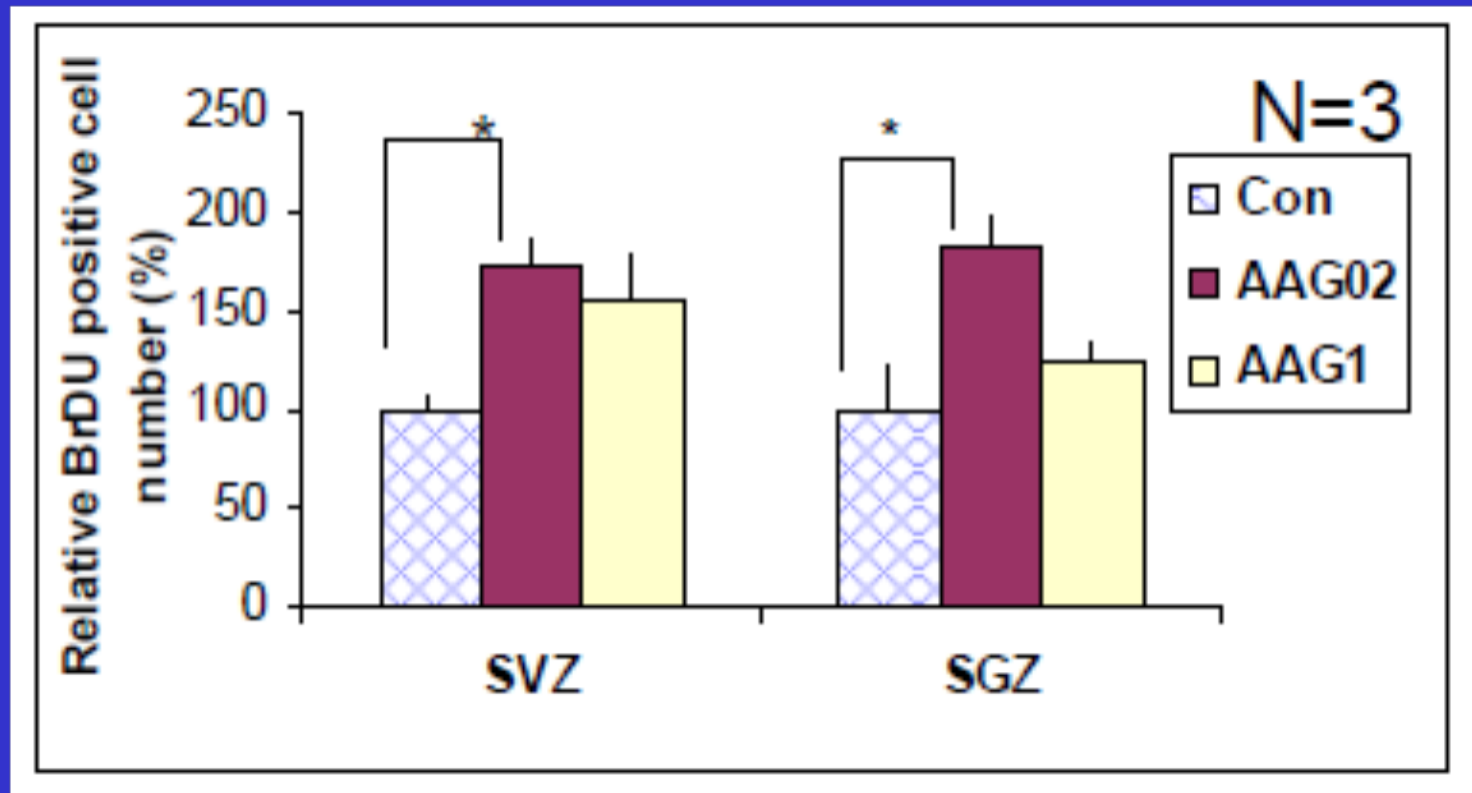
Low dose 17-AAG Induces Transient Phosphorylation of Erk1/2



Low-dose 17-AAG Induces Protective Factors *in vivo*



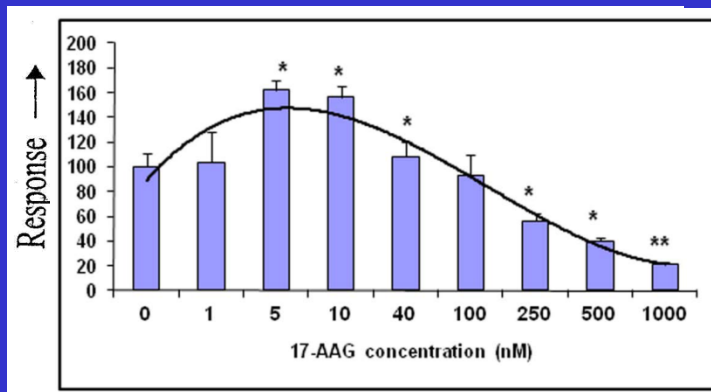
17-AAG Protected Neural Cells *in vivo*



A Typical Hormesis

Preconditioning, Thermotolerance, Stress adaptation, etc

- A common paradigm found throughout nature. An initial exposure of a cell or an organism to a mild stressful stimulus results in an adaptive response by which a second exposure to the same stimulus produces a minimal or beneficial response.
- The term hormesis was recently defined as a dose-response relationship in which there is an inhibitory response at higher doses but a stimulatory response at lower doses, resulting in a U-shaped or inverted U-shaped dose response



Norgaard et al. 2006,
Geraci *et al.* 2006,
Kraft *et al.* 2006,
Madhavan *et al.* 2006,
Mattson 2008,
Kendig *et al.* 2010

- A more interesting phenomenon is cross-tolerance, by which an initial exposure to a stressful stimulus results in an adaptive response such that the cell or organism acquires resistance to a different stress.

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THANK YOU