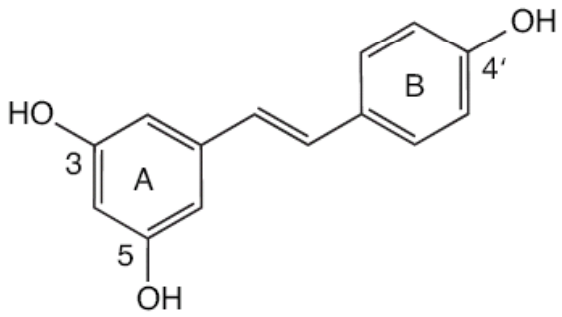
Biological activities of resveratrol



1. The research program: cell and molecular biology of longevity

2. Biological activities of resveratrol in mammals (including humans)

Animal lifespans

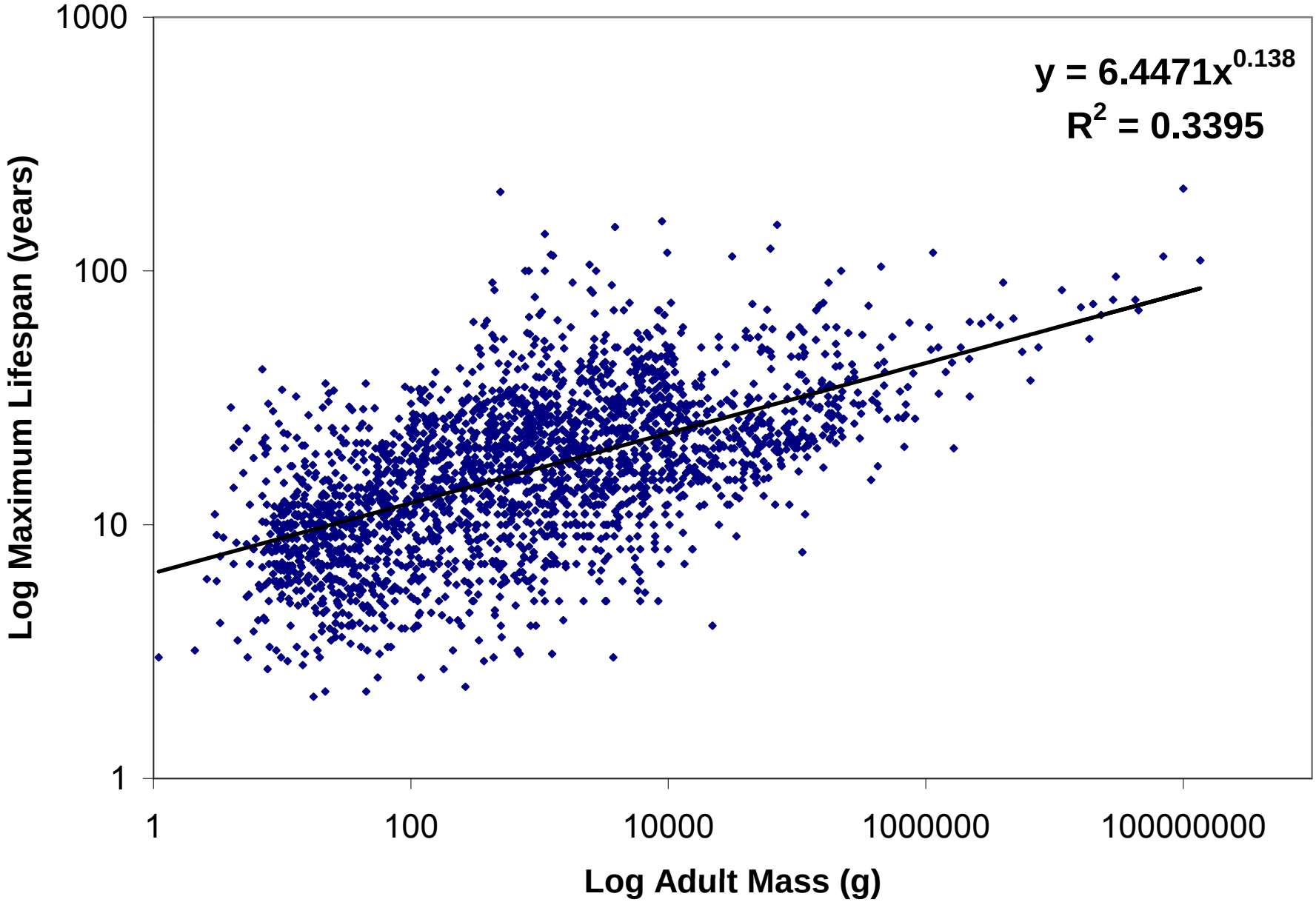
Several days

The mayfly
Lifespan: ~ 1day!

lifespan

Centuries

Harriet, who died on Friday, June 23, 2006 at the age of 176 years is said to be the oldest animal in captivity, according to the Guinness Book of Records.
(AP/Australia Zoo)


y = 6.4471x^0.138
R^2 = 0.3395
Log Maximum Lifespan (years)
1000
100
10
1
1
100
10000
1000000
100000000
Log Adult Mass (g)

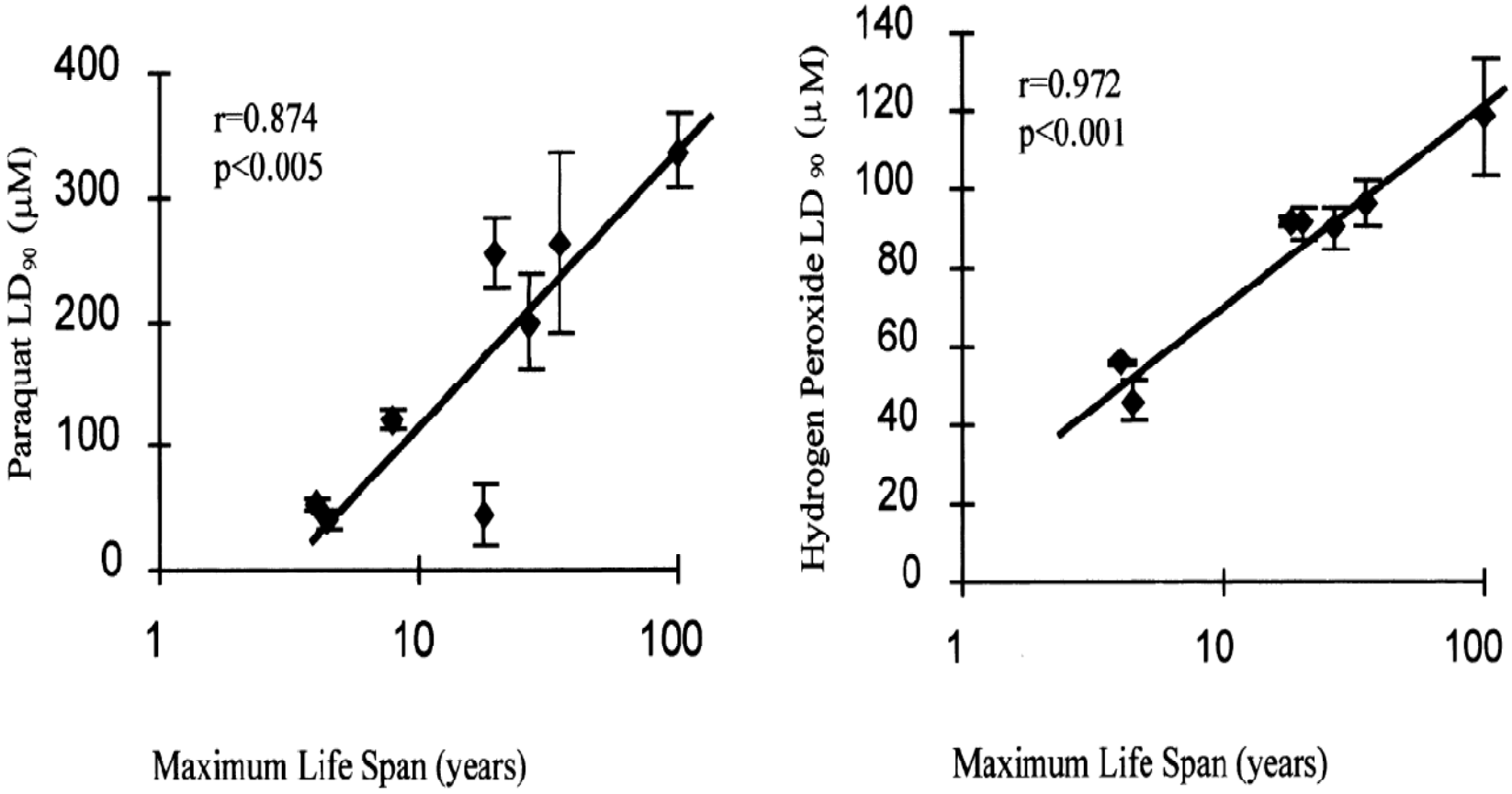
Why?

How?

Cells of longer-lived animals are hard to kill

- increased cellular stress resistance in longer-lived animals

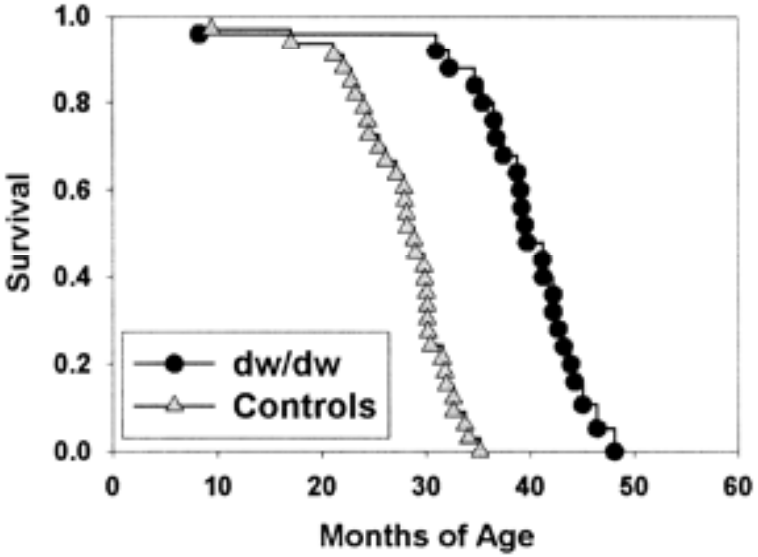
Stress resistance of skin fibroblasts correlates with species MLSP



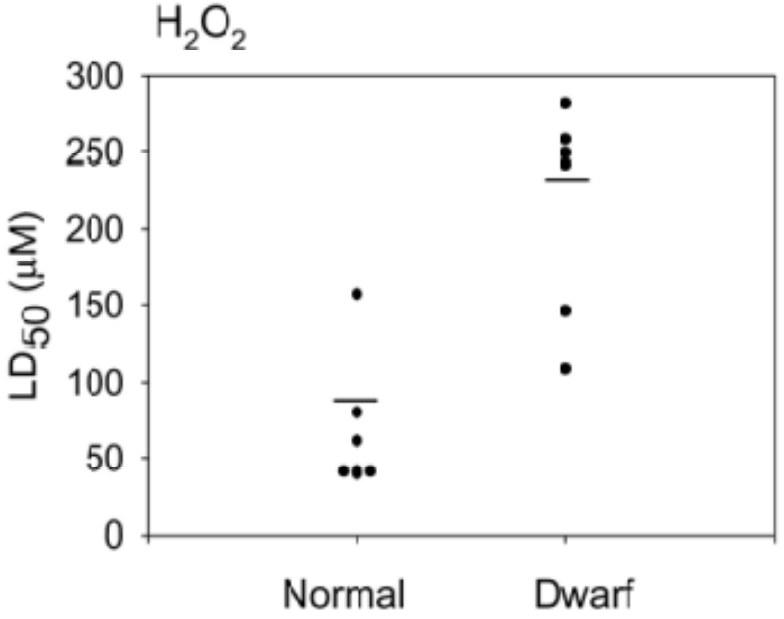
Kapahi et al., 1999, Free Radic. Biol. Med.

Long-lived Snell dwarf mice have stress resistant fibroblasts

Snell & normal mouse lifespan plot



Snell cells resistant to stressors



Murakami et al., Am. J. Physiol. 2003

‘Species-omics’

Identifying cellular characteristics that co-evolve with longevity and might explain stress resistance

Molecular mechanisms underlying longevity in animals

Two experimental models:

(1) The long-lived Snell dwarf mouse

(2) A comparative model using mammalian and avian species














What have we learned?

Cellular characteristics
that do not correlate,
or correlate negatively,
with longevity

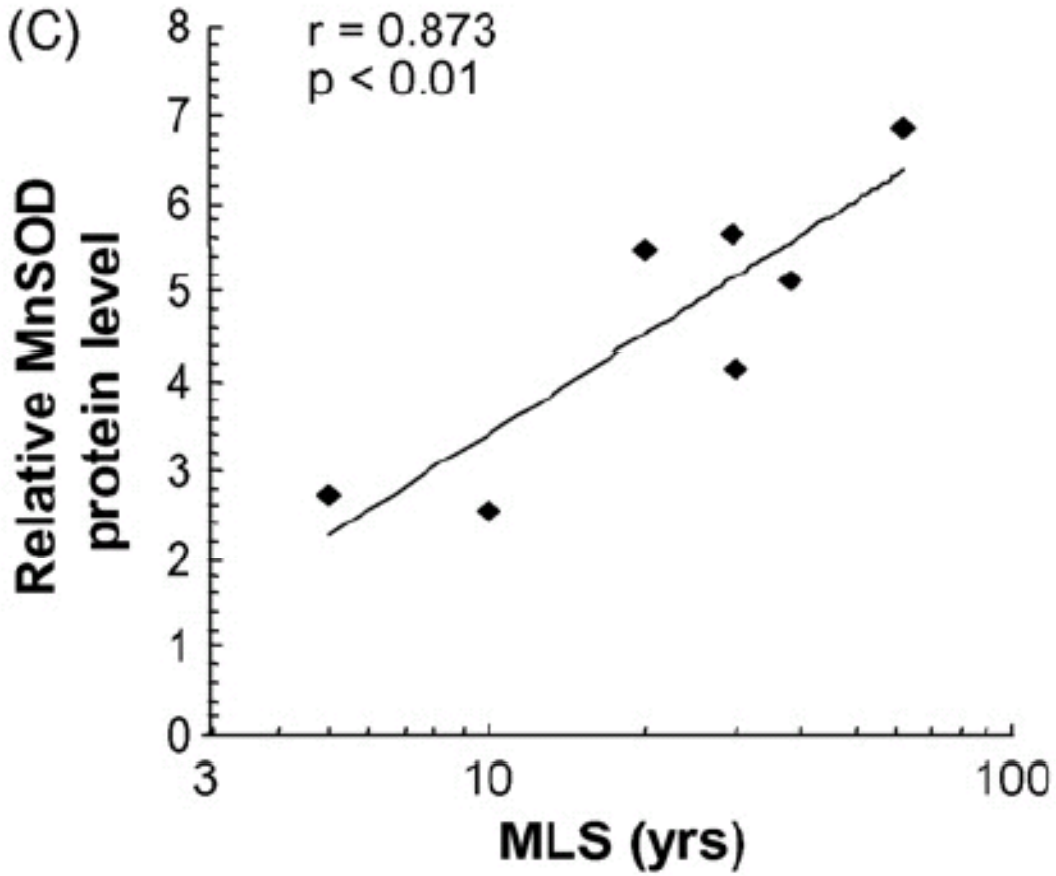
12

Cellular characteristics
that correlate
positively with longevity

1

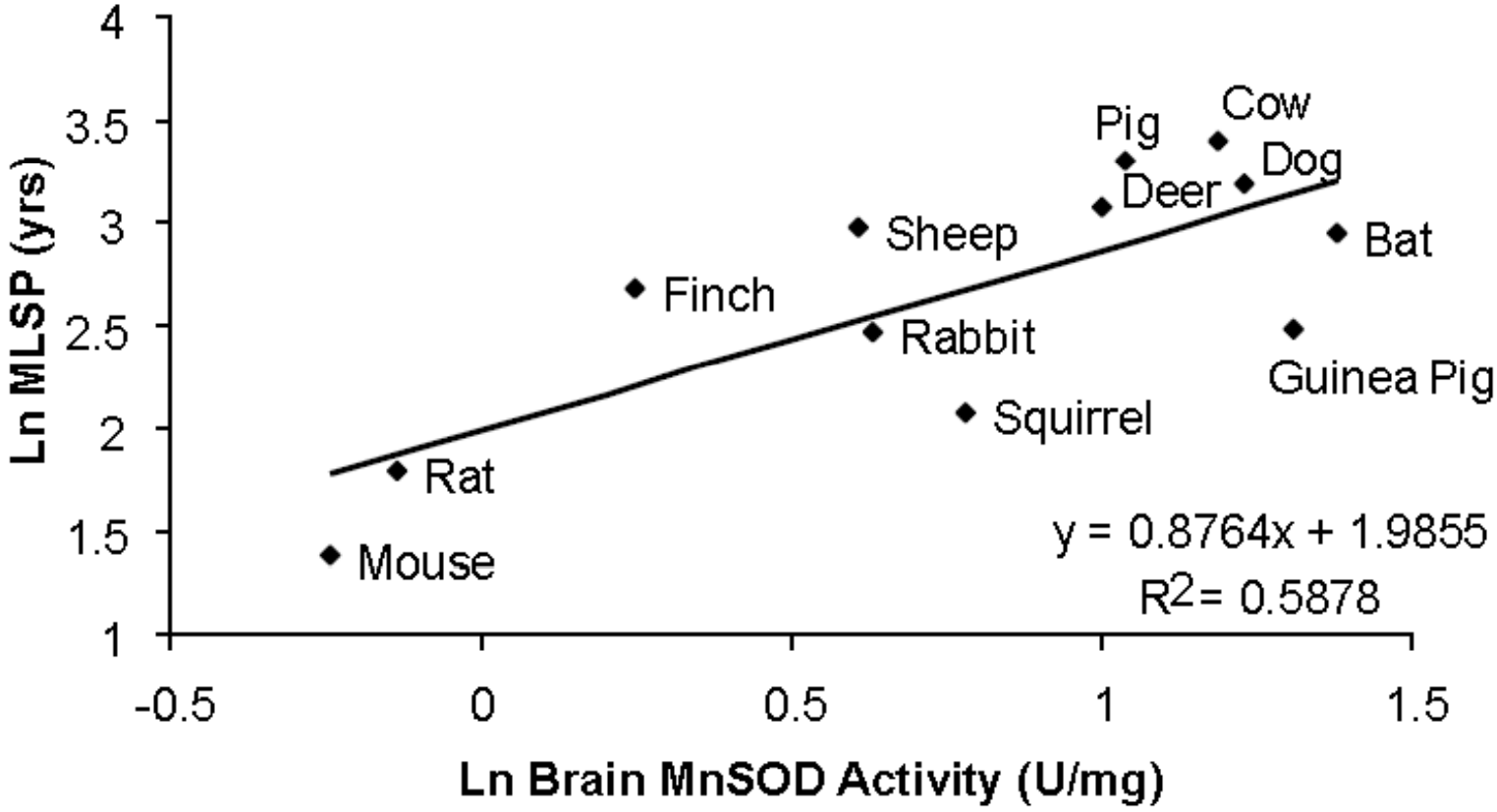
MnSOD correlates with longevity

Dermal fibroblasts

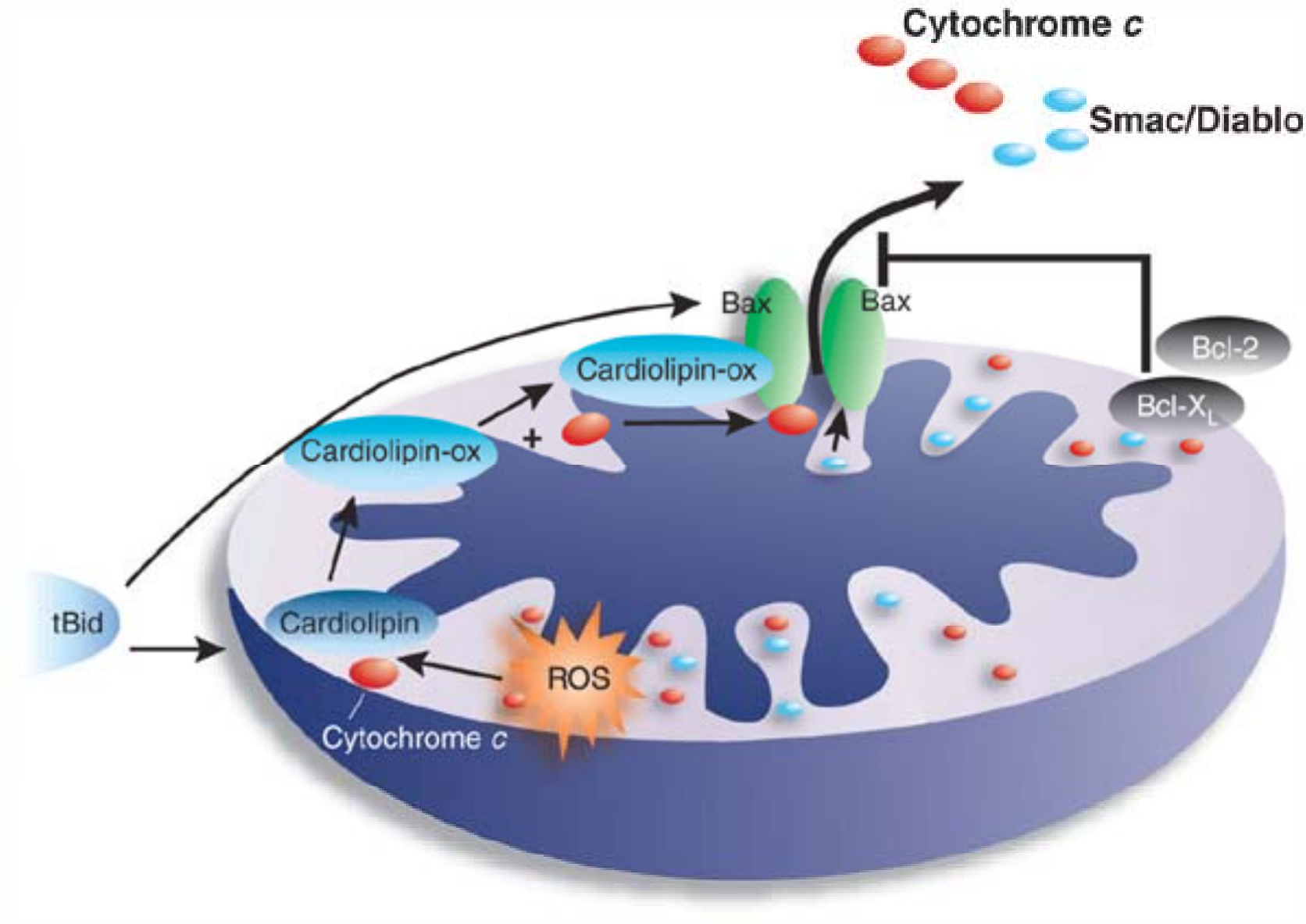


MnSOD correlates with longevity

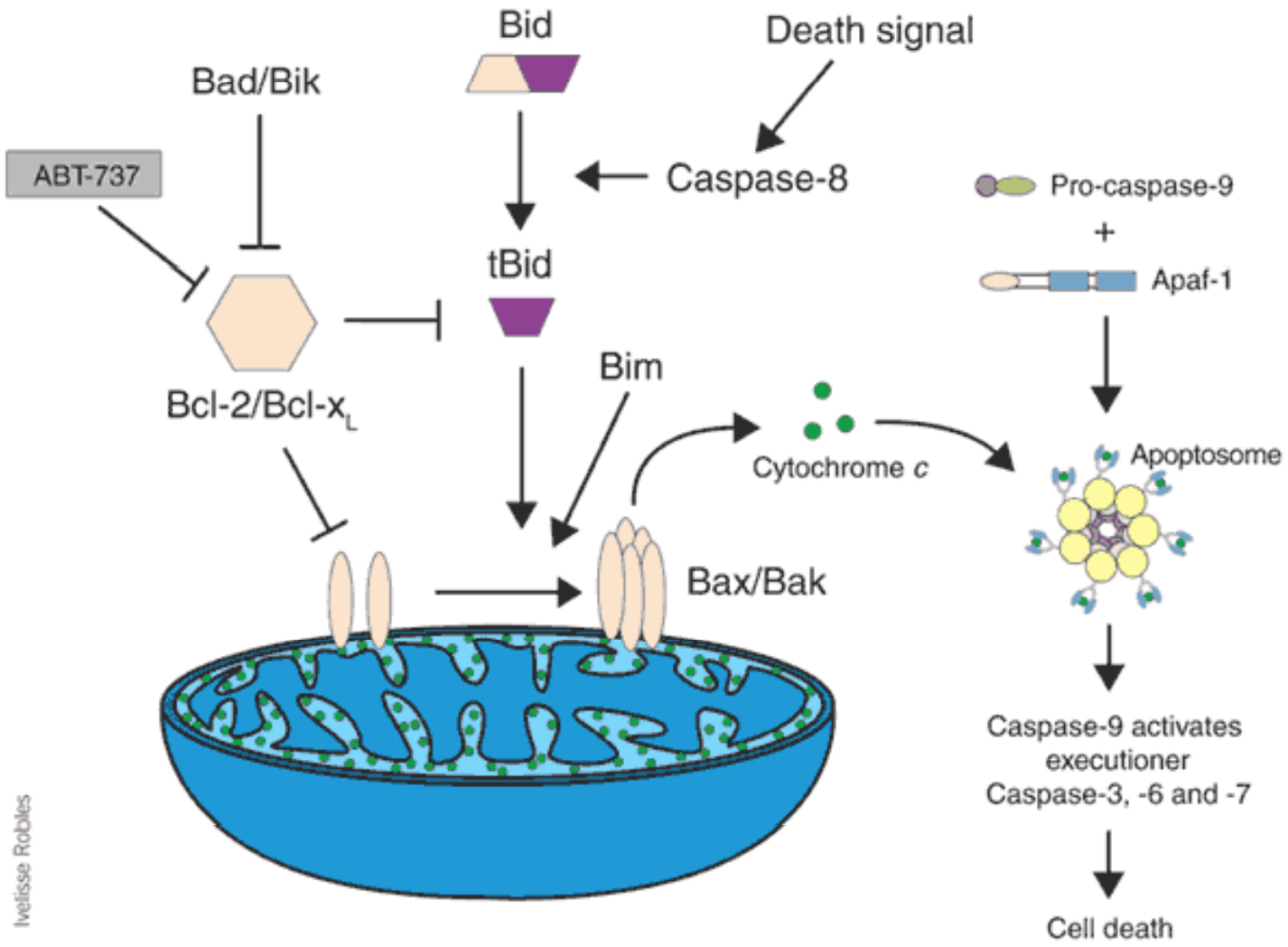
mammalian brain tissue



MnSOD prevents cytochrome c release during cell stress



Cytochrome c is a key cell death signal



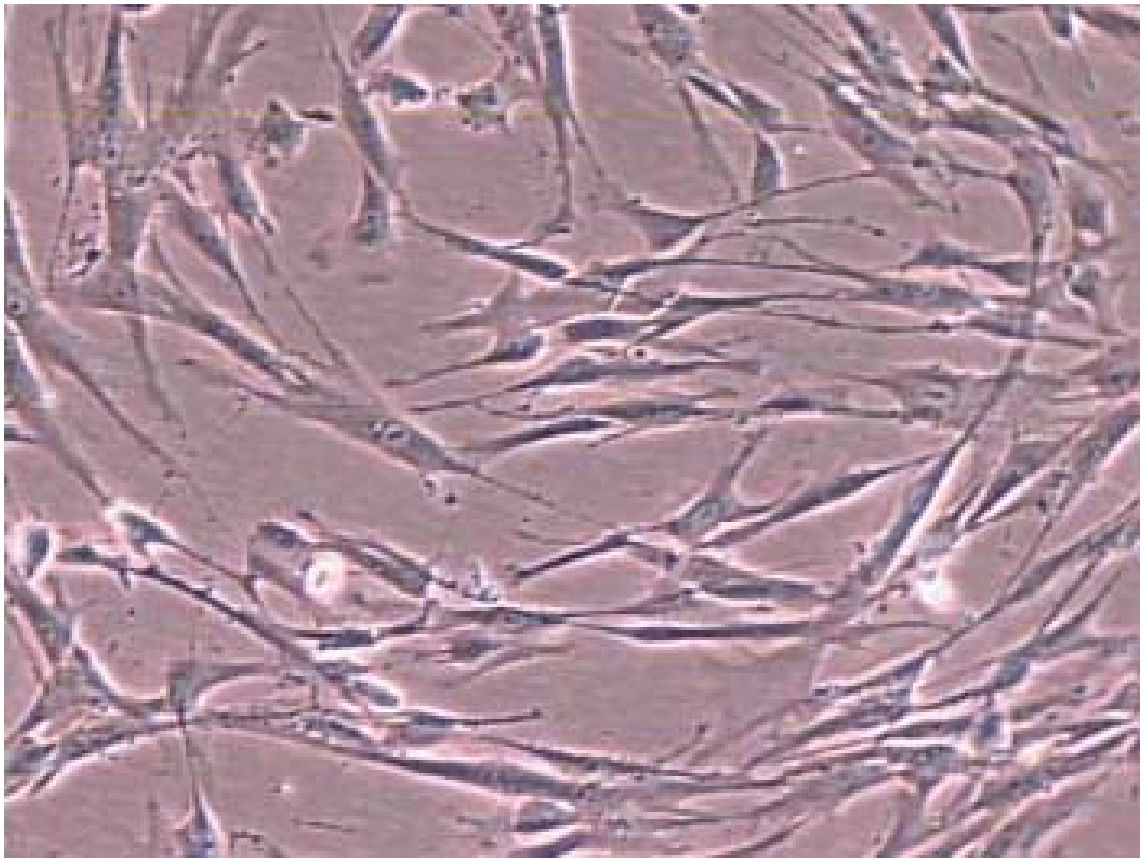
Ellen Robb, PhD candidate

Bourses d'études supérieures du Canada
Vanier
Canada Graduate Scholarships

Resveratrol does everything!

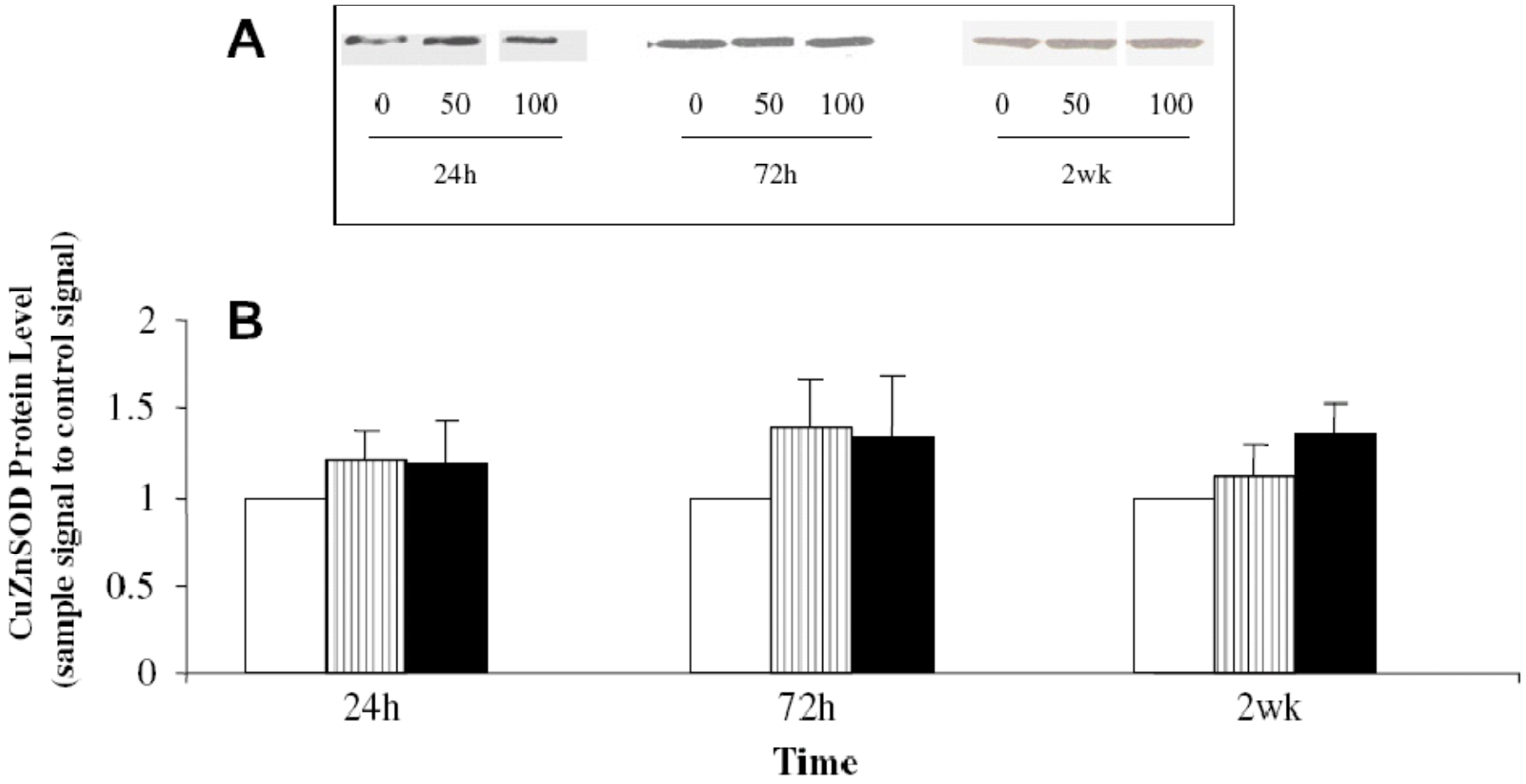
- Anti-cancer activity
- Anti-oxidant
- Anti-aging
- Neuroprotective

What is the effect on human cells of long-term exposure to resveratrol?



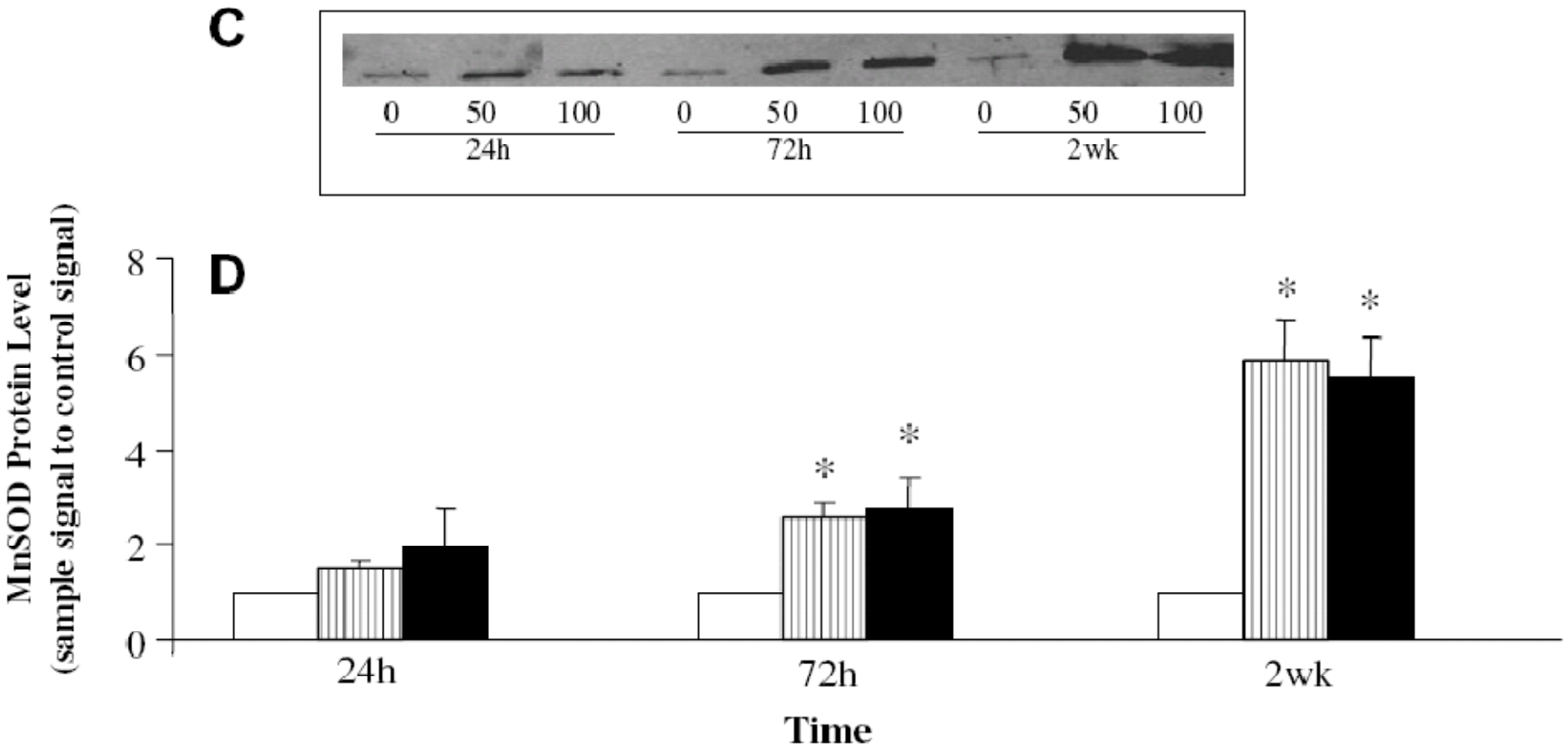
No effect of resveratrol on most antioxidant enzymes

e.g. cytosolic superoxide dismutase



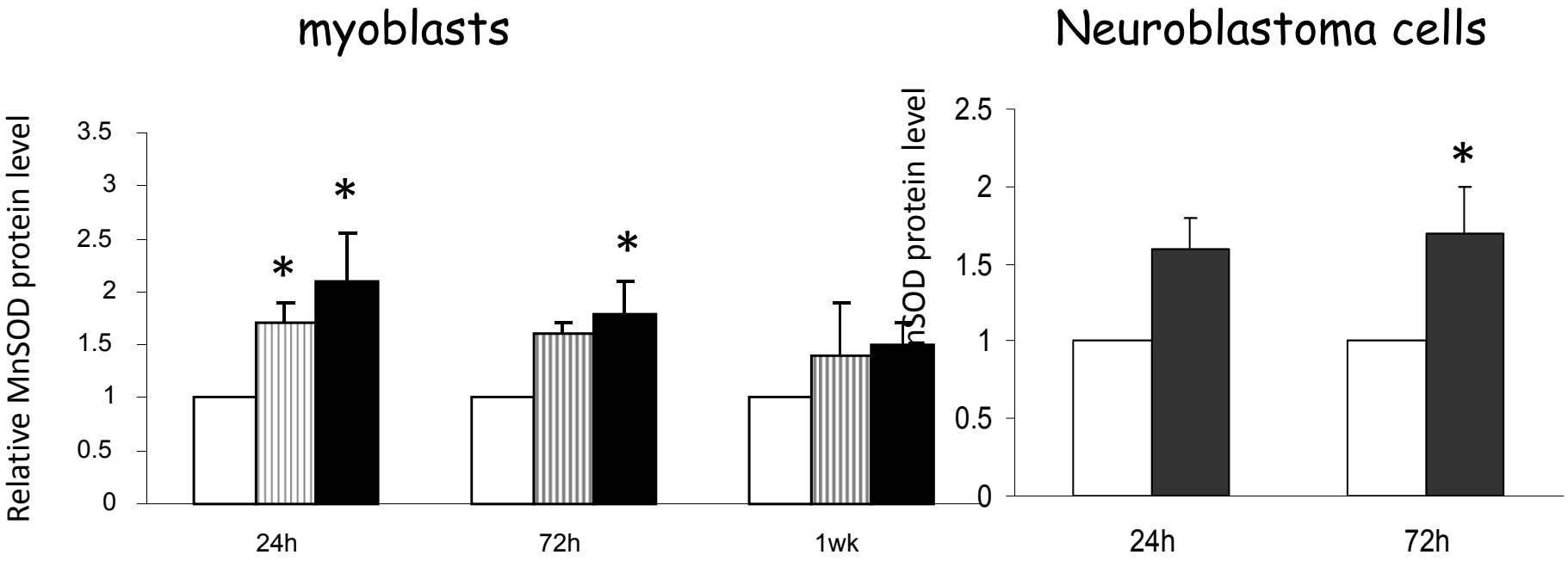
0, 50 or 100 μM *trans*-resveratrol

But, a huge effect on MnSOD!



0, 50 or 100 μM *trans*-resveratrol

MnSOD effect observed in a wide variety of cell types



0, 50 or 100 μM *trans*-resveratrol

Proof that this matters?

Greater MnSOD levels paralleled by greater cellular stress resistance

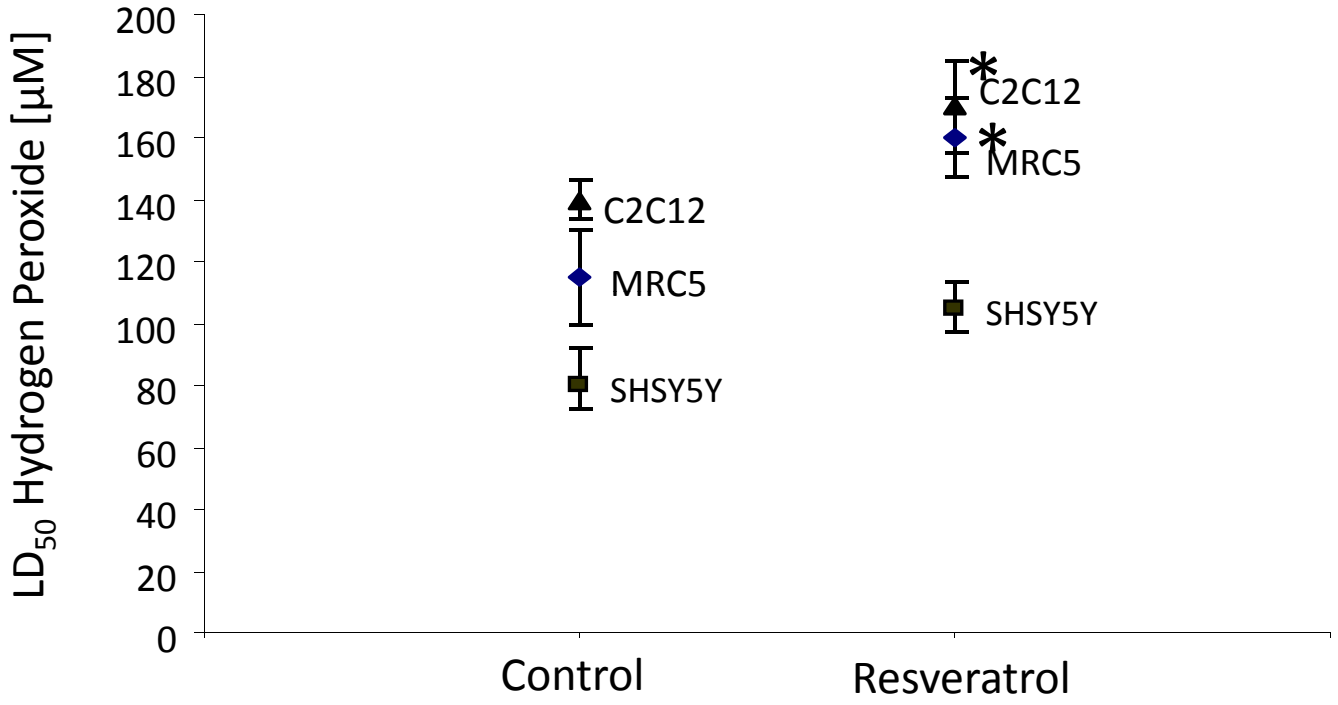


Figure 1: **Chronic exposure of muscle cells, lung cells and neural cells to 50µM resveratrol affords protection against cell death induced by the oxidative stressors hydrogen peroxide and paraquat**. Data point represents LD50 for a given toxin, Cell survival was evaluated by trypan blue exclusion. Data represents the mean of 5 independent measurements ± SEM. *=P<0.05

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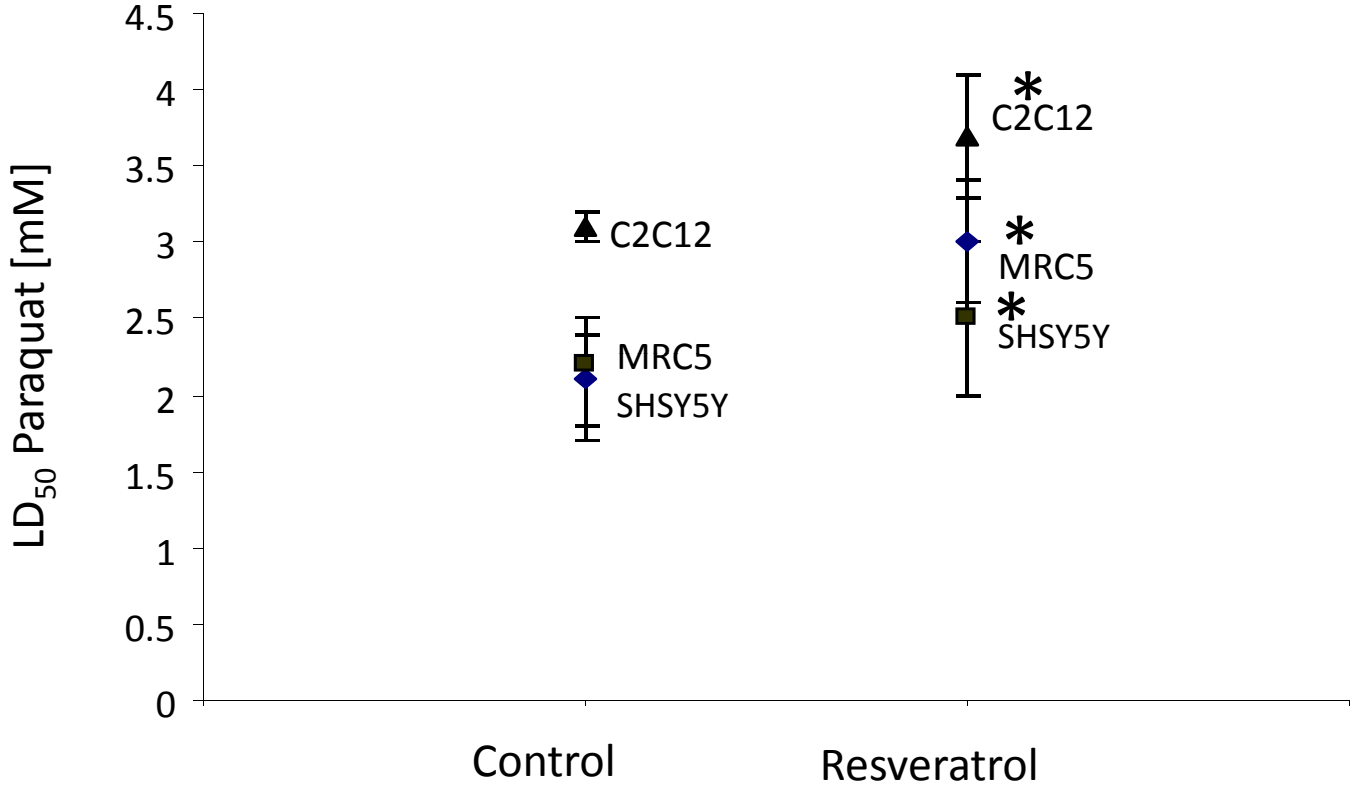

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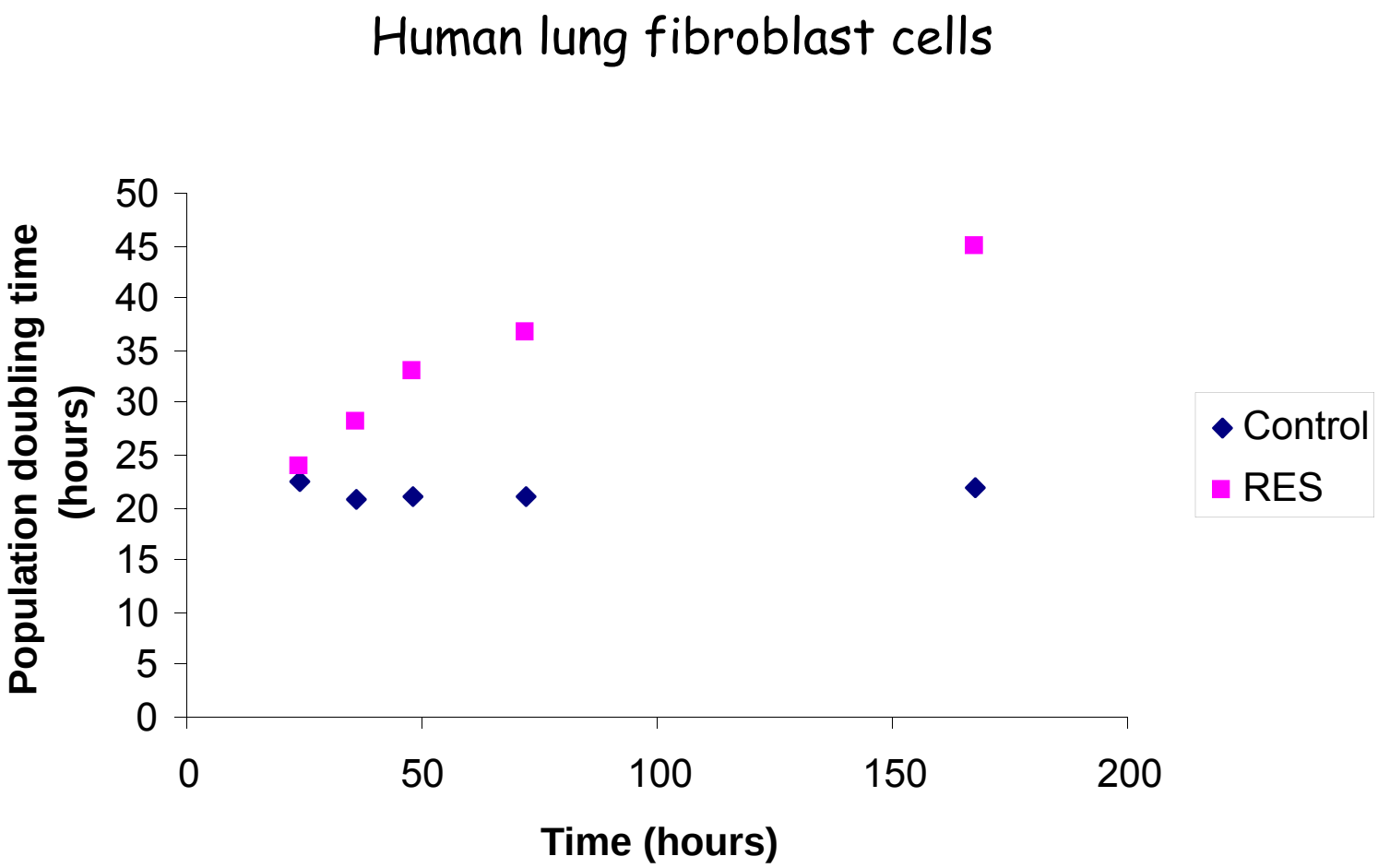
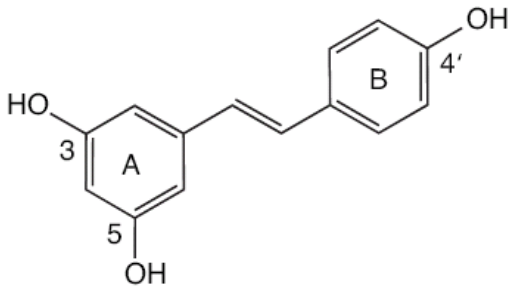
Greater MnSOD levels paralleled by reduced replicative growth rate

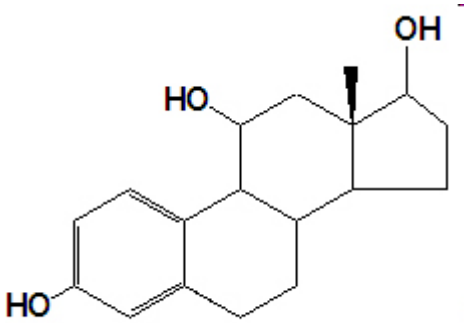


How is resveratrol regulating MnSOD levels?

Resveratrol is a phytoestrogen

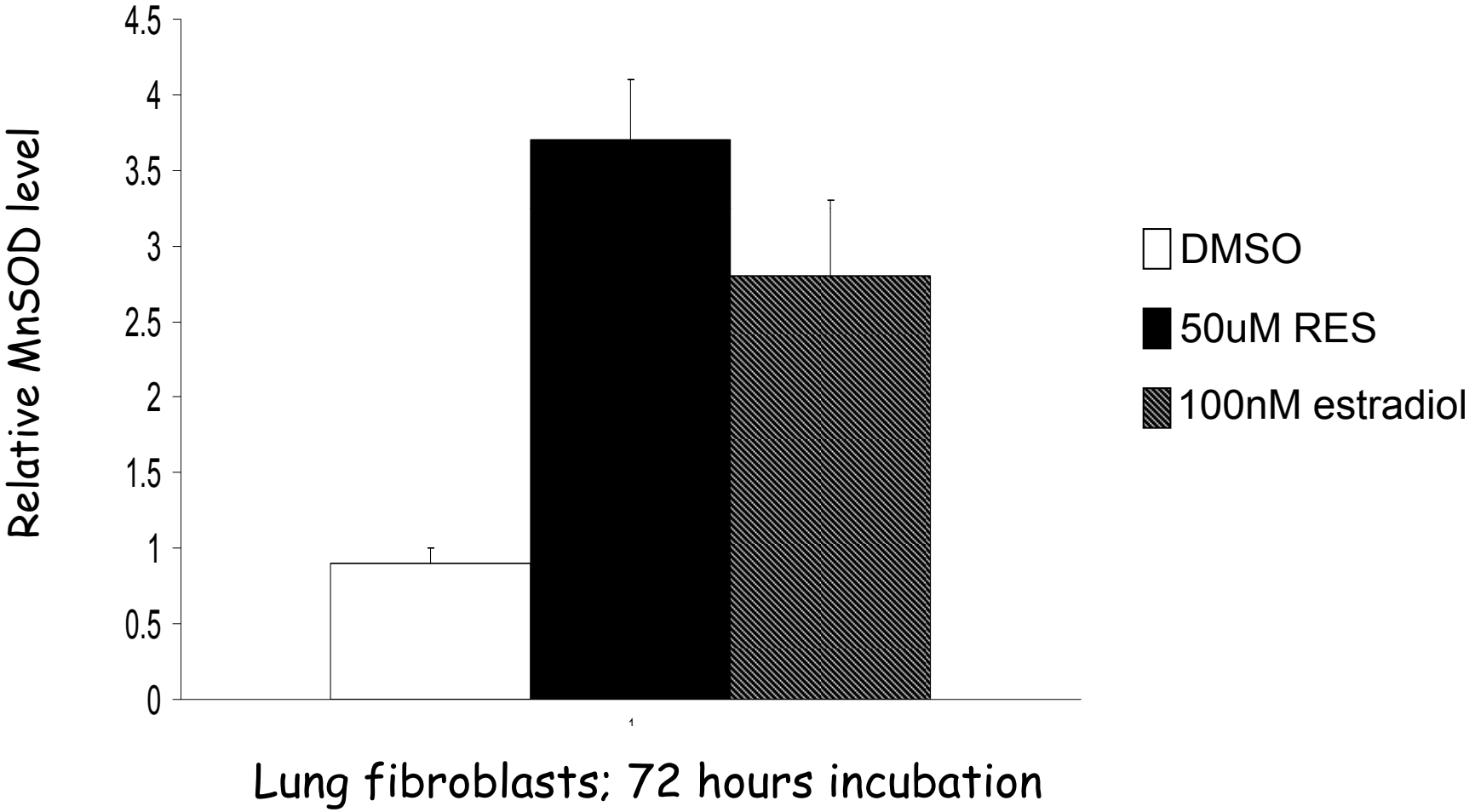


Resveratrol

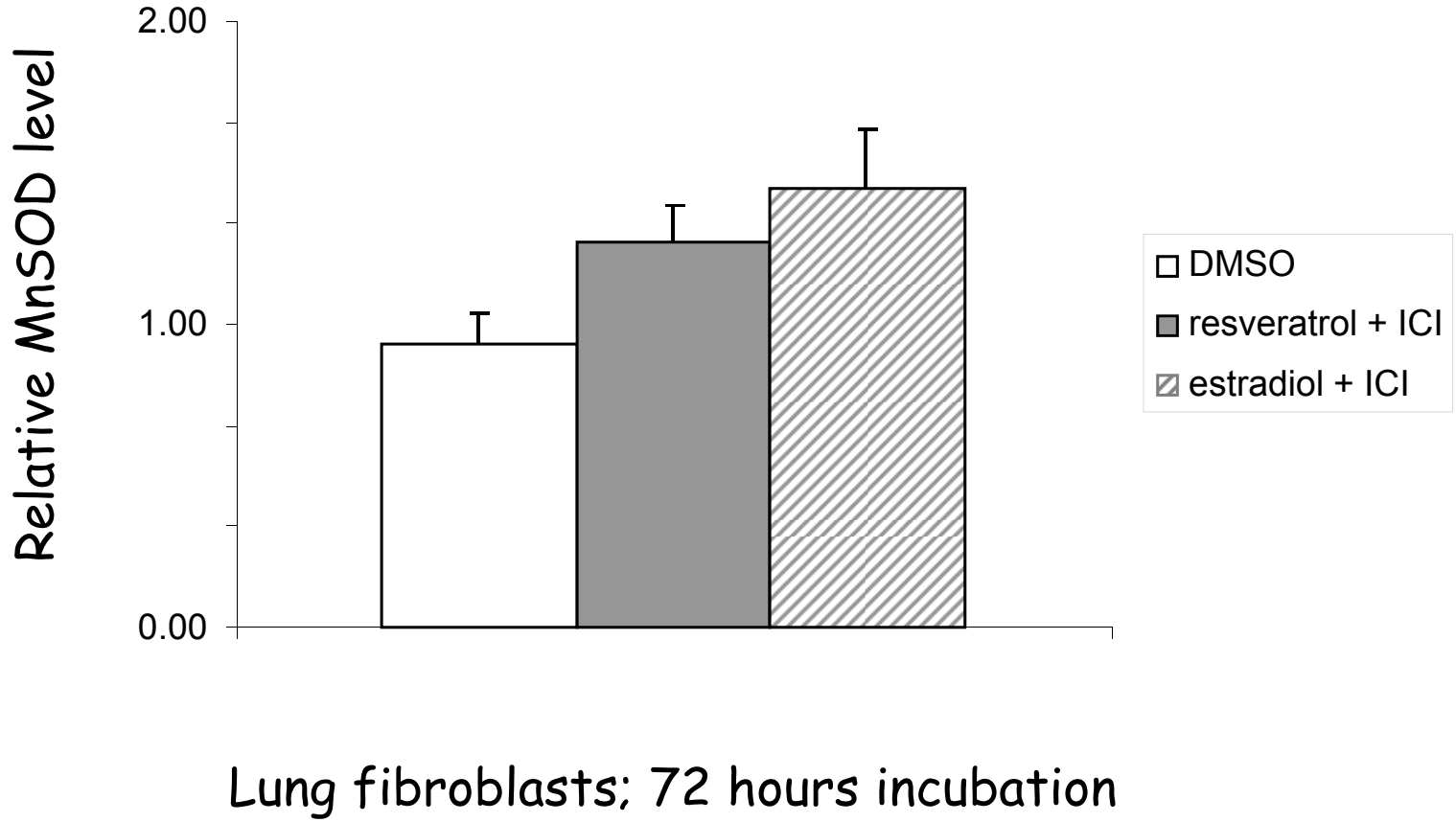


Estradiol

Estrogen (estradiol) elicits a similar MnSOD effect



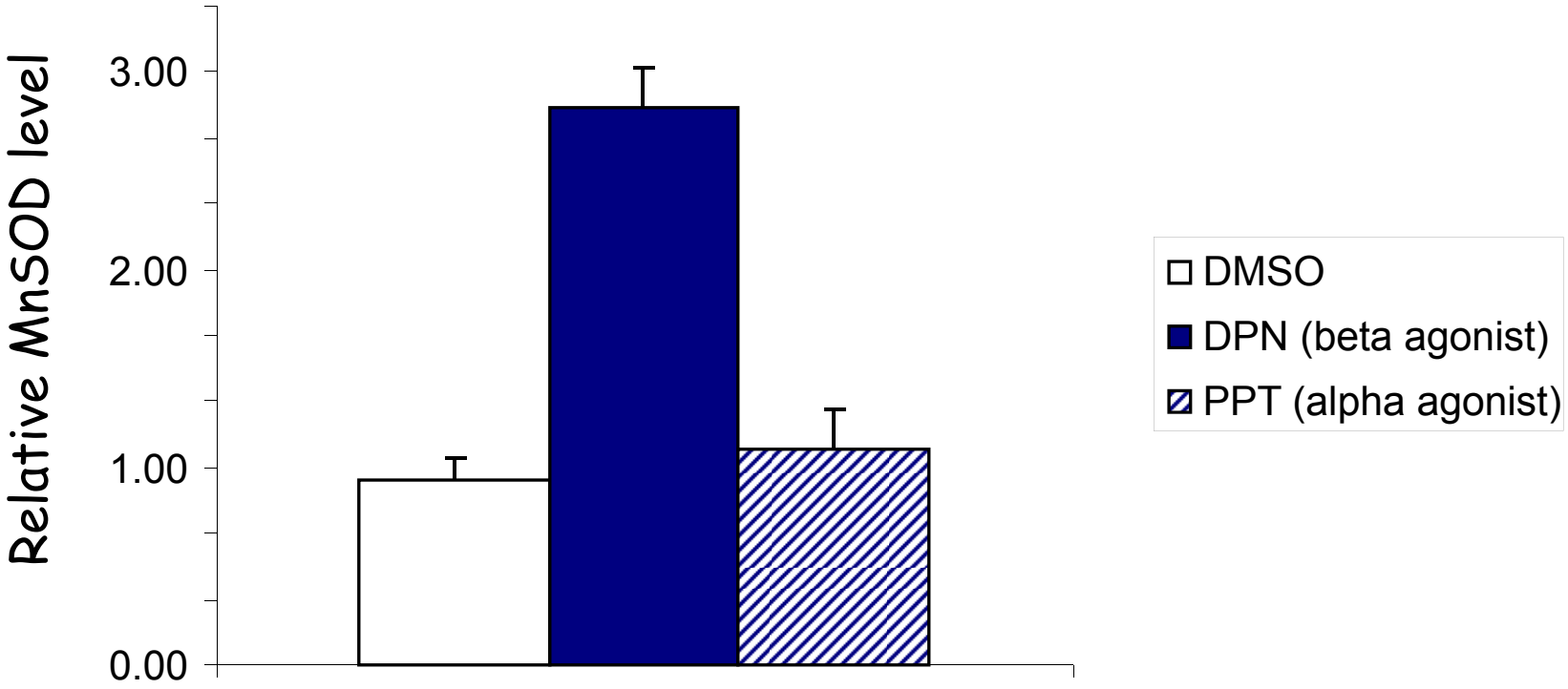
An estrogen receptor inhibitor abolishes (nearly) effects of resveratrol or estradiol on MnSOD



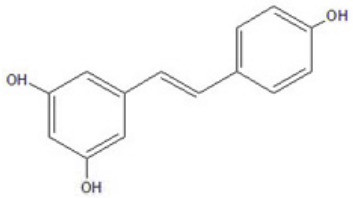
An ER beta agonist, but not an ER alpha agonist reproduces resveratrol effect on MnSOD

2,3-bis(4-hydroxyphenyl) proprionitrile (DPN)

propylpyrazole triol (PPT)



Our working model



ER

Cytosol

MAPK
ERK1/2

NFκB

Nucleus

MnSOD

MnSOD

↑MnSOD
- altered ROS metabolism
- antiapoptotic

Mitochondria

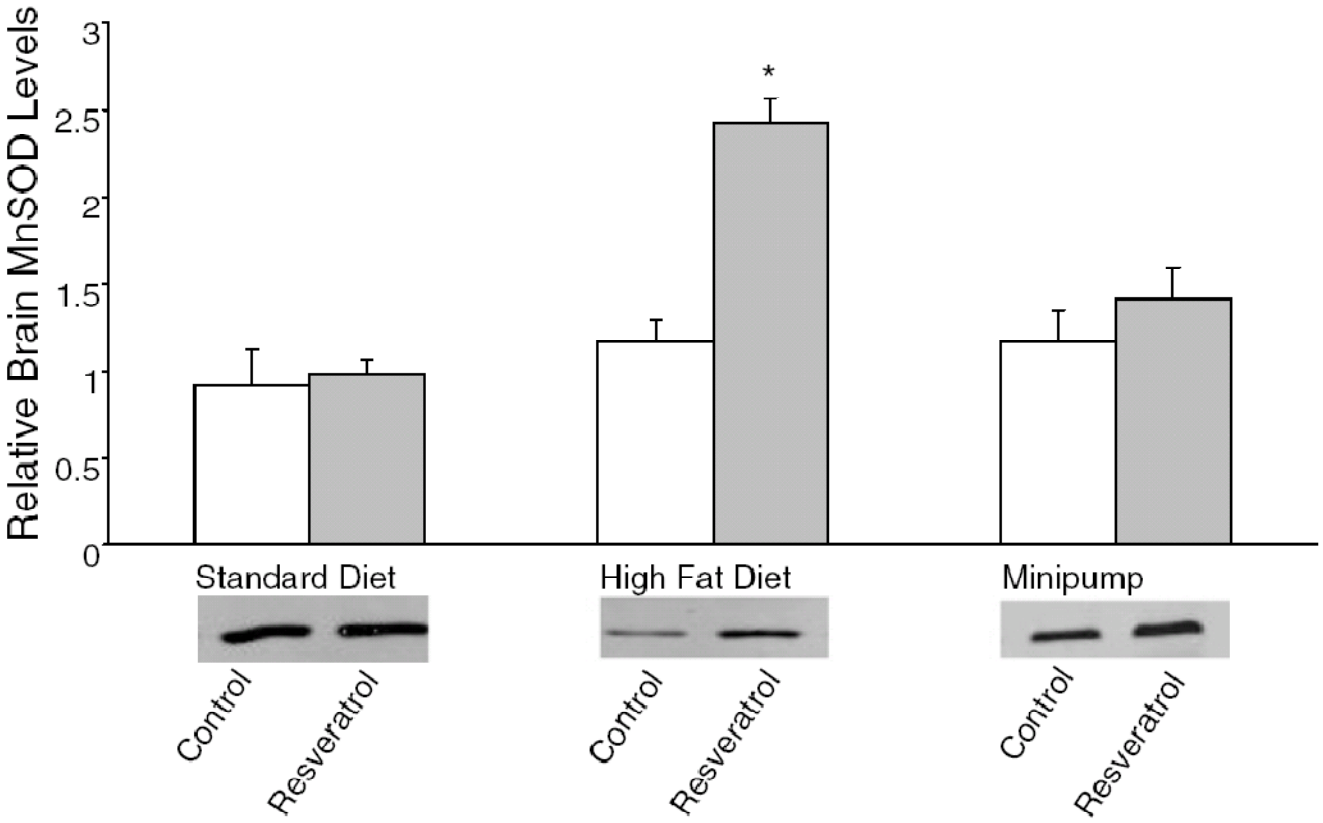
Other genes

Delivering results

Problems with resveratrol bioavailability

Dietary resveratrol delivery in mice

Increasing brain MnSOD



Jonathon Brotchie

Dietary resveratrol delivery in mice

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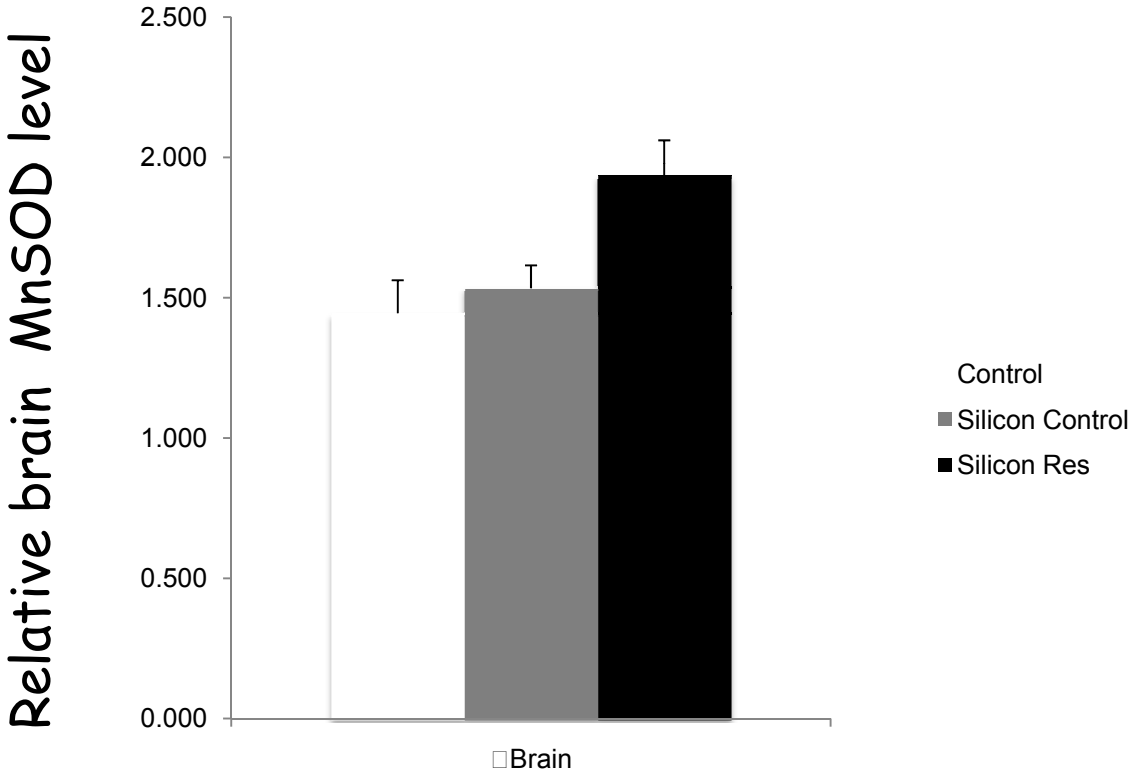
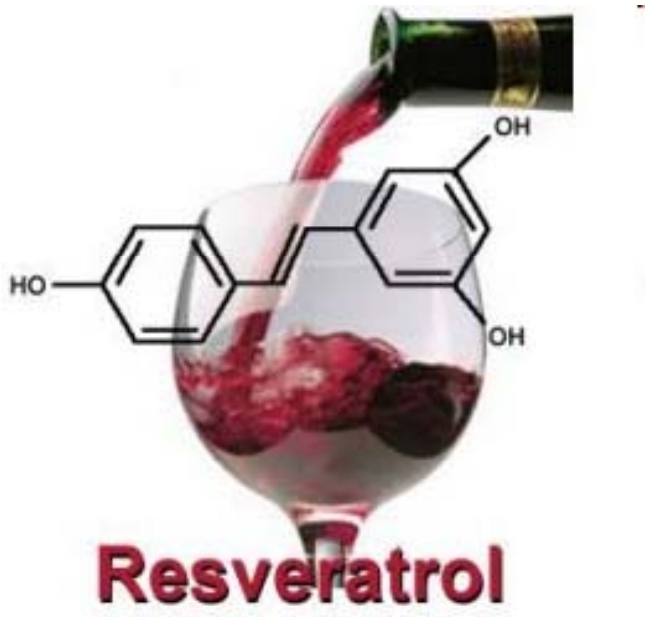


Silicon nanocapsule delivery of resveratrol with Paul Zelisko

Conclusions



- In human cells resveratrol interacts with ERbeta
- Transcriptional upregulation of MnSOD (progressive and big!)
- Increased MnSOD makes mitochondria resistant to cyt c release
- Increased MnSOD alters mitochondrial reactive oxygen metabolism
- Altered ROS metabolism influences cell replication (signal)
- Red wine consumption provides low amount of bioavailable resveratrol
- Resveratrol-mediated MnSOD induction assisted by delivering in lipid
- Maybe promote also using silicon nanocapsules (more work)

Future goals

• Refine strategy to increase RES bioavailability (RES supplemented wines?)

• Explore related polyphenols & phytoestrogens (-quercetin does not work similarly)

• Explore activities of RES metabolites

• Human trials?

This work was done by:

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