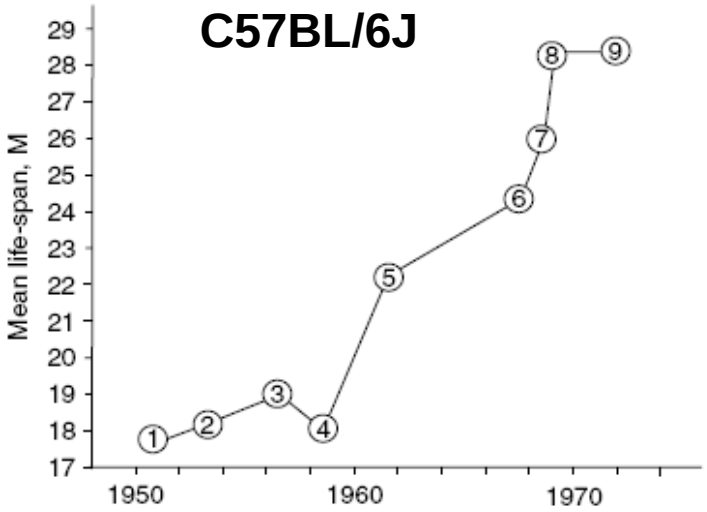
Overview of Lifespan Analysis

Arlan Richardson, PhD
University of Oklahoma Health Sciences Center
Oklahoma Nathan Shock Aging Center

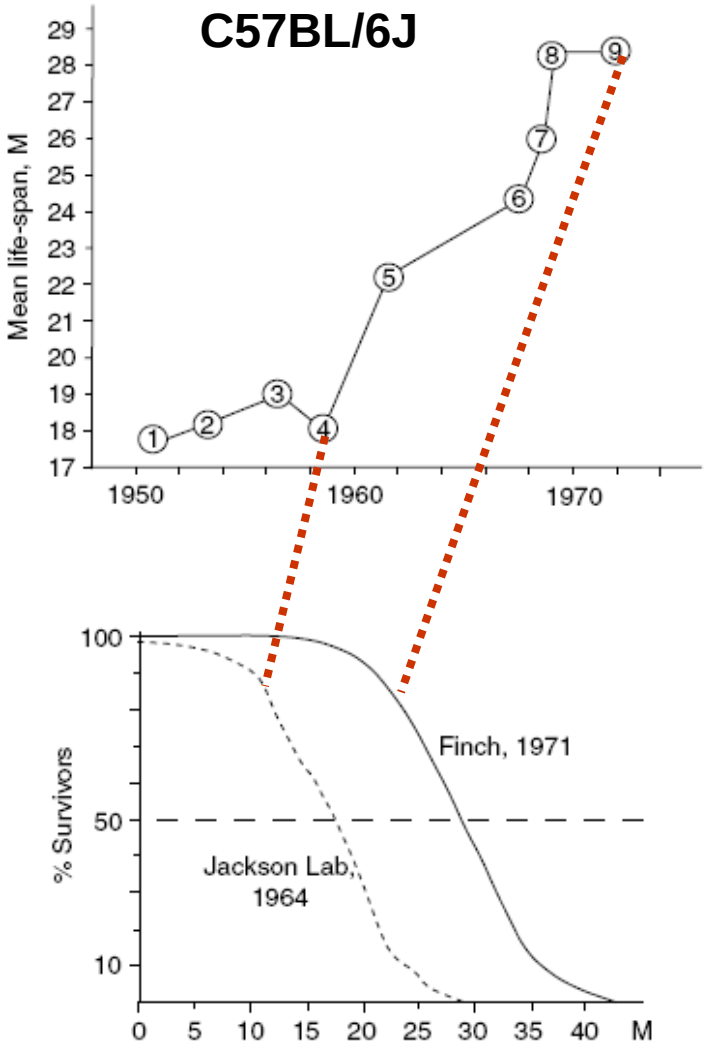
Critical Issues in Lifespan Analysis

- Husbandry
- Number of Animals

Importance of Husbandry in Lifespan Analysis



Importance of Husbandry in Lifespan Analysis



C57BL/6J lifespan increased by 50% after 1956 from reduced infections,
e.g., *Mycoplasma, Salmonella*; ectromelia, MHV, Sendai
(Finch 2007, p.137)

Two Factors to Consider in Husbandry

- **Method of housing rodents: conventional vs barrier**
  - **No two conventional colonies have the same set of diseases, i.e., makes it more difficult to reproduce research from one laboratory to another.**
  - **The pathogens in a colony can change over time.**

Two Factors to Consider in Husbandry

- **Method of housing rodents: conventional vs barrier**

Conventional

Barrier

HEPA filters can remove at least 99.97% of airborne particles 0.3 µm in diameter--prevention of the spread of airborne bacterial and viral organisms and, therefore, infection.

Microisolator Caging

<u>Barrier Conditions</u>: All staff have to change cloths and go through an air shower to get into the barrier facilities and then have to put on a gown and new foot covers and glovers, etc. before entering a specific room.

Two Factors to Consider in Husbandry

- **Method of housing rodents: conventional vs barrier**
- **Pathogen Status: Specific Pathogen Free (SPF) colony is free of a defined list of pathogens by regular testing of colonies.**

List of some of the pathogens absent in the OUHSC colony:

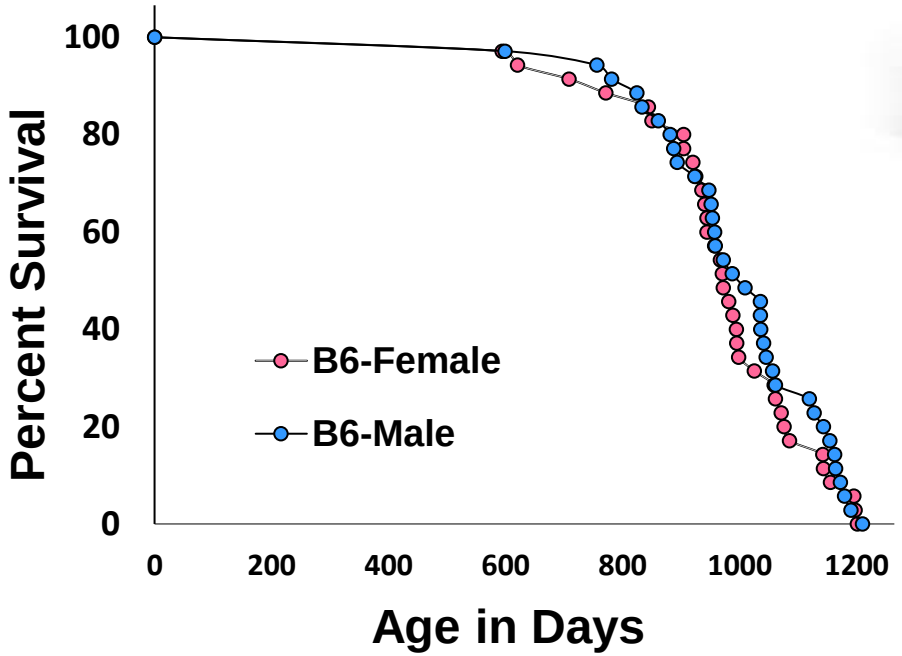
–Sendai virus

–Mouse hepatitis virus (coronavirus)

–Pinworm & fur mites

–Mycoplasma pulmonis, mouse encephalomyelitis virus, ectromelia, pneumonia virus of mice, parvovirus, mouse adenovirus, helicobacter, etc.

Survival/Lifespan of Mice is an Indication of the Quality of Husbandry



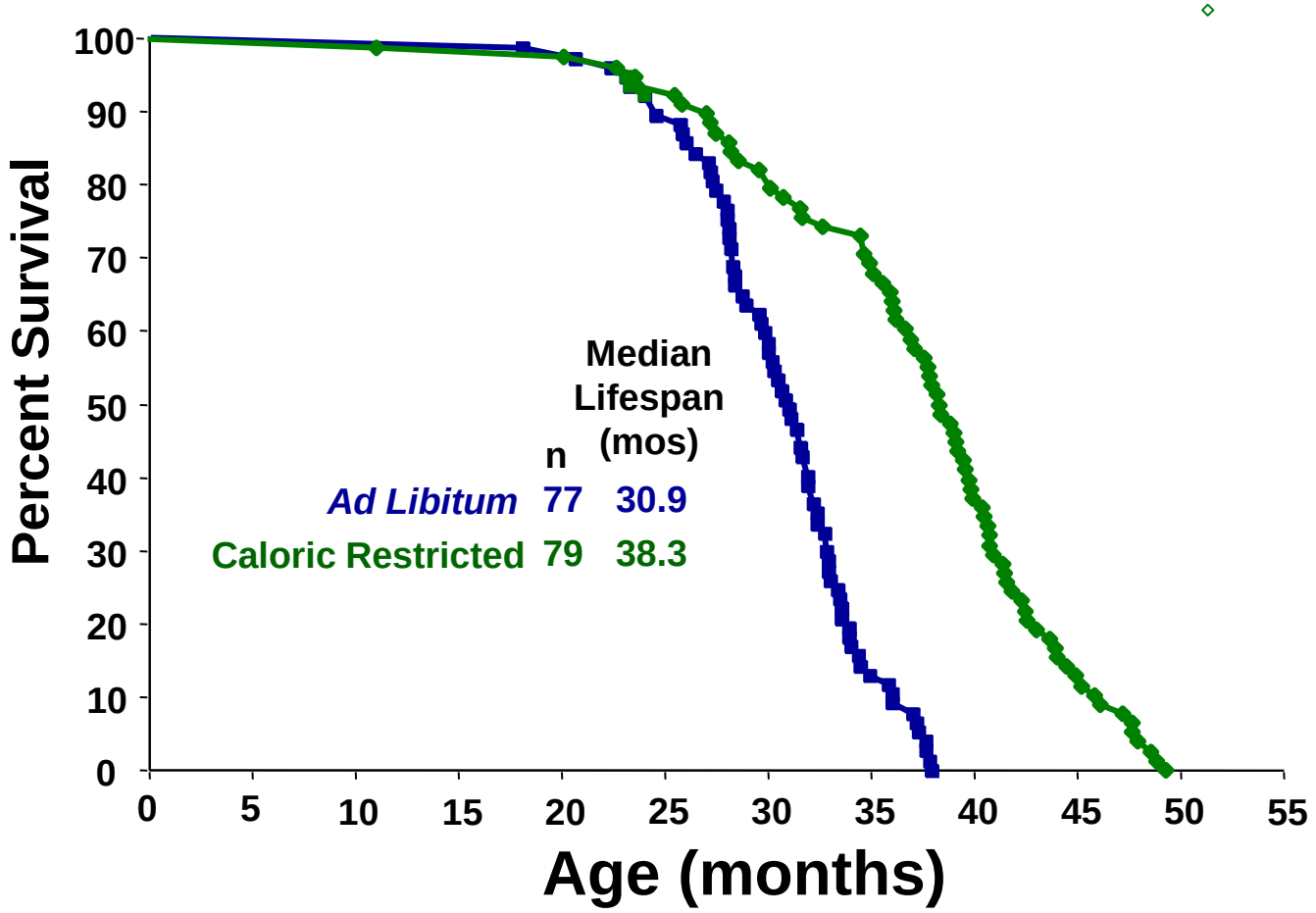
Lifespan of C57BL/6J Mice at University of Oklahoma Health Sciences Center

Mean Survival (days)		Maximum Lifespan (Days)	
Females: 972	JAX: 856	Females:1201	JAX: 1180
Males: 997	JAX: 894	Males: 1210	JAX: 1140

Critical Issues in Lifespan Analysis

- Husbandry
- Number of Animals

How Many Mice Per Group is Needed in a Lifespan Study?



Power to detect a fractional change between the mean survival of two groups of mice either fed *ad libitum*

	Mean	SD	CV			Fractional Change				
	(days)	(days)	(%)	n	5%	7.5%	10%	15%	20%	30%
	912	143	15.7	10	0.10	0.17	0.27	0.53	0.77	0.98
				20	0.17	0.31	0.50	0.84	0.98	0.99
				30	0.23	0.45	0.68	0.95	0.99	0.99
				40	0.29	0.56	0.80	0.99	0.99	0.99
				50	0.35	0.66	0.88	0.99	0.99	0.99
				60	0.41	0.74	0.93	0.99	0.99	0.99
				100	0.61	0.92	0.99	0.99	0.99	0.99

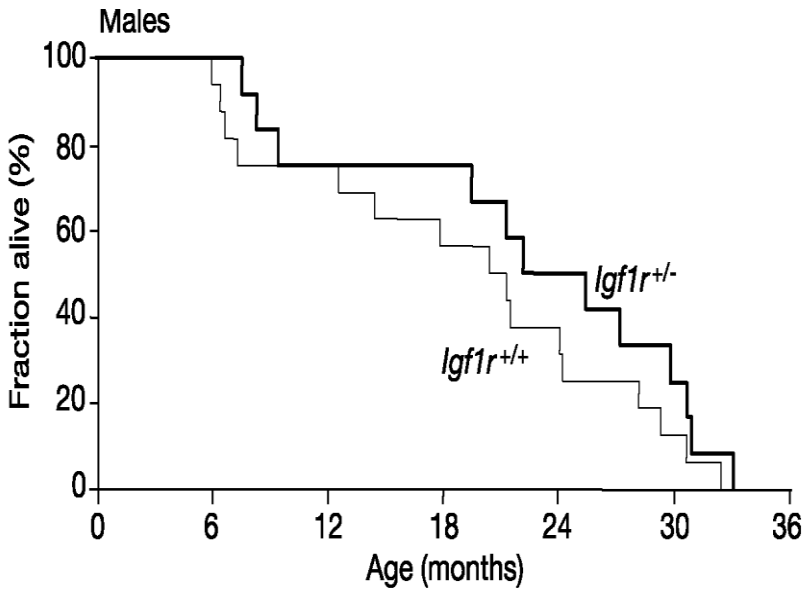
Liang, E.J. Masoro, J.F. Nelson, R. Strong, C.A. McMahan, and A. Richardson. "Genetic mouse models of extended life span." *Exp. Gerontol.*, 38: 1353-1364, 2003

Two Examples of Major Publications on Lifespan that were not Replicable

IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice

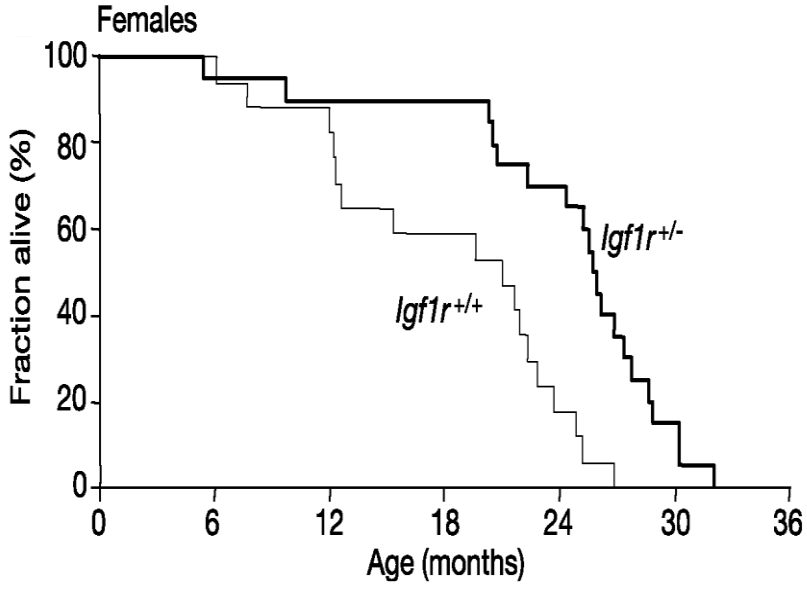
Martin Holzenberger*, Joëlle Dupont†, Bertrand Ducos*, Patricia Leneuve*, Alain Géloën‡, Patrick C. Even§, Pascale Cervera‖ & Yves Le Bouc*

Nature. 2003 Jan 9;421(6919):182-7.



Mean Survival (days)

WT	586
+/-	679
	16%



Mean Survival (days)

WT	568
+/-	756
	33%

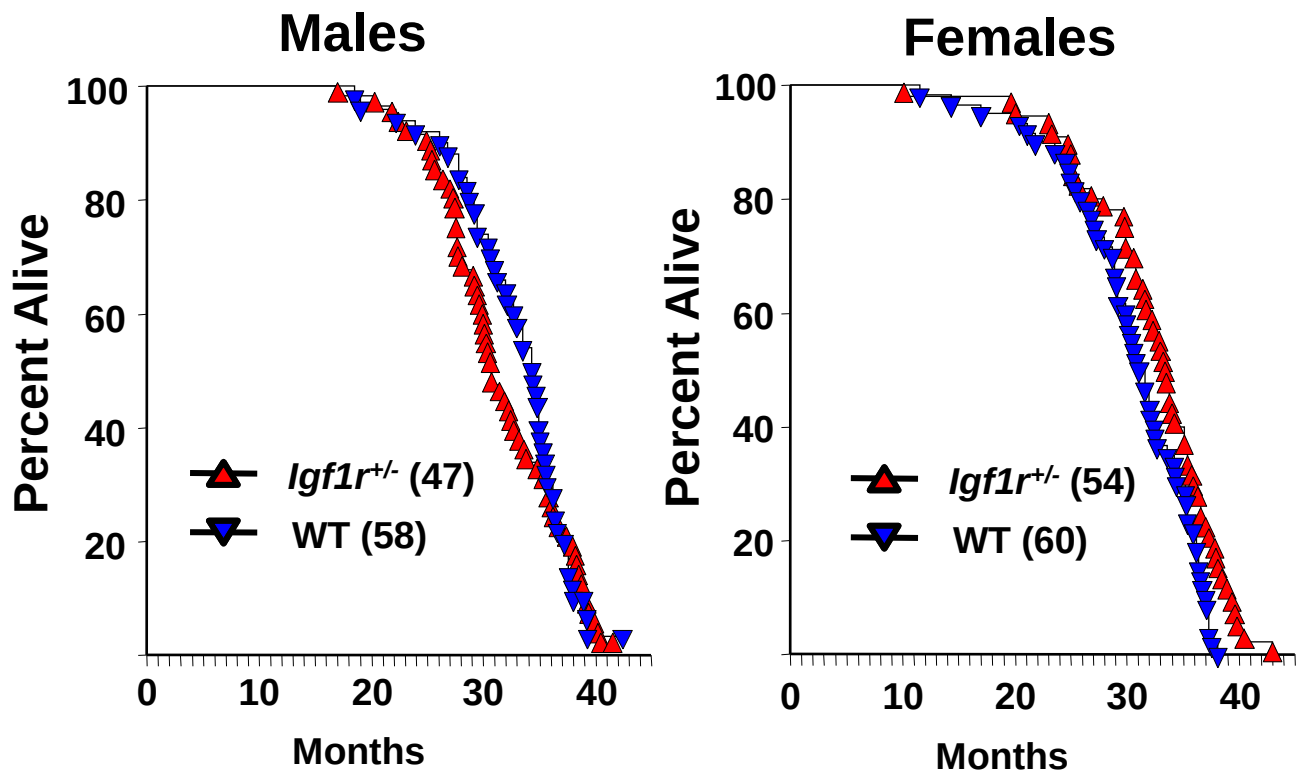
OPEN ACCESS Freely available online

PLoS one

Does Reduced IGF-1R Signaling in *Igf1r*$^{+/-}$ Mice Alter Aging?

Alex F. Bokov[1,2☯], Neha Garg[3☯], Yuji Ikeno[1,5,7☯], Sachin Thakur[3], Nicolas Musi[1,6,7], Ralph A. DeFronzo[6], Ning Zhang[6], Rebecca C. Erickson[8], Jon Gelfond[1,4], Gene B. Hubbard[1,5], Martin L. Adamo[1,3], Arlan Richardson[1,2,7*]

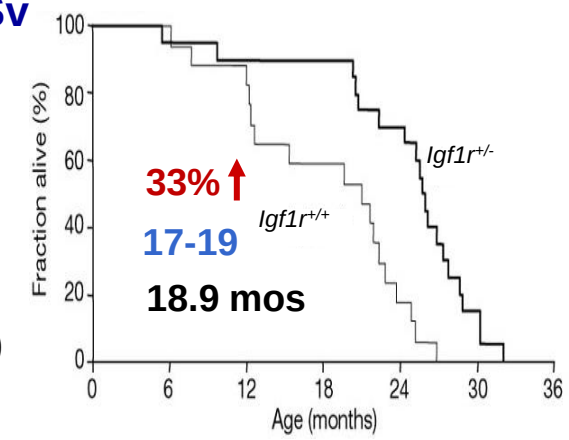
PLoS ONE | www.plosone.org November 2011 | Volume 6 | Issue 11 | e26891



Current Data on Lifespan of IGF1r$^{+/-}$ Mice

Holzenberger et al., 2003

129Sv

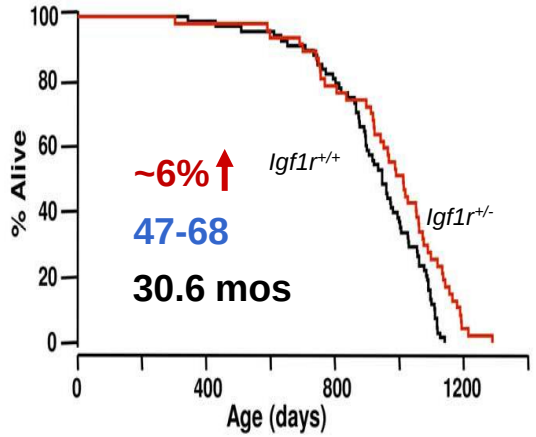


 # Mice/group

Mean Lifespan of WT (Control)

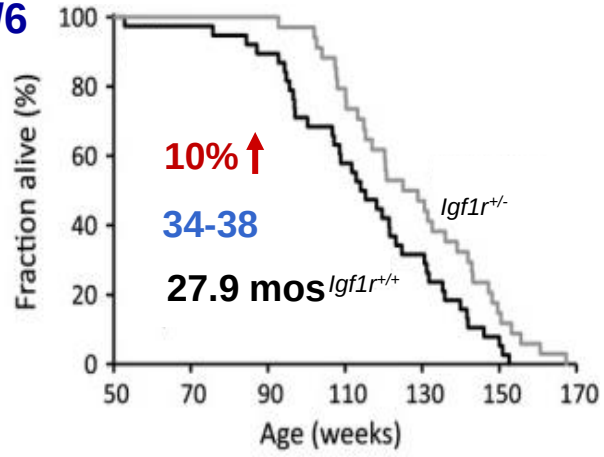
Bokov et al., 2011

C57BL/6



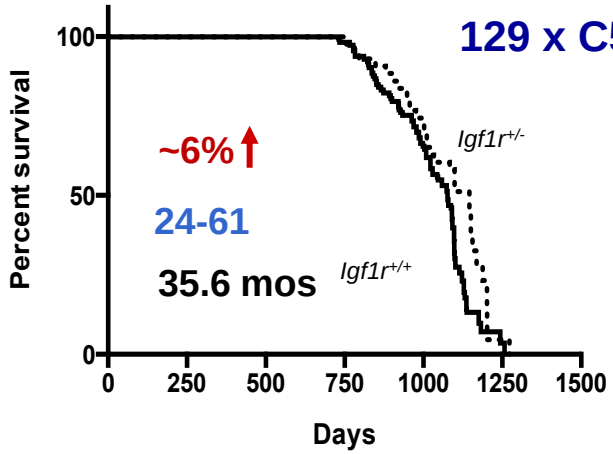
Xu et al, 2014

C57BL/6



Unnikrishnan et al, 2017

129 x C57BL/6 F1

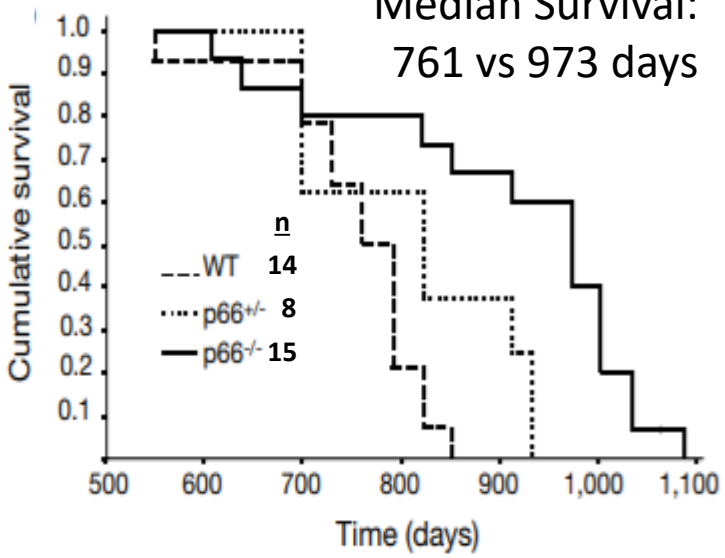


Lifespan of $p66^{sch-/-}$ Mice

The $p66^{shc}$ adaptor protein coı oxidative stress response and life span in mammals

Enrica Migliaccio*†, Marco Giorgio*†, Simonetta Mele‡, Giuliana Pelicci*, Paolo Reboldi§, Pier Paolo Pandolfi‖, Luisa Lanfrancone* & Pier Giuseppe Pelicci*‡

Nature 402: 309, 1999

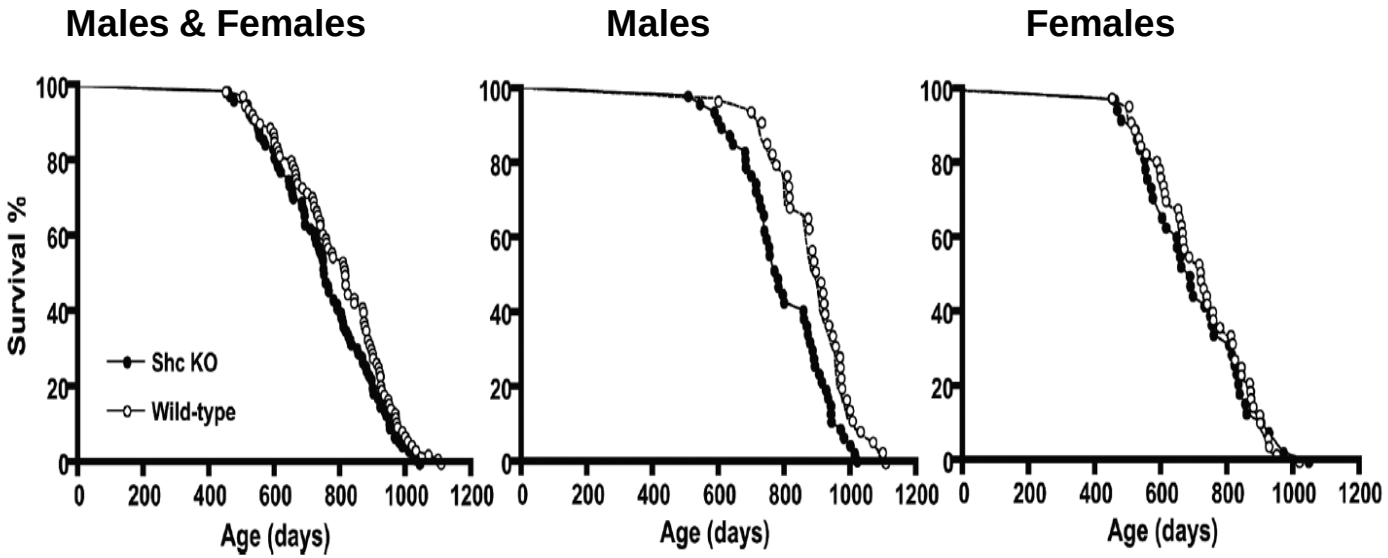


Median Survival:
761 vs 973 days

The Influence of Shc Proteins on Life Span in Mice

Jon J. Ramsey,[1] Dianna Tran,[1] Marco Giorgio,[2] Stephen M. Griffey,[3] Amanda Koehne,[3] Steven T. Laing,[3] Sandra L. Taylor,[4] Kyoungmi Kim,[4] Gino A. Cortopassi,[1] K. C. Kent Lloyd,[5] Kevork Hagopian,[1] Alexey A. Tomilov,[1] Enrica Migliaccio,[2] Pier Giuseppe Pelicci,[2] and Roger B. McDonald[6]

Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci 2014 October;69(10):1177–1185
doi:10.1093/gerona/glt198



35 to 47 mice per group and a median survival of 800 days in the WT (control) mice

Summary

- Husbandry can make a major difference on whether an intervention has an impact on longevity.
- Lifespan/survival of the control mice is a good surrogate for the quality of the husbandry.
- Forty mice per group appears to be an appropriate number of mice when comparing an intervention to a control.

THIS MAY CHANGE AT THE END OF THE WEBINAR WHEN DR. ALLISON SPEAKS