

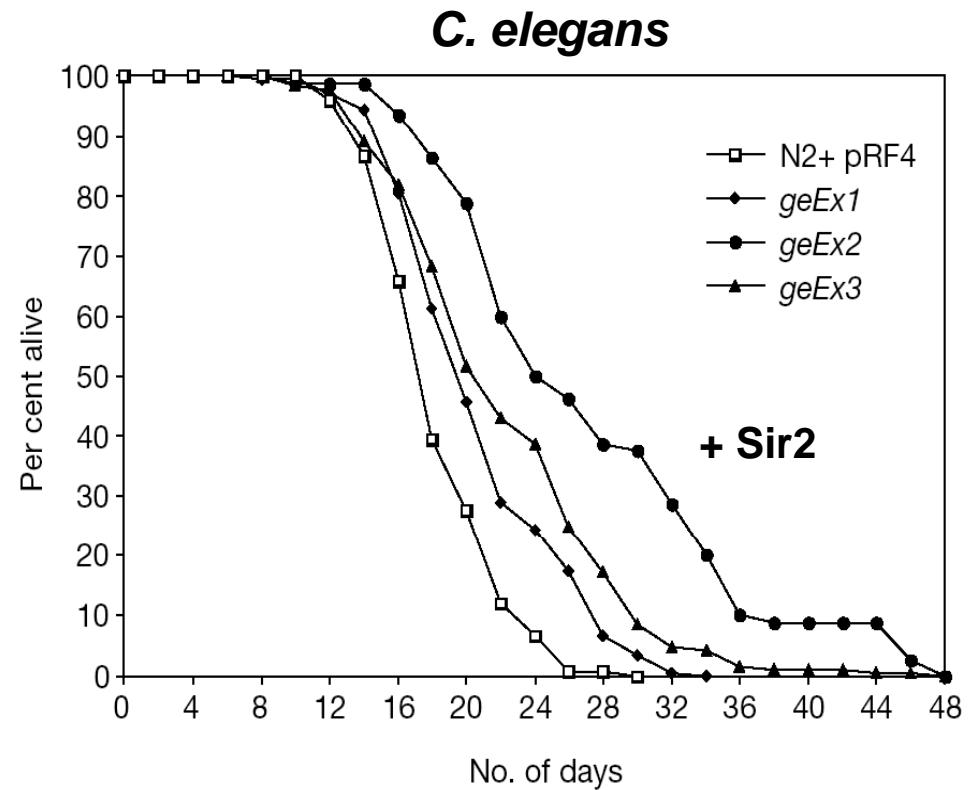
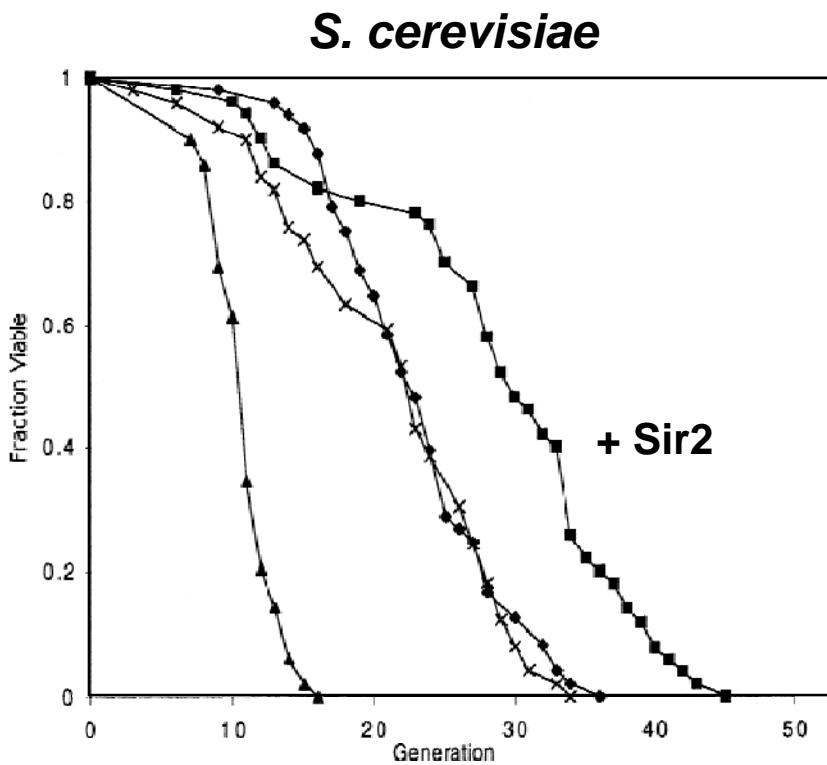
Genes and small molecules that regulate lifespan: Evidence for xenohormesis?



Joseph Baur, PhD
Harvard Medical School
May 1, 2007

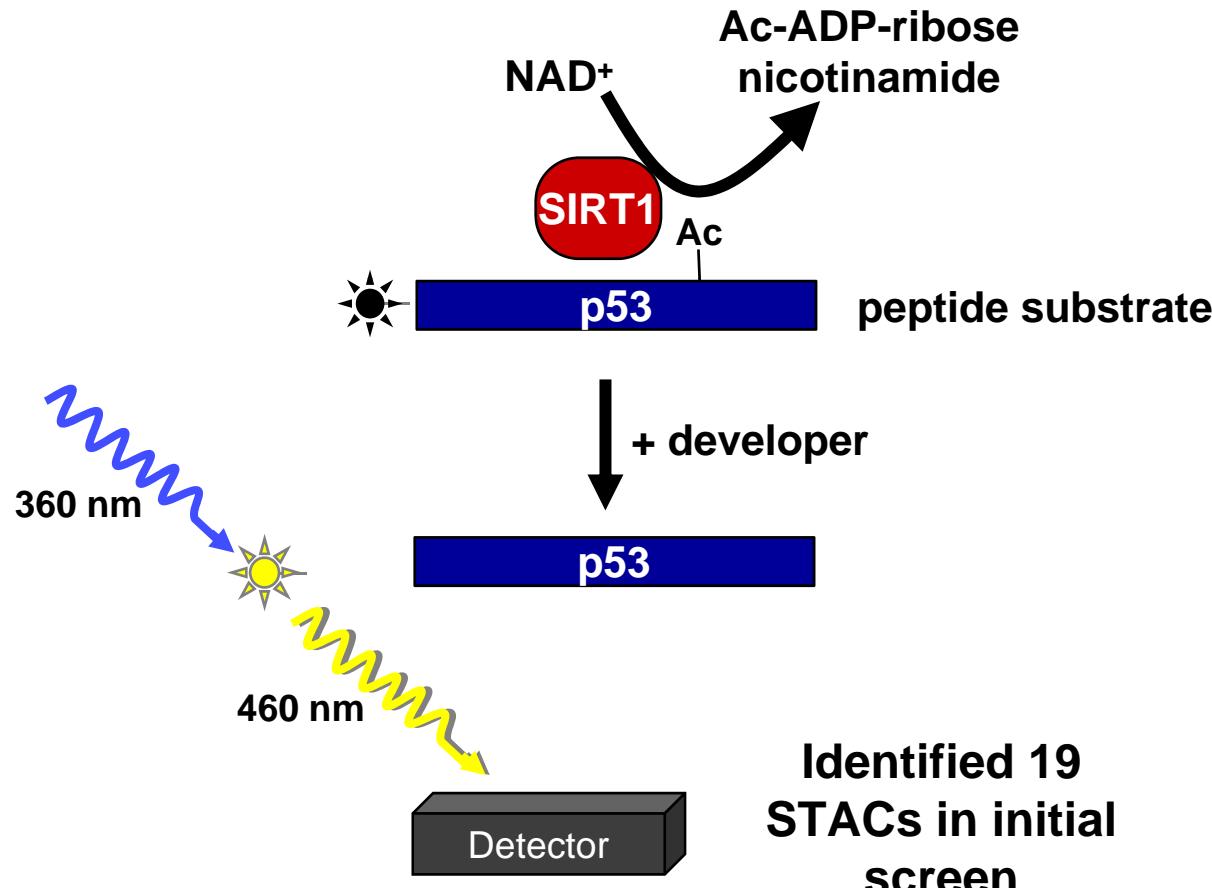
The Sir2 family (sirtuins)

- Additional gene copies extend lifespan of yeast, worms, flies.



Kaeberlein et al., Genes Dev, 1999
Tissenbaum et al, Nature, 2000
Rogina et al., Nature, 2004

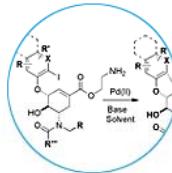
Screen for sirtuin activators (STACs)



ICCB ICG INSTITUTE of CHEMISTRY and CELL BIOLOGY INITIATIVE for CHEMICAL GENETICS



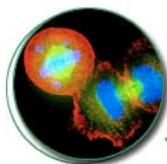
screening
...screening



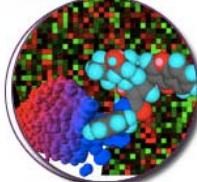
chemistry
chemistry
...chemistry



informatics
informatics
...informatics



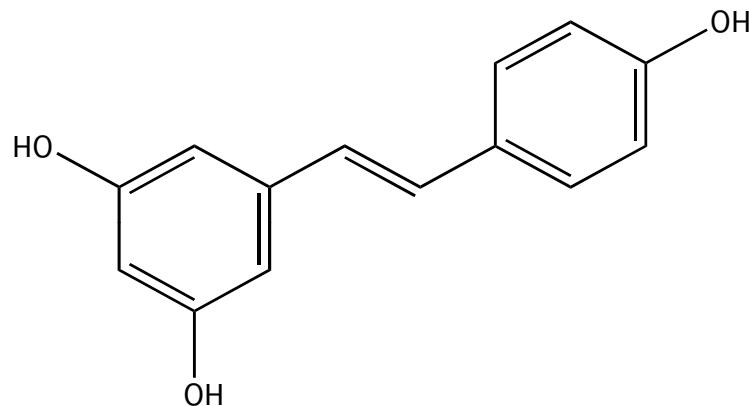
biology
...biology



systematics
systematics
...systematics

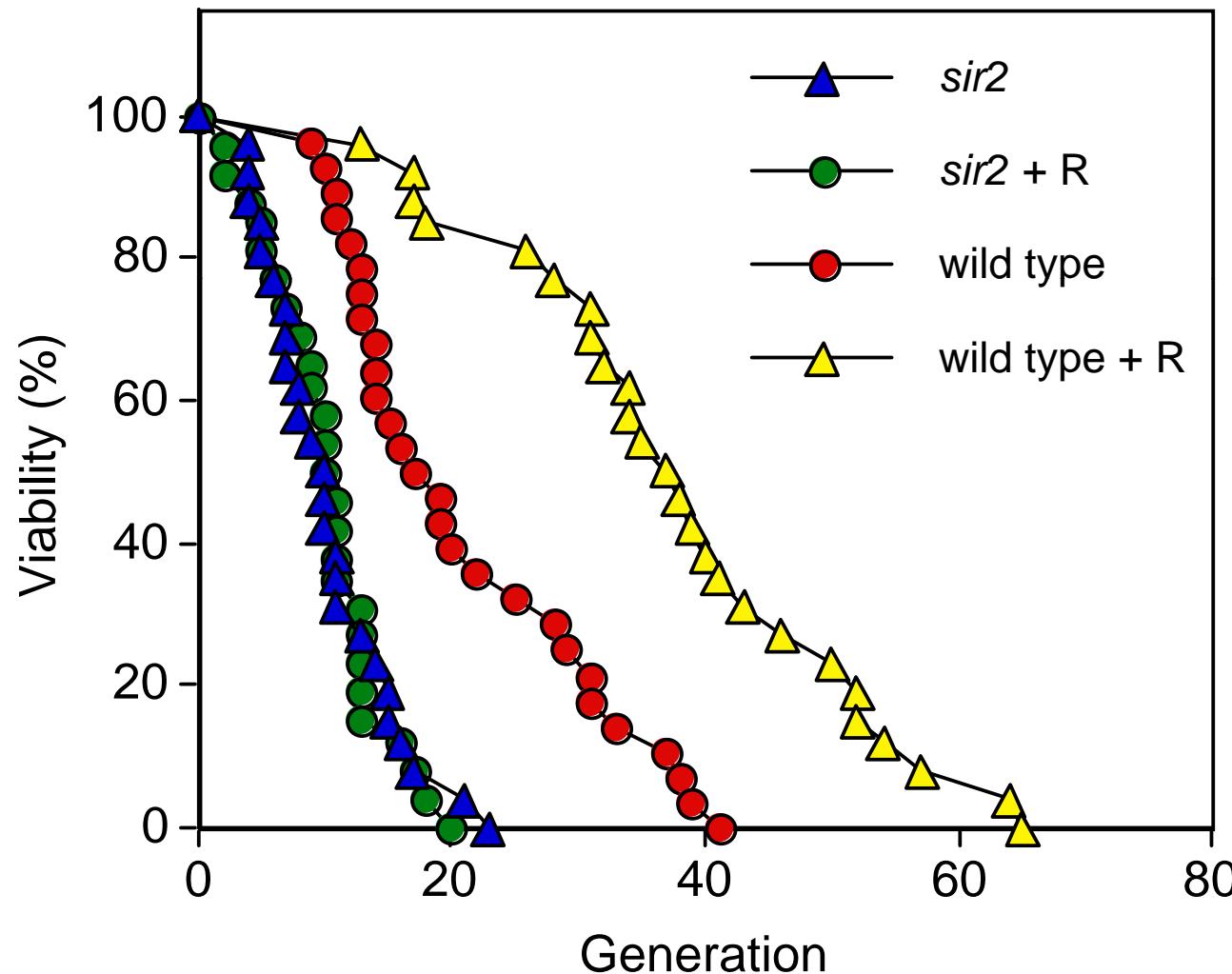


3,5,4'-hydroxy-stilbene (Resveratrol)



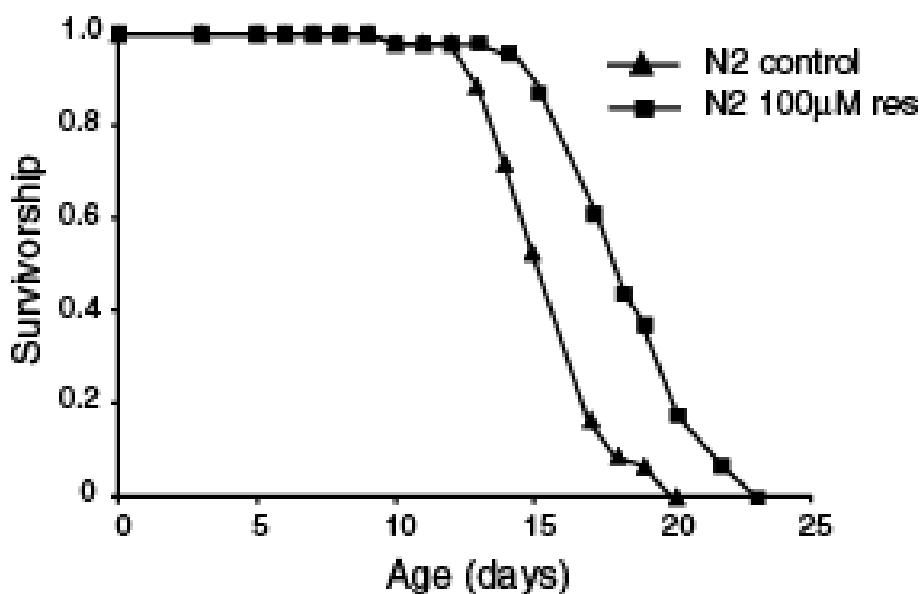
- Produced by plants in response to stress (e.g. drought, heat, UV).
- Found in red wine (<1 mg/glass) and Chinese medicinal herbs.
- Potent suppressor of tumorigenesis in mice.
- Suspected cardioprotection and neuroprotection.

Resveratrol Extends Yeast Lifespan in a Sir2-Dependent Manner



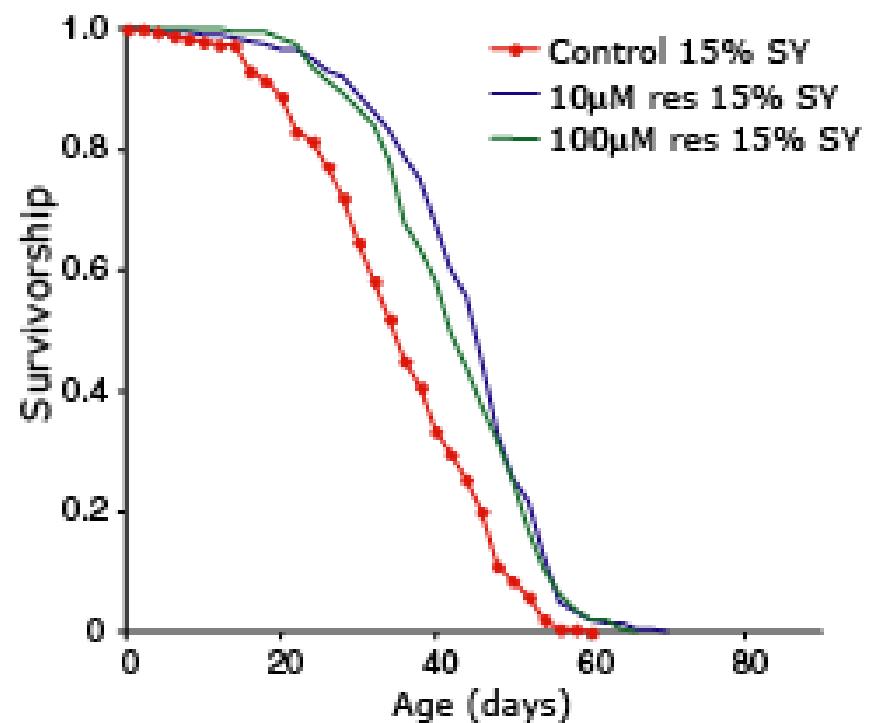
Resveratrol Extends Lifespan in Worms and Flies

C. elegans

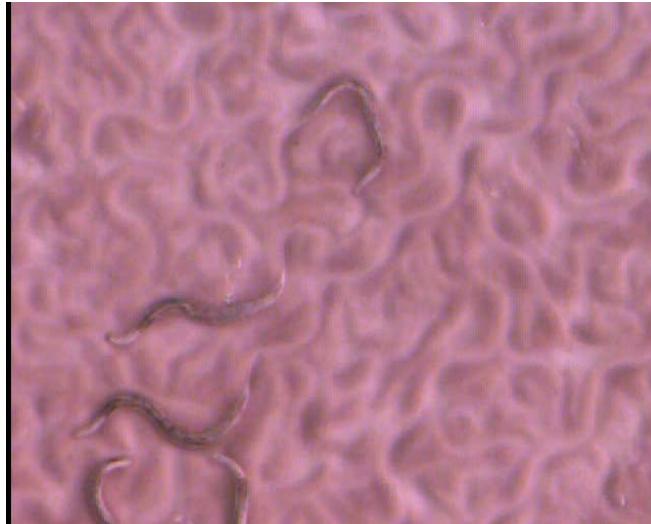


~ 15% extension

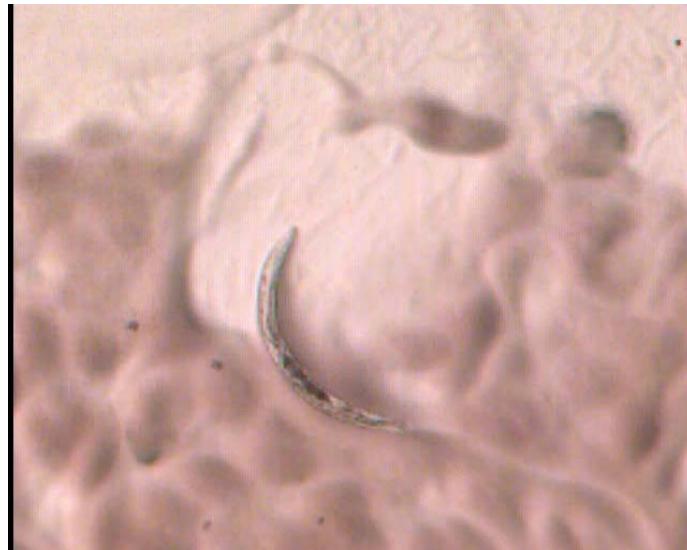
Drosophila



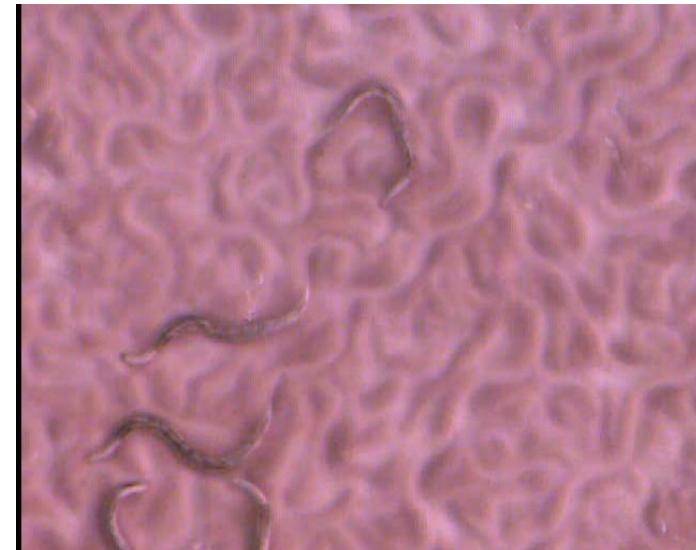
~ 25% extension



Normal, healthy worms



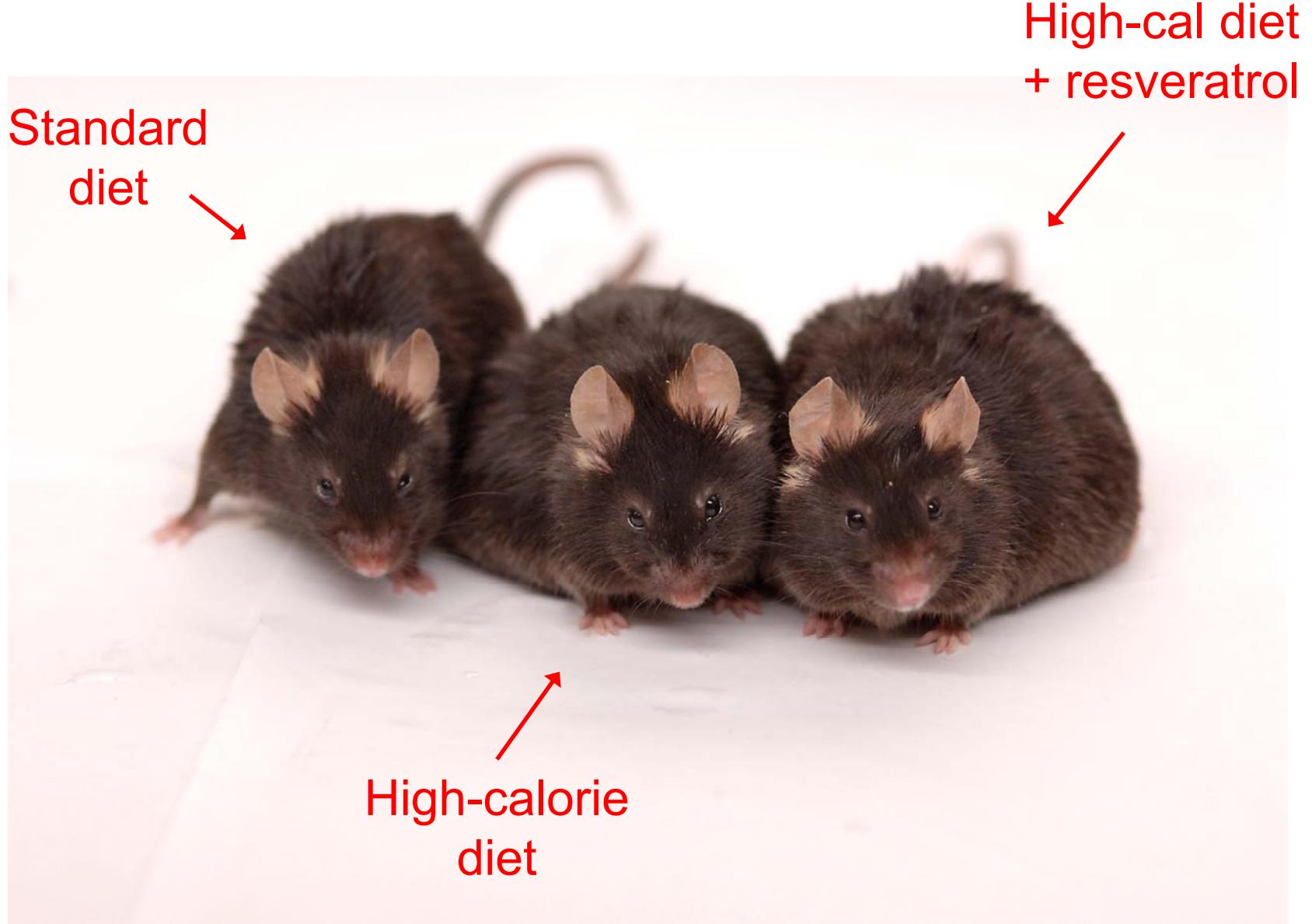
Old control worms



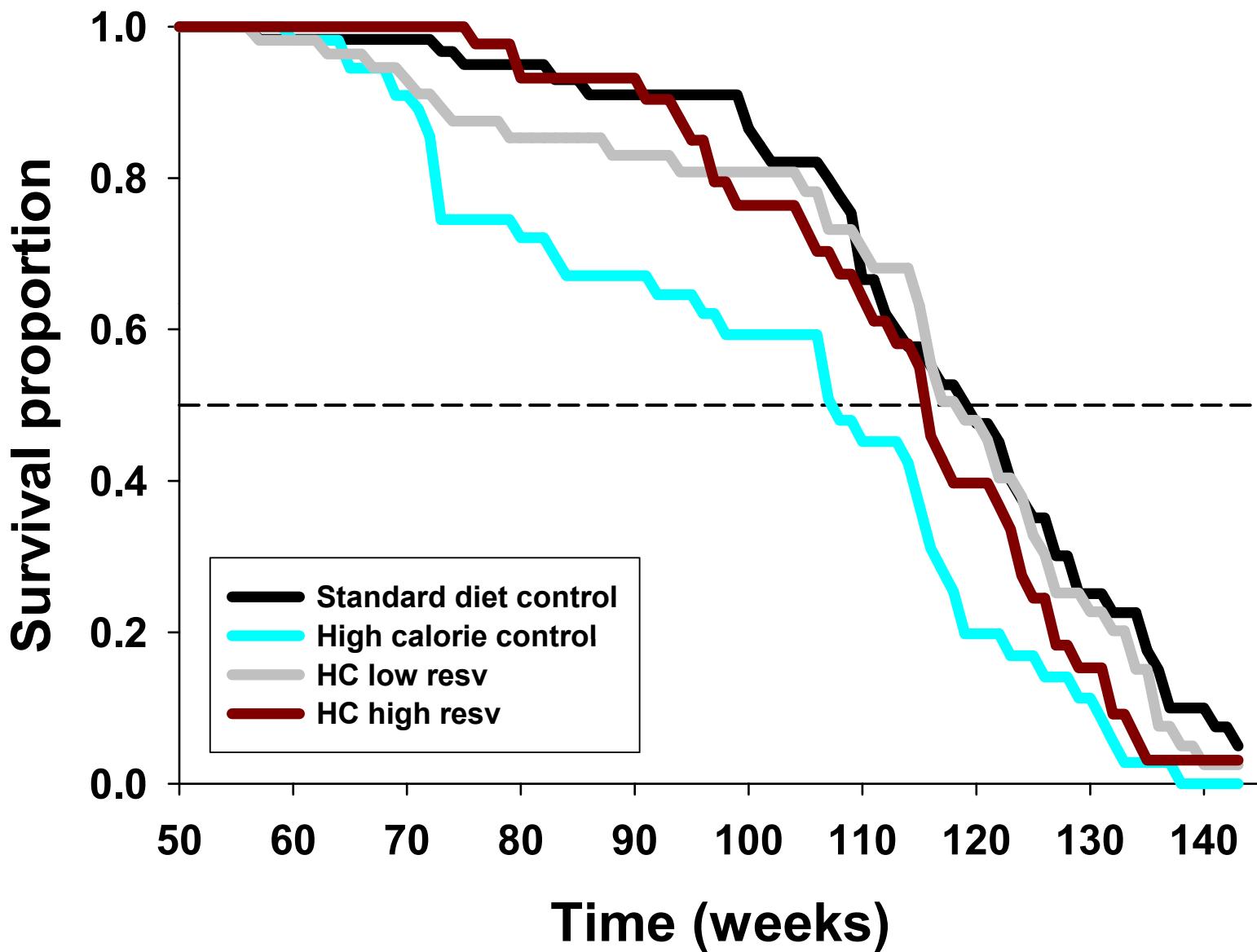
Old resveratrol treated
worms

What about mammals?

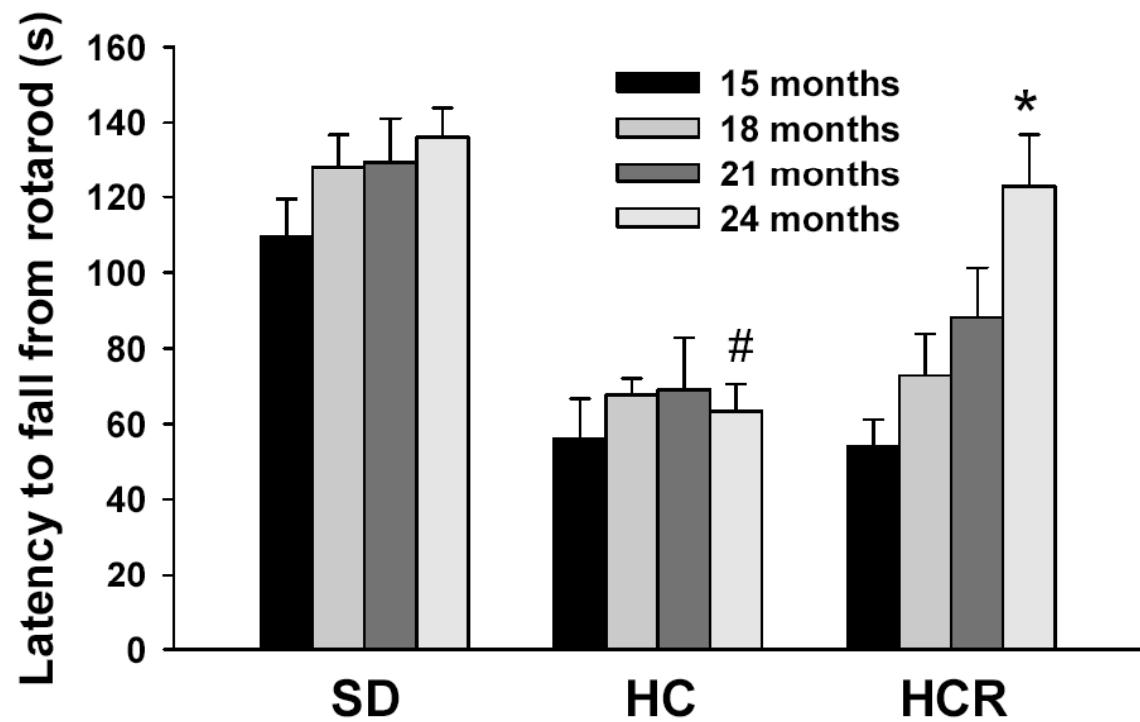
- Sir2 is conserved in mammals - SIRT1-7
- Many other potential targets for resveratrol based on *in vitro* work



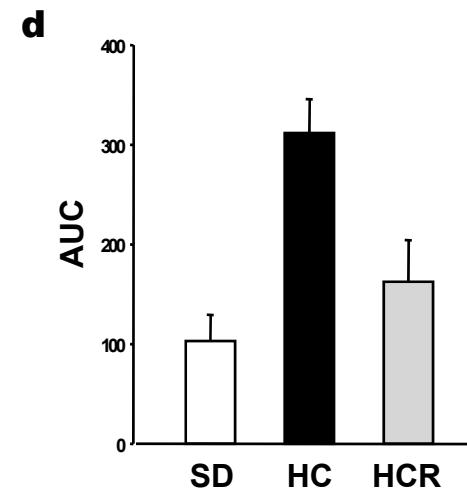
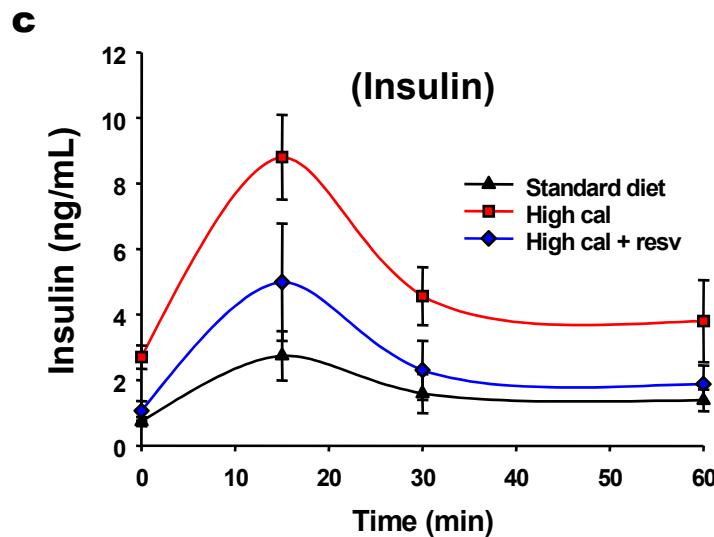
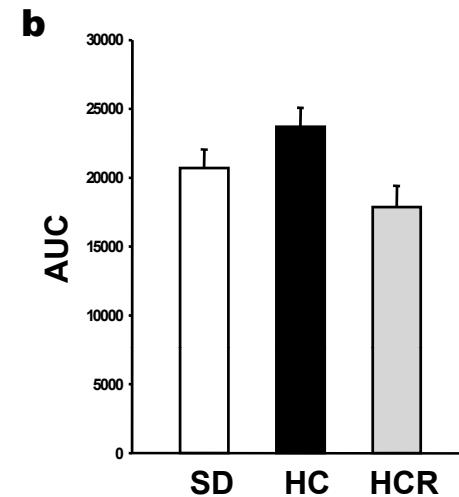
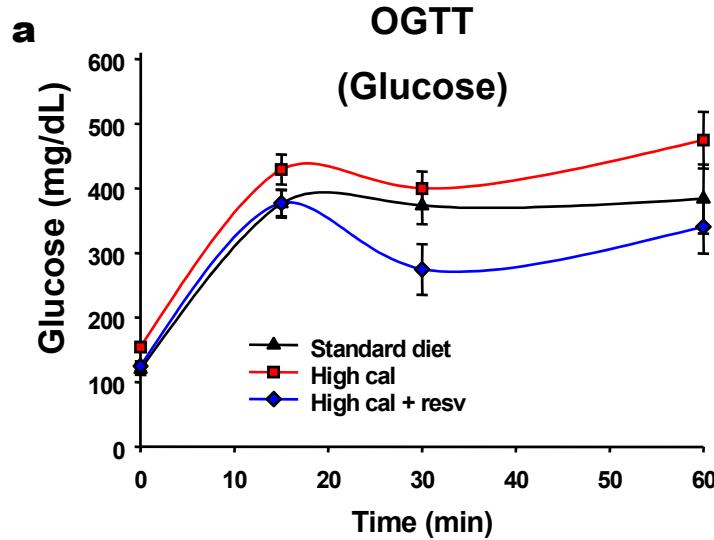
Survival – High Calorie Diet



Improved quality of life?



Better insulin sensitivity



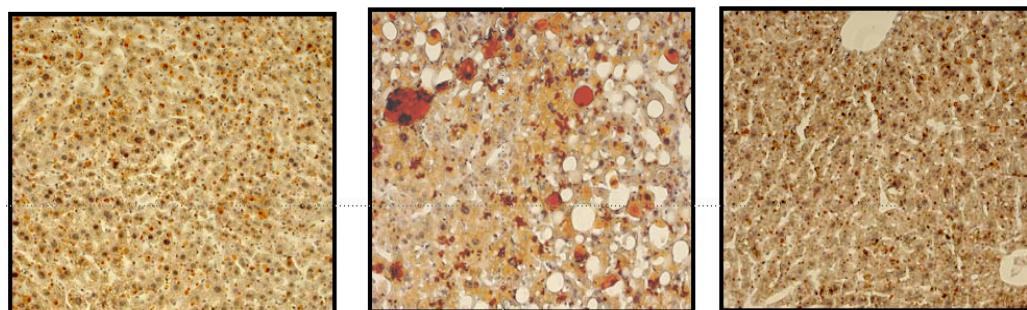
LIVER

Standard diet (SD) High calorie (HC) High calorie + resv (HCR)

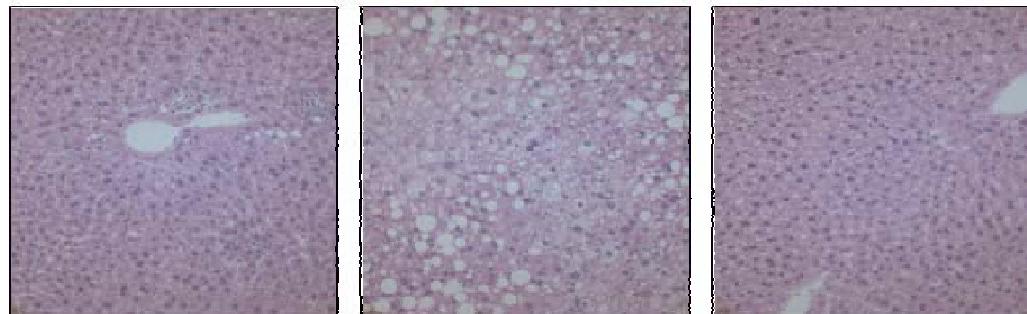
Perfused whole liver

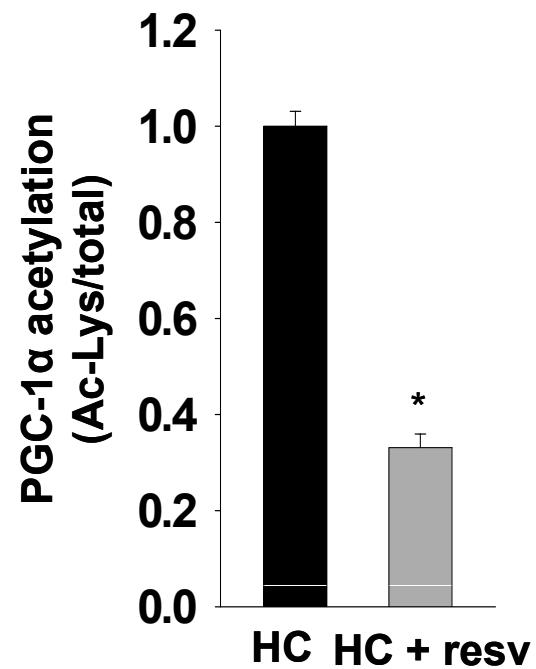
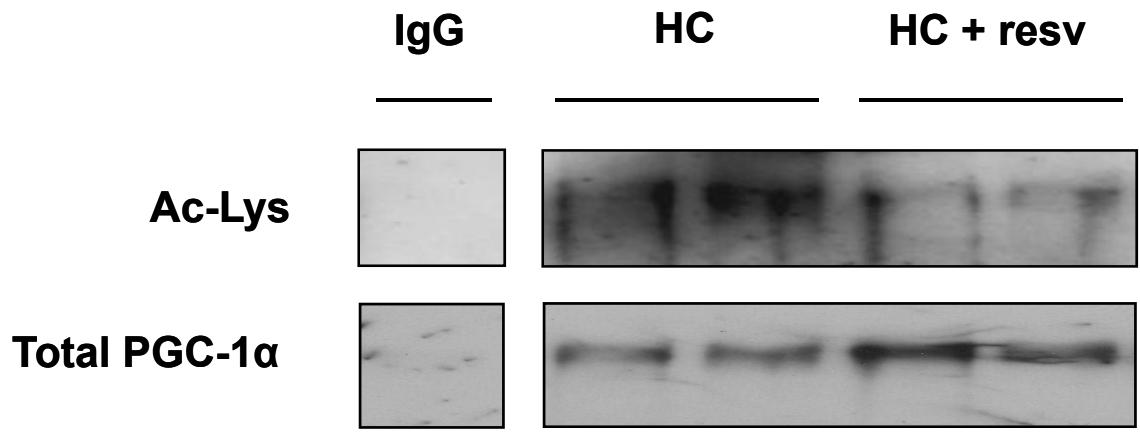
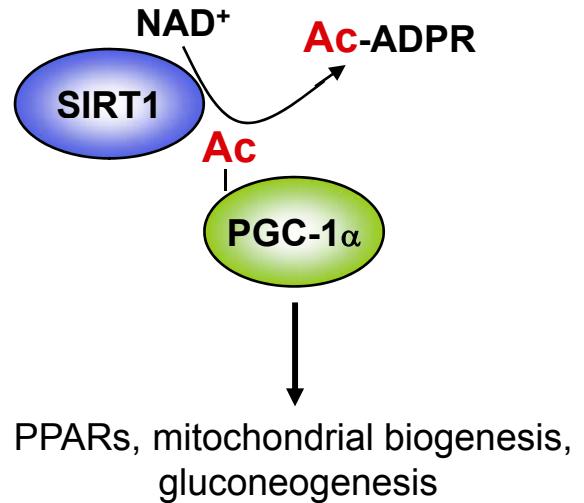


Oil Red O fat stain



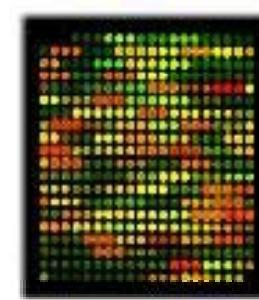
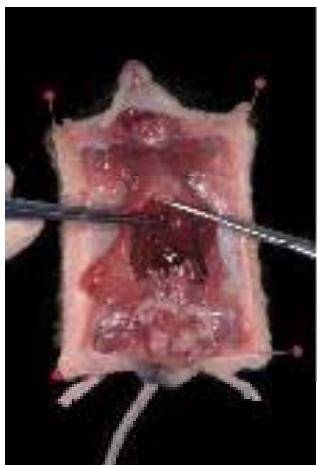
H&E



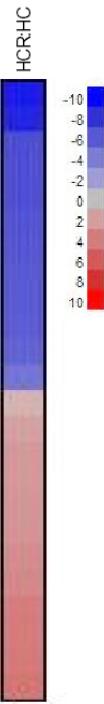


Parametric Analysis of Gene Set Enrichment (PAGE)

Uses a priori defined groupings of genes
into functional pathways

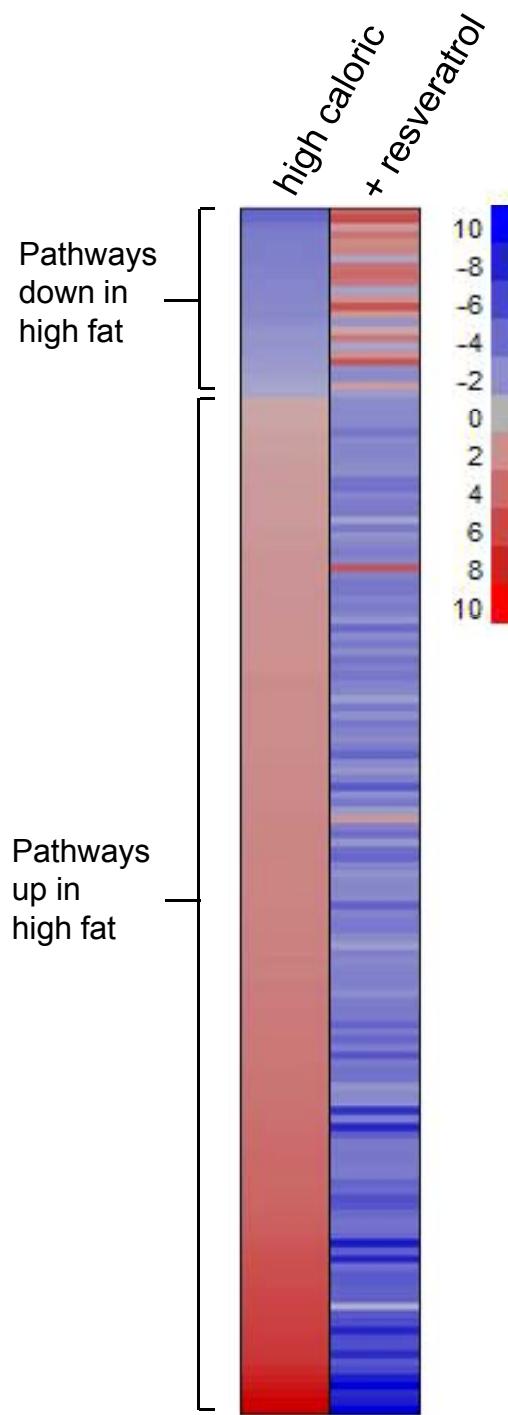


Pathway	HCR/HC
mitochondrial genes 1	-10
mitochondrial genes 2	-8
glutathione metabolism	-6
mitochondrial genes 3	-4
val leu ile degradation	-2
pepsinogen C related genes	0
Krebs TCA cycle	2
electron transport chain	4
butanoate metabolism	6
upregulated by insulin	8
oxidative phosphorylation	10
propanoate metabolism	
small leu-rich proteoglycans	
stat3 pathway	
erythropoietin pathway	
extrinsic clotting pathway	
acute inflammatory response	
HOX genes/hematopoiesis	
classic complement pathway	
lechitin pathway	
fibrinolysis pathway	
GPCRs - class A	
sterol biosynthesis	
alternative complement pathway	



http://www.broad.mit.edu/gsea/msigdb/msigdb_index.html

Resveratrol opposes effects of the high-calorie diet



Resveratrol Improves Mitochondrial Function and Protects against Metabolic Disease by Activating SIRT1 and PGC-1 α

Marie Lagouge,^{8,1} Carmen Argmann,^{8,1} Zachary Gerhart-Hines,² Hamid Meziane,³ Carles Lerin,² Frederic Daussin,⁴ Nadia Messadeq,³ Jill Milne,⁵ Philip Lambert,⁵ Peter Elliott,⁵ Bernard Geny,⁴ Markku Laakso,⁶ Pere Puigserver,² and Johan Auwerx^{1,3,7,*}

¹Institut de Génétique et de Biologie Moléculaire et Cellulaire, CNRS / INSERM / ULP, 67404 Illkirch, France

²Department of Cell Biology, John Hopkins University School of Medicine, Baltimore, MD 21205, USA

³Institut Clinique de la Souris, BP10142, 67404, Illkirch, France

⁴Department of Respiratory, Cardiocirculatory and Exercise Physiology, Hôpitaux Universitaires, 67000 Strasbourg, France

⁵Sirtris Pharmaceutical, Cambridge, MA 02139, USA

⁶Department of Medicine, University of Kuopio, 70211 Kuopio, Finland

⁷IGBMC-ICS, 67404 Illkirch, France

*These authors contributed equally to this work.

*Contact: auwerx@igbmc.u-strasbg.fr

DOI 10.1016/j.cell.2006.11.013

Resveratrol increases endurance

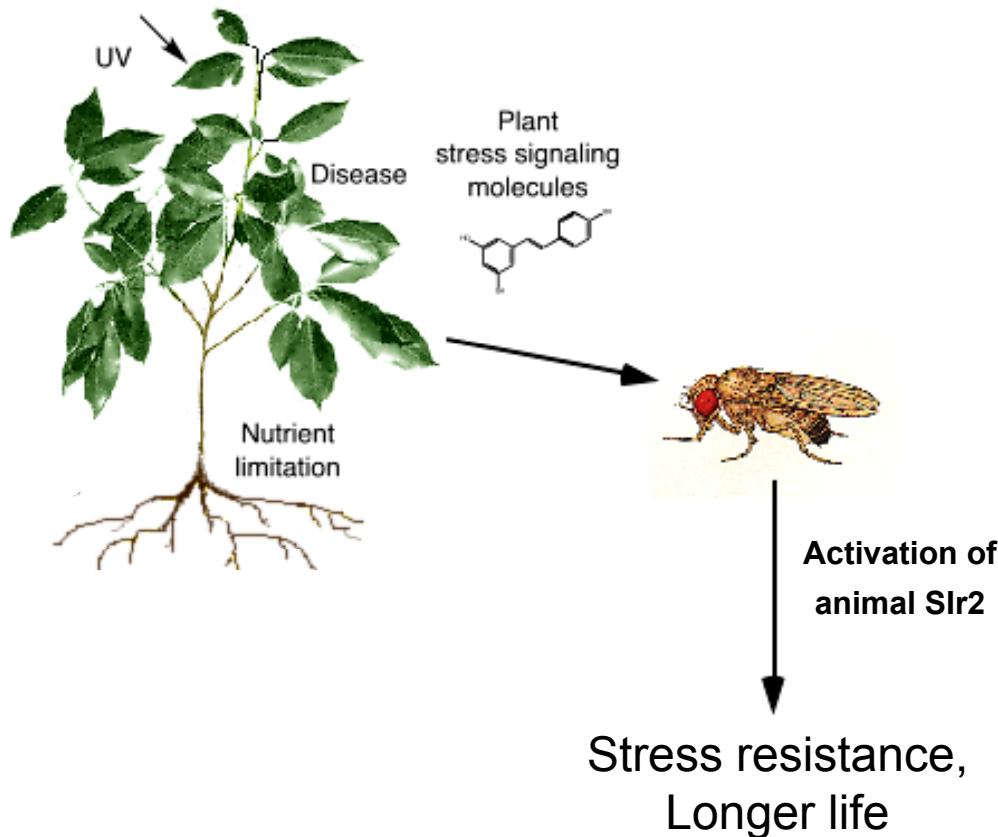
Control



Why should a simple plant polyphenol have all these beneficial effects?

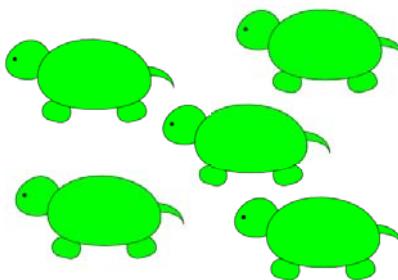
The Xenohormesis Hypothesis:

Organisms have evolved to pick up on chemical signals that other species produce to turn on their own defenses against adversity. In this way, animals can prepare in advance of a deteriorating environment.



A

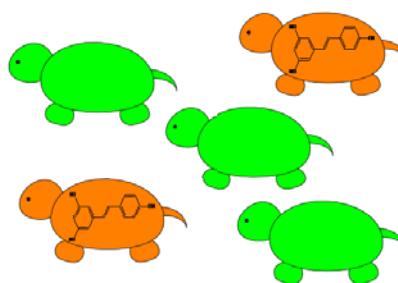
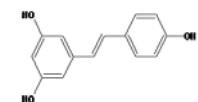
Abundant Resources



Natural selection based on reproductive ability only, individual longevity unimportant ("disposable soma")

**B**

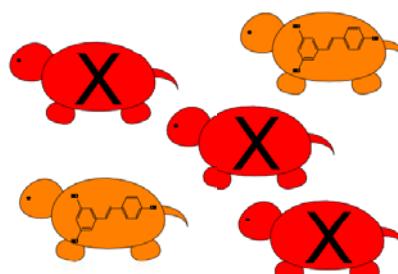
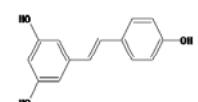
Stress (i.e. infection, UV, starvation, drought) leads to production of phytochemicals such as flavinoids, anthocyanins, and resveratrol



Some animals respond by conserving resources and upregulating defenses, focusing on individual survival

C

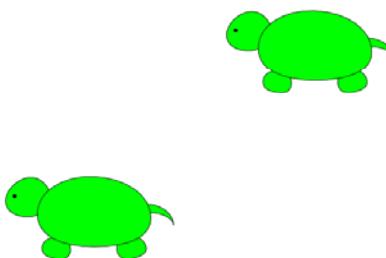
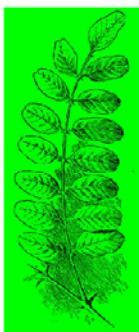
Resources become severely limiting



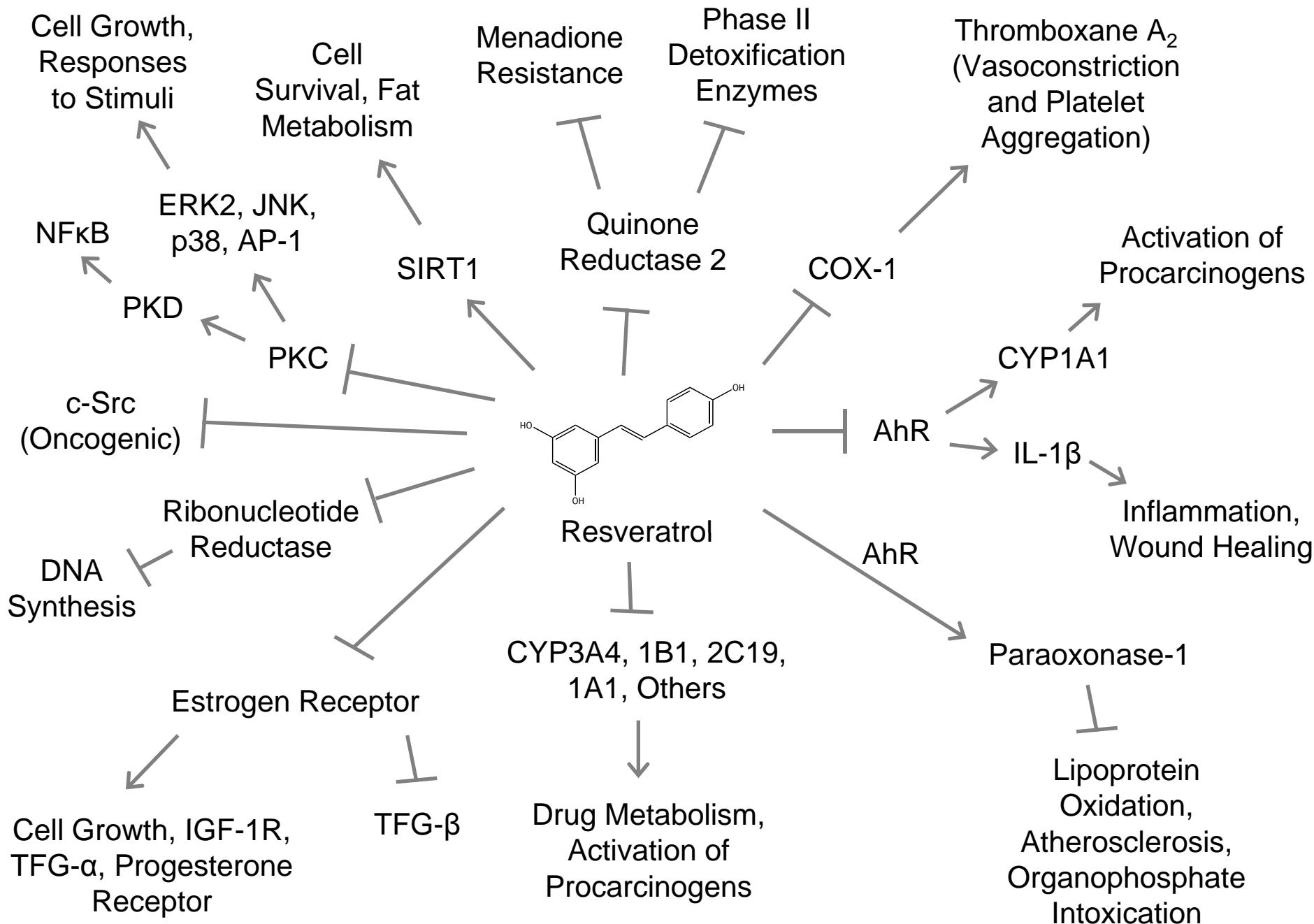
Remaining animals attempt to respond to direct stress

D

Abundant Resources



Those that respond to early cues are more likely to survive



Acknowledgements

Resveratrol improves health and survival of mice on a high-calorie diet

Joseph A. Baur^{1*}, Kevin J. Pearson^{2*}, Nathan L. Price², Hamish A. Jamieson⁷, Carles Lerin⁸, Avash Kalra², Vinayakumar V. Prabhu³, Joanne S. Allard², Guillermo Lopez-Lluch⁹, Kaitlyn Lewis², Paul J. Pistell², Suresh Poosala⁴, Kevin G. Becker³, Olivier Boss¹⁰, Dana Gwinn¹¹, Mingyi Wang⁵, Sharan Ramaswamy⁶, Kenneth W. Fishbein⁶, Richard G. Spencer⁶, Edward G. Lakatta⁵, David Le Couteur⁷, Reuben J. Shaw¹¹, Placido Navas⁹, Pere Puigserver⁸, Donald K. Ingram^{2,12}, Rafael de Cabo² & David A. Sinclair¹

Laboratory of Experimental Gerontology, NIA, Baltimore, MD

