Why do we age? The role of biology

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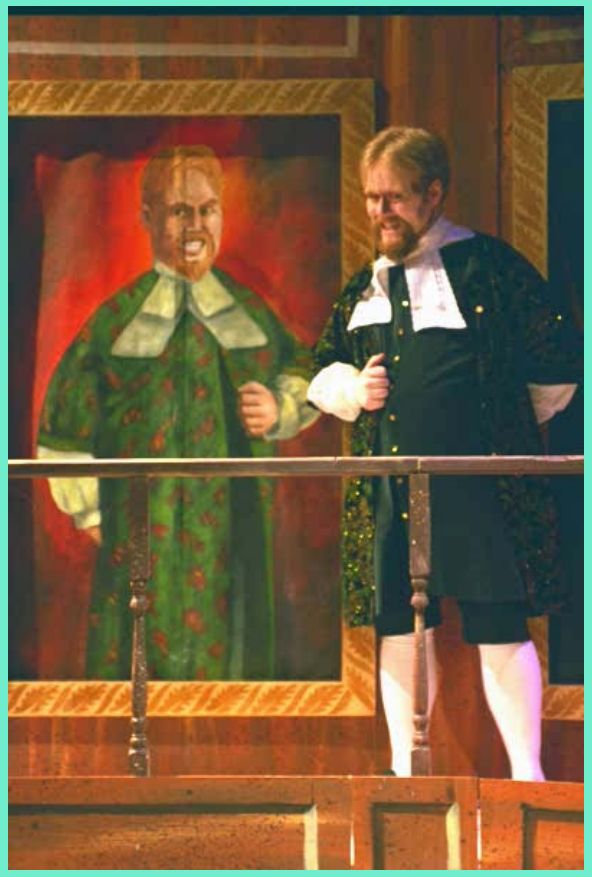
What is Aging?

A natural, non-pathologic process affecting all organisms which leads to:

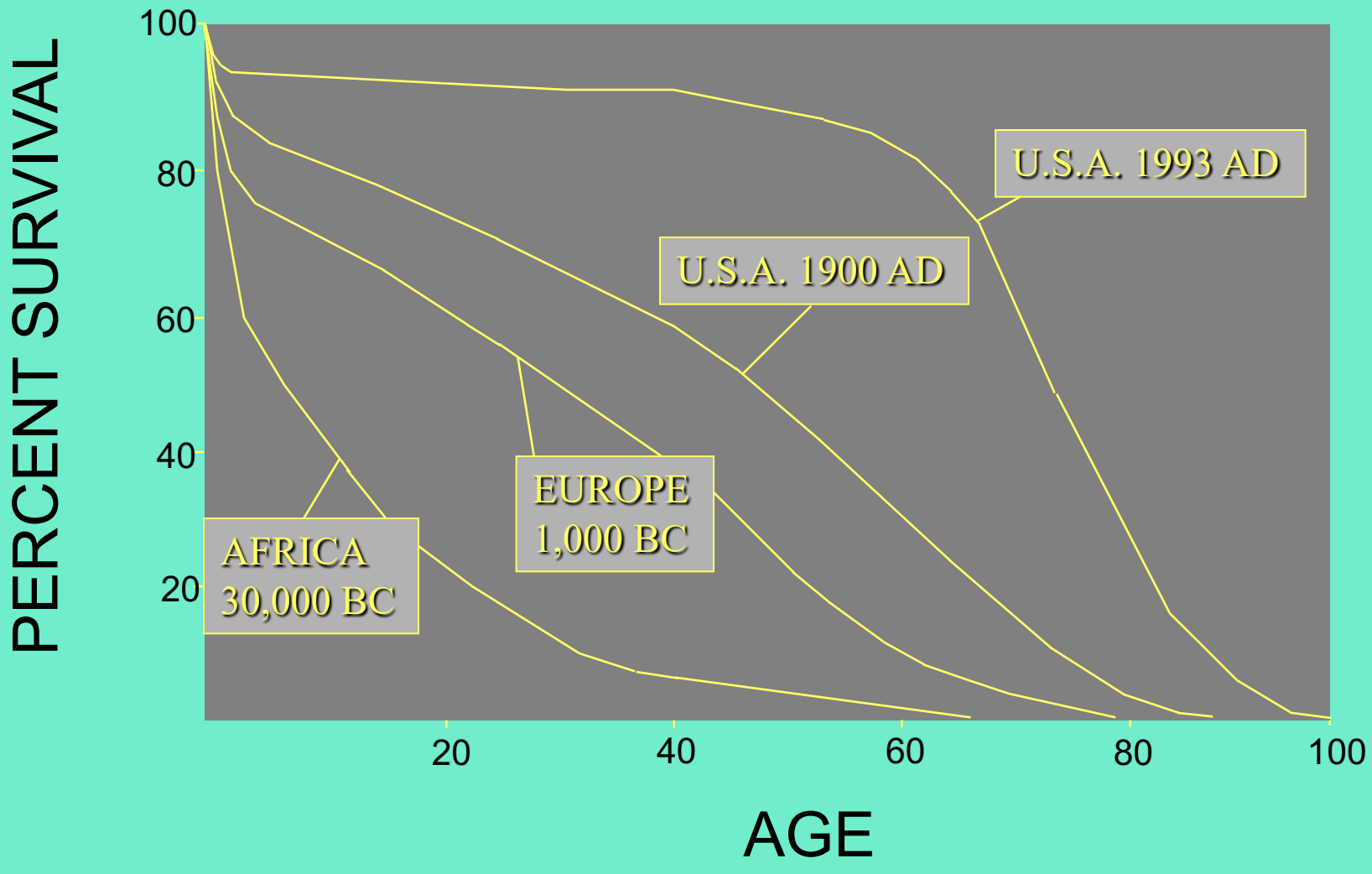
- Characteristic Phenotypic Features
- Loss of Reproductive Capability
- Decreased Physiologic Reserves
- Increased Susceptibility to Disease

Why is Aging of Interest?

- Age is a major risk factor for virtual all adult illnesses
- Age is a major risk factor for disability and dependence
- Aging is the only health-related Condition that affects each and every person
- Aging has been of keen interest to humans throughout time



Is Human Lifespan and Aging Immutable?



But has this altered aging?

- Environment influences mean lifespan

  - Nutrition, safer environment, clean water, sanitation

- In contrast, maximal longevity is genetically determined

  - Naked mole rat vs rat

- Hence both mean and maximal lifespan can be altered

How do you Study Aging Biology?

Quite a Challenge:

- Animals of interest have long lifespans
- Difficulty of separating causes from effects
- Global effects of aging
- Lack of model organisms
- Lack of interventions with known effects

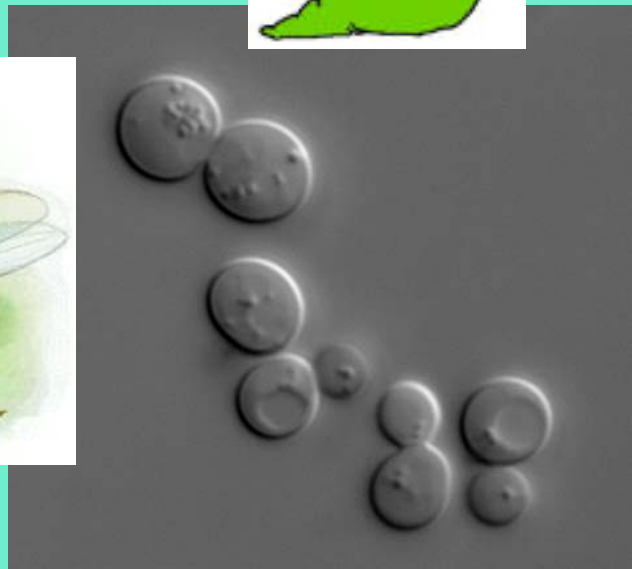
Remarkably Model Systems were Developed

- Simple Manipulations can Alter Aging

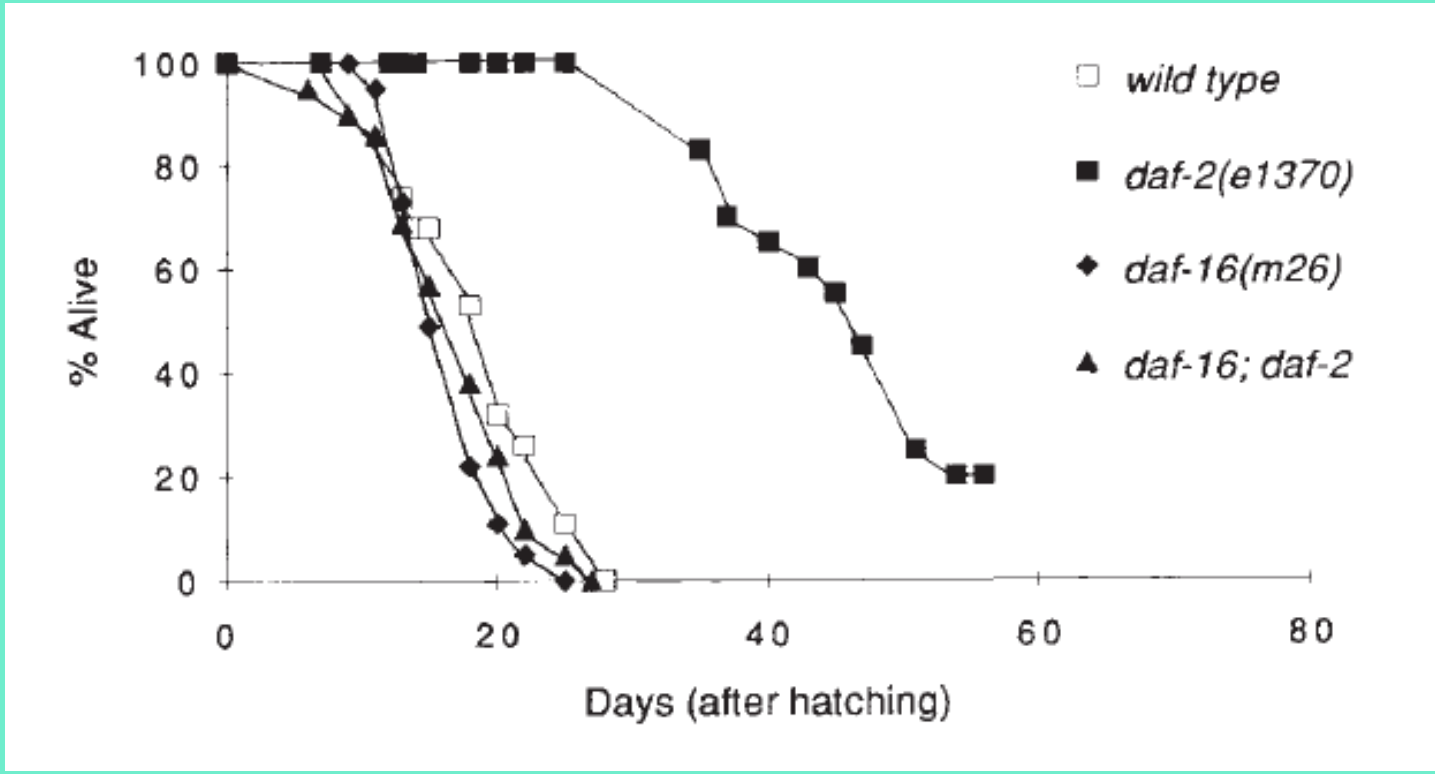
  -Caloric Restriction
  -Delayed Reproduction

- Genes were Identified in Many Species

  -Yeast
  -C. elegans
  -Drosophila
  -Mice
  -Humans



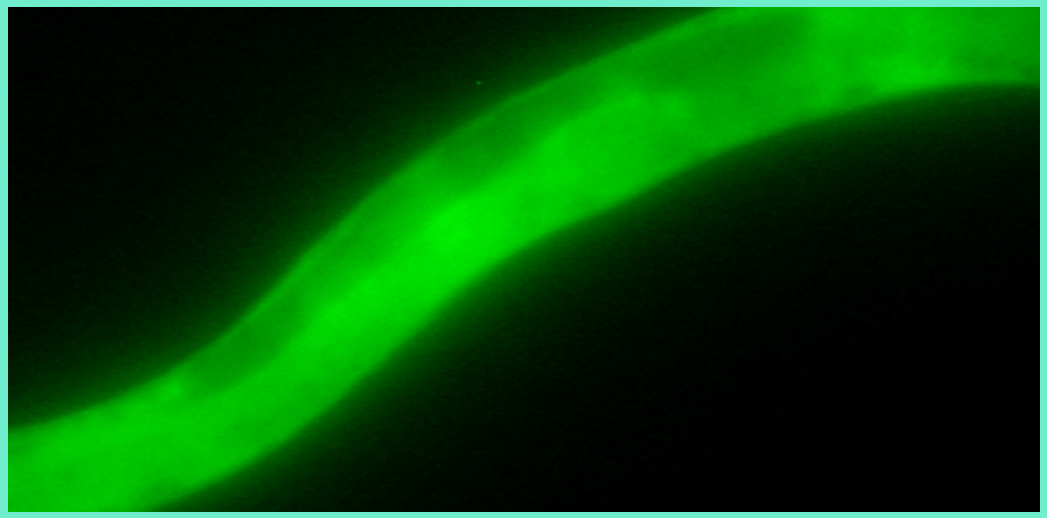
Insights from Lower Animals



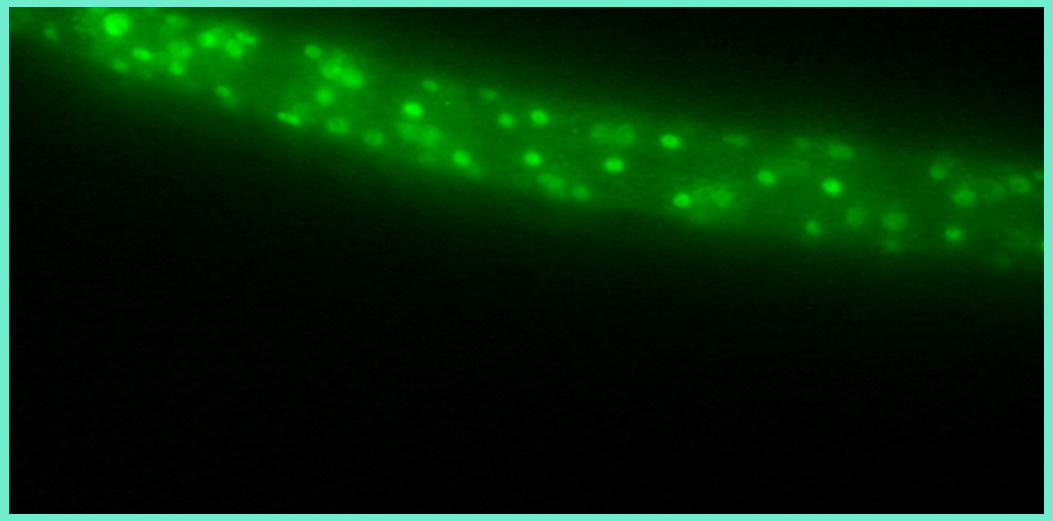
What does *daf-2* do?

DAF-16 GFP

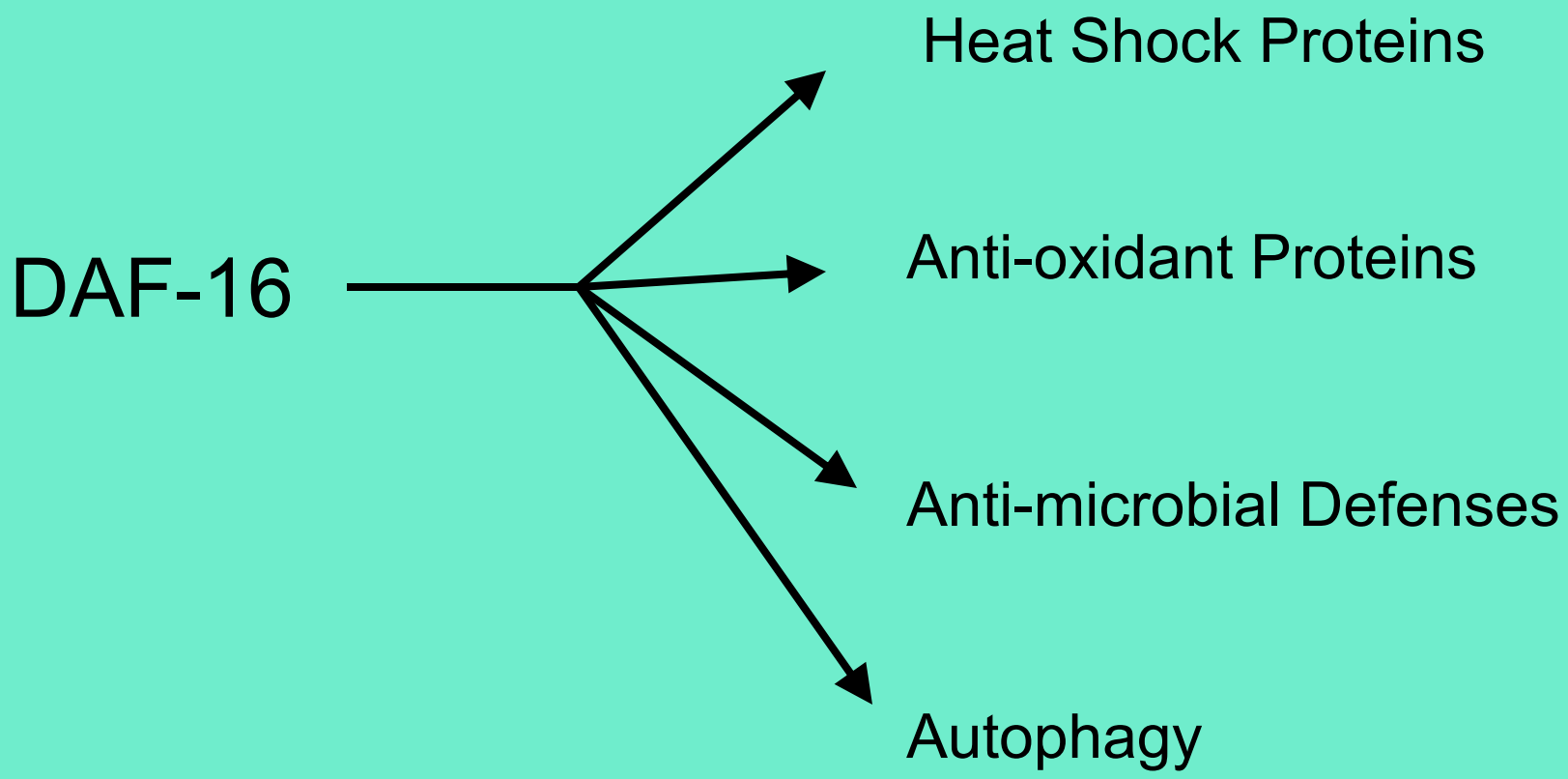
DAF-2 On



DAF-2 Off



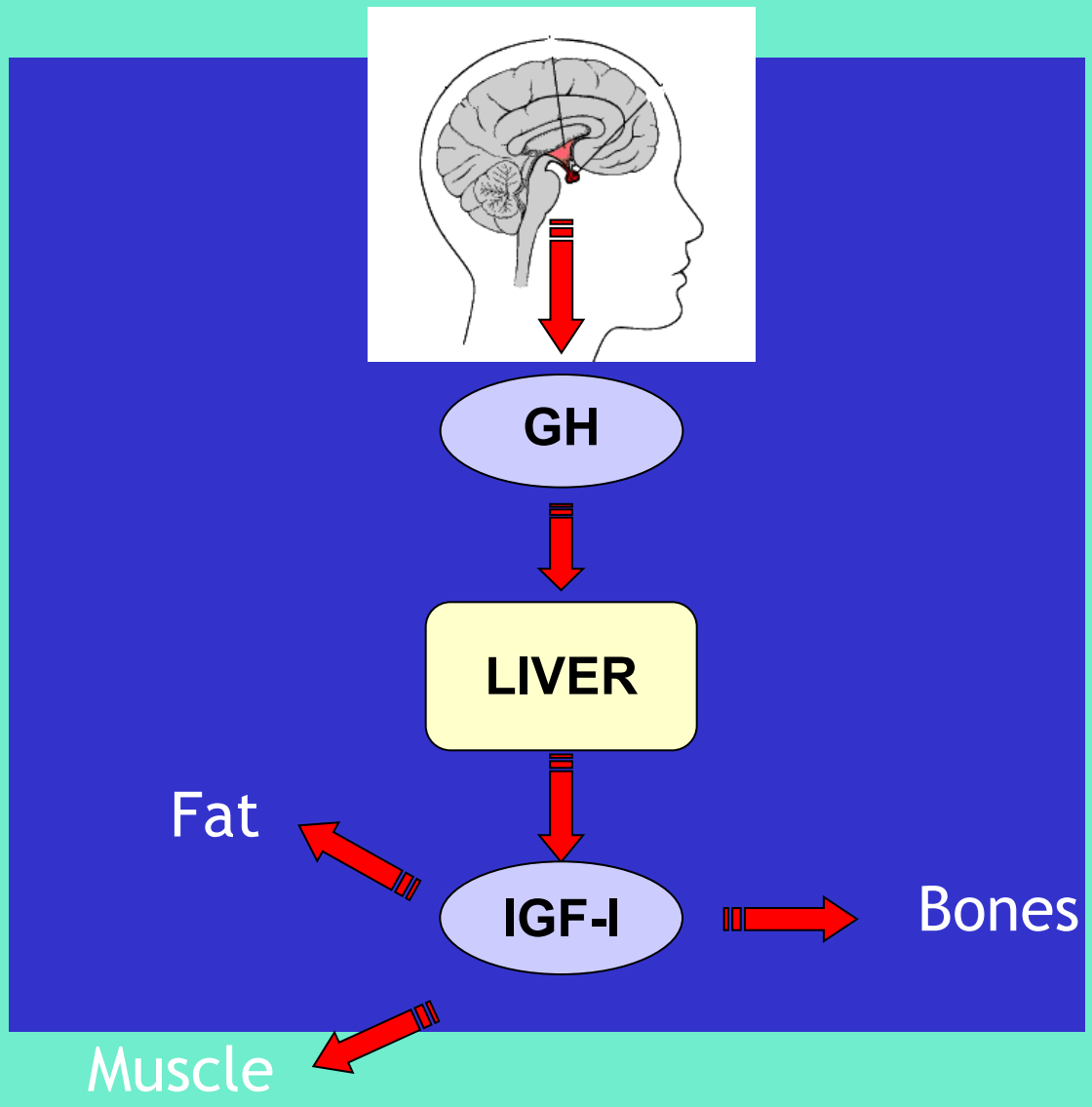
What does *daf-2* do?



What are *daf-2* and *daf-16*?

- *daf-2* is analogous to the insulin and IGF-1 receptors in people
- *daf-16* is analogous to the FOXO3 transcription factor in people
- These genes work together in insulin signaling in the liver

Growth Hormone – IGF-1 Axis



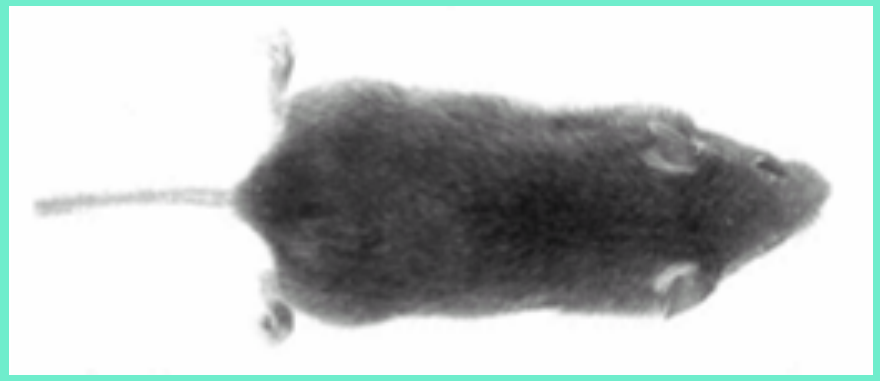
GH/IGF-1 in Mice

Ames and Snell Dwarf Mice lack GH and are Long-lived.

Laron Dwarf Mice lack the GH receptor and are Long-lived.

GH →

Mice with mutations in the IGF-1 receptor are Long-lived. → IGF-1 →



Giving Mice GH results in Big Mice and Accelerated Aging →

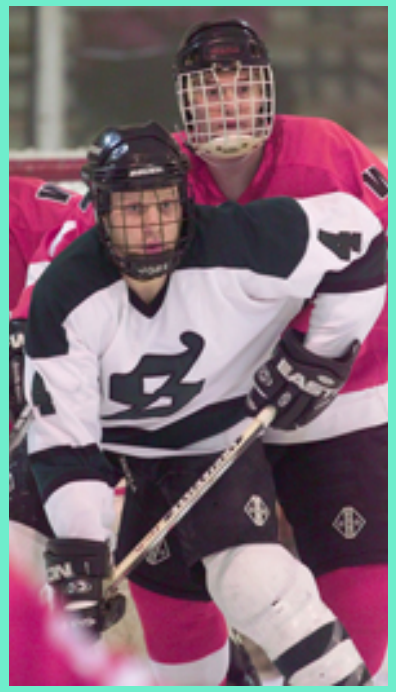
Body size and lifespan in humans

77 years

5ft 8in

75.5years

5ft 9.5in



72.5 years

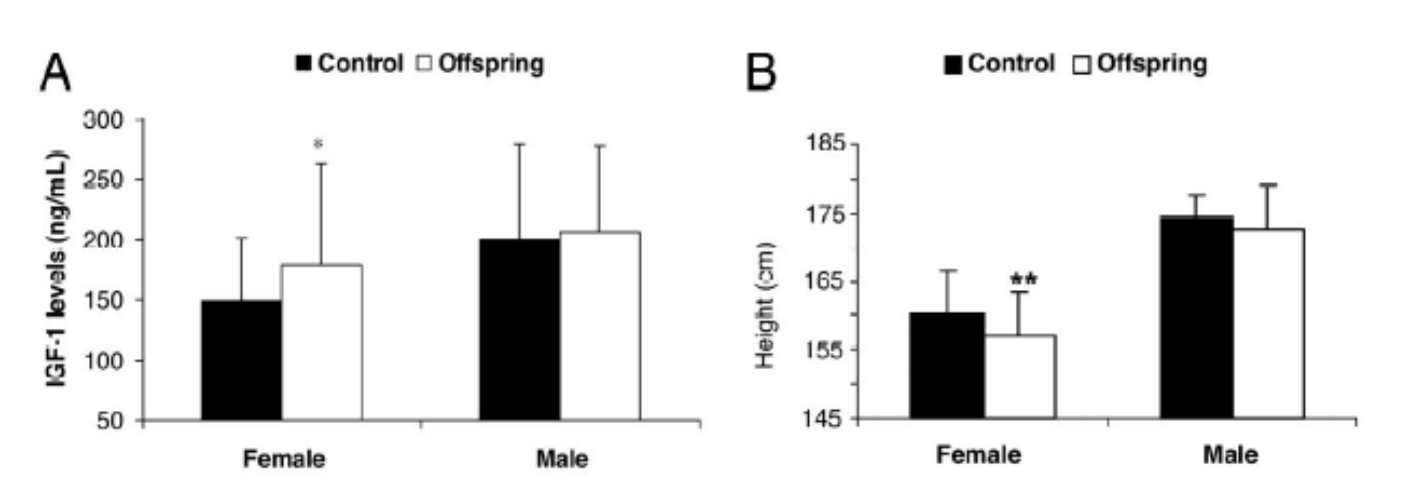
5ft 10in

70 years

6ft 1in

Samaras *et al.*, Life Sciences 2003 72:1781-1802

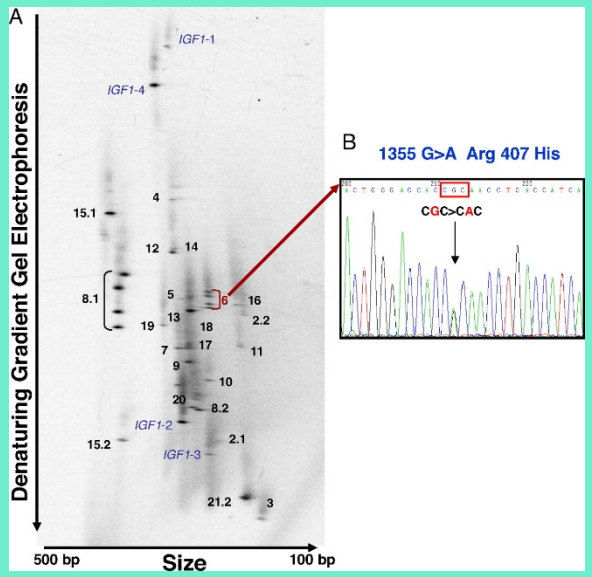
Studies of IGF-1 signaling in the Centenarian cohort



- Female Offspring of centenarians have higher IGF-1 levels but are shorter than control from non-centenarian families

- Is IGF-1 signaling impaired?

Identification of IGF-1 Receptor Mutations in Centenarians

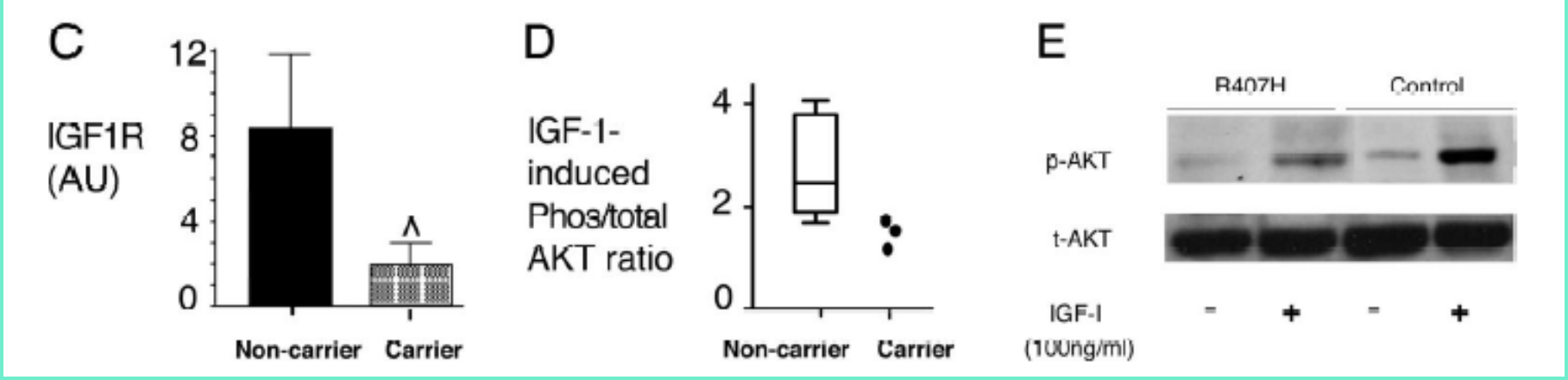


Category	Nucleotide change	Protein change	Centenarians, $n = 79$ Het	Centenarians, $n = 79$ Hom	Control, $n = 161$ Het	Control, $n = 161$ Hom
Nonsynonymous	**244G>A**	**Ala-37–Thr**	1	0	0	0
	1355G>A	Arg-407–His	1	0	0	0
Synonymous	948C>A	Gly-271–Gly	7	0	16	0
	1545G>A	**Thr-470–Thr**	1	0	0	0
	1959C>T	Asn-608–Asn	0	0	1	0
	1995G>T	**Arg-620–Arg**	0	0	1	0
	2343C>T	Thr-736–Thr	3	0	2	0
	2745C>T	**Asn-870–Asn**	1	0	3	0
	3174G>A	Glu-013–Glu	48	20	67	29
	4083C>T	Tyr-1316–Tyr	5	0	7	0
	4103C>T	**Arg-1323–Arg**	1	0	0	0
Intronic	IVS2+20C>T		42	8	65	12
	IVS8–20T>C		49	13	67	34
	IVS13+17G>A		1	0	2	0
	IVS13+21A>C		47	3	62	41
	IVS13+29_30delGT		26	1	38	3
	IVS15+49insG		1	0	0	0
	IVS15+52A>G		0	0	1	0
	IVS17−5C>T		1	0	3	0
	IVS21–34G>A		46	15	59	42

Het, number of heterozygote carriers of variant; Hom, number of homozygote carriers of variant. Previously unknown, novel variants are indicated in bold.

- 9/384 centenarians (2.3%) but only 1/312 controls (0.3%) had a non-synonymous mutation

Lymphocytes from Carriers have Less IGF-1R and Less Receptor Signaling



• These centenarians are resistant to IGF-1 effects and hence resemble the *daf-2* mutants

Is All of Aging Controlled by IGF-1?

- Over 100 genes have effects on lifespan in model animals
- These have lead to the identification of aging pathways:
  - mTOR signaling
  - Autophagy
  - Sirtuins
  - Mitochondrial signaling
  - Cell senescence

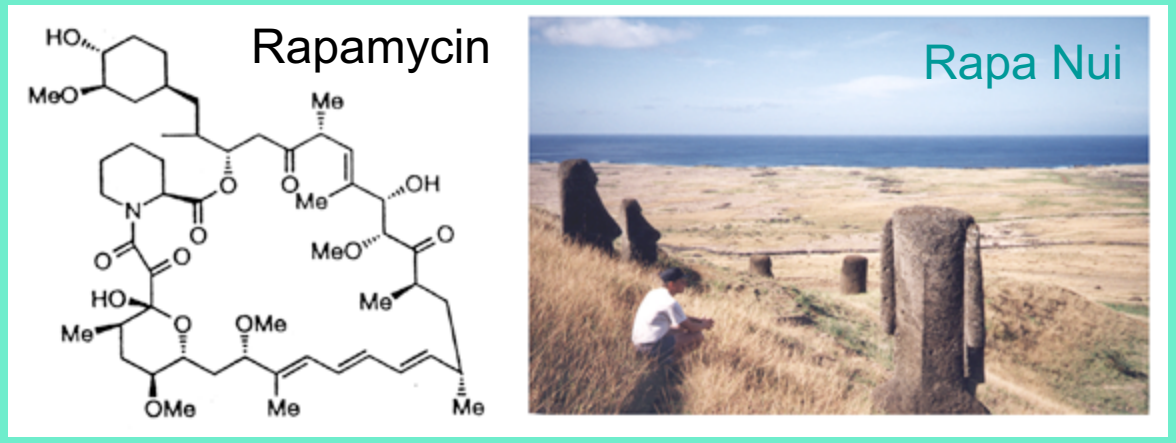
Can We Find Drugs that Could Extend Lifespan or Healthspan?

- Multiple drugs can increase lifespan in lower animals
  - Resveratrol
  - Rapamycin
  - Acarbose
  - ACE inhibitors
  - Metformin
  - Weak pro-oxidants
  - Some anti-seizure medications

- Could these play a role to:
  - Address role of aging in CV disease, DM, etc.
  - Prevent age-related diseases (AD or PD)
  - Modify Geriatric syndromes

What is Rapamycin?

- Macrolide molecule made by Streptomyces hygroscopicus
- Discovered in 1970 by Brazilian scientists from soil from Easter Island
- Easter Island is called Rapa Nui by natives

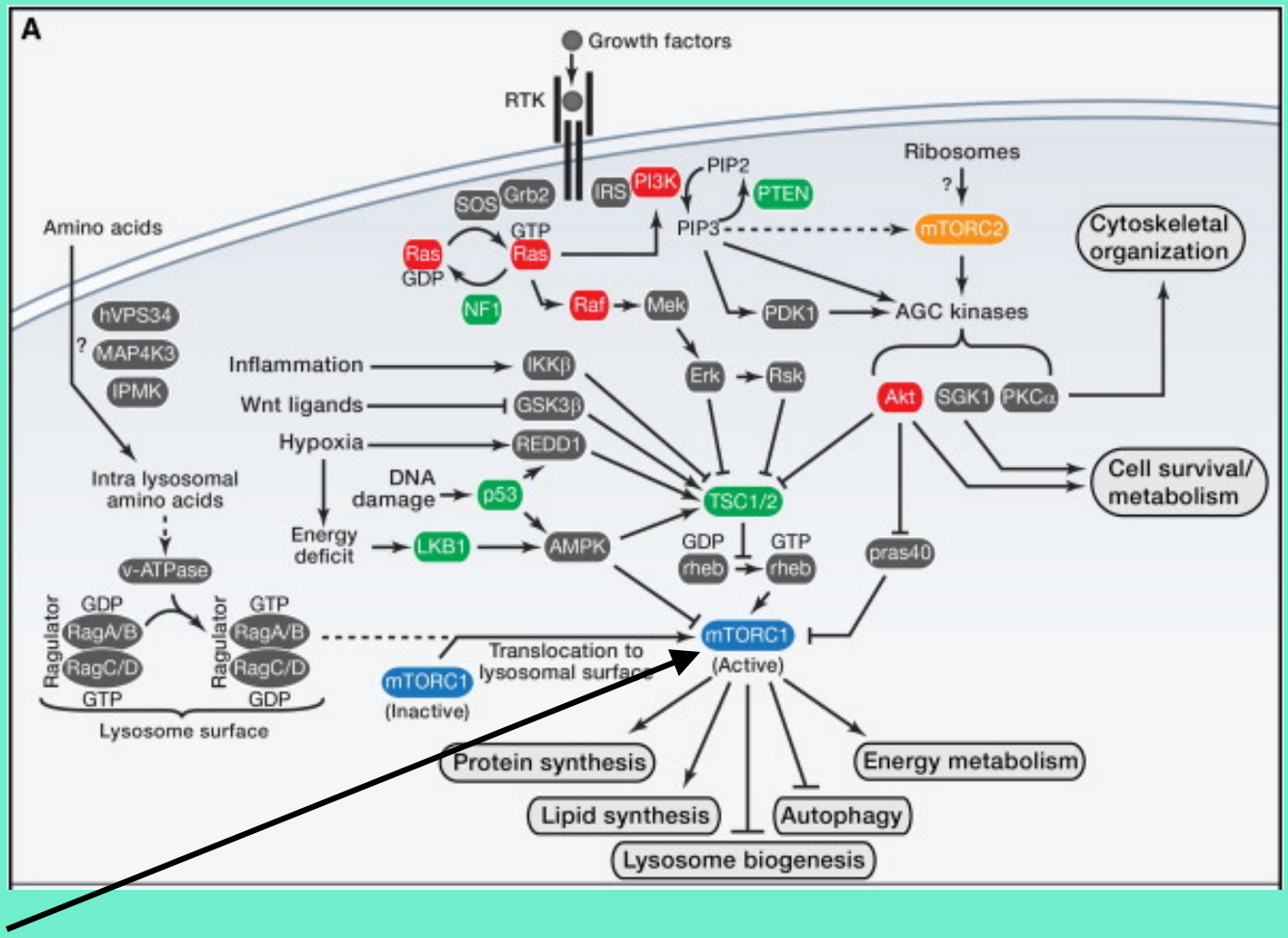


How did Rapamycin become a Drug?

- Developed in 1972 as an antifungal drug by Ayerst
- Found to suppress immunity in animals (died as antifungal)
- Found by NCI to be first cytostatic chemotherapeutic with wide spectrum of activity in mid-1970's (becomes high priority preclinical chemotherapeutic)
- In 1982, Wyeth closes Ayerst division in Canada (died as chemotherapeutic)
- In 1986, Wyeth changes CEO's. Rapamycin tested in animals as an immunosuppressant (becomes high priority drug for transplants)
- Use of Rapamycin in organ transplant published in Lancet in 1989. FDA approved for renal transplantation and drug-eluting stents

JNCI, 2001

What Does Rapamycin Do?



Inhibits the activity of TOR

Laplante, 2012

This then leads to:

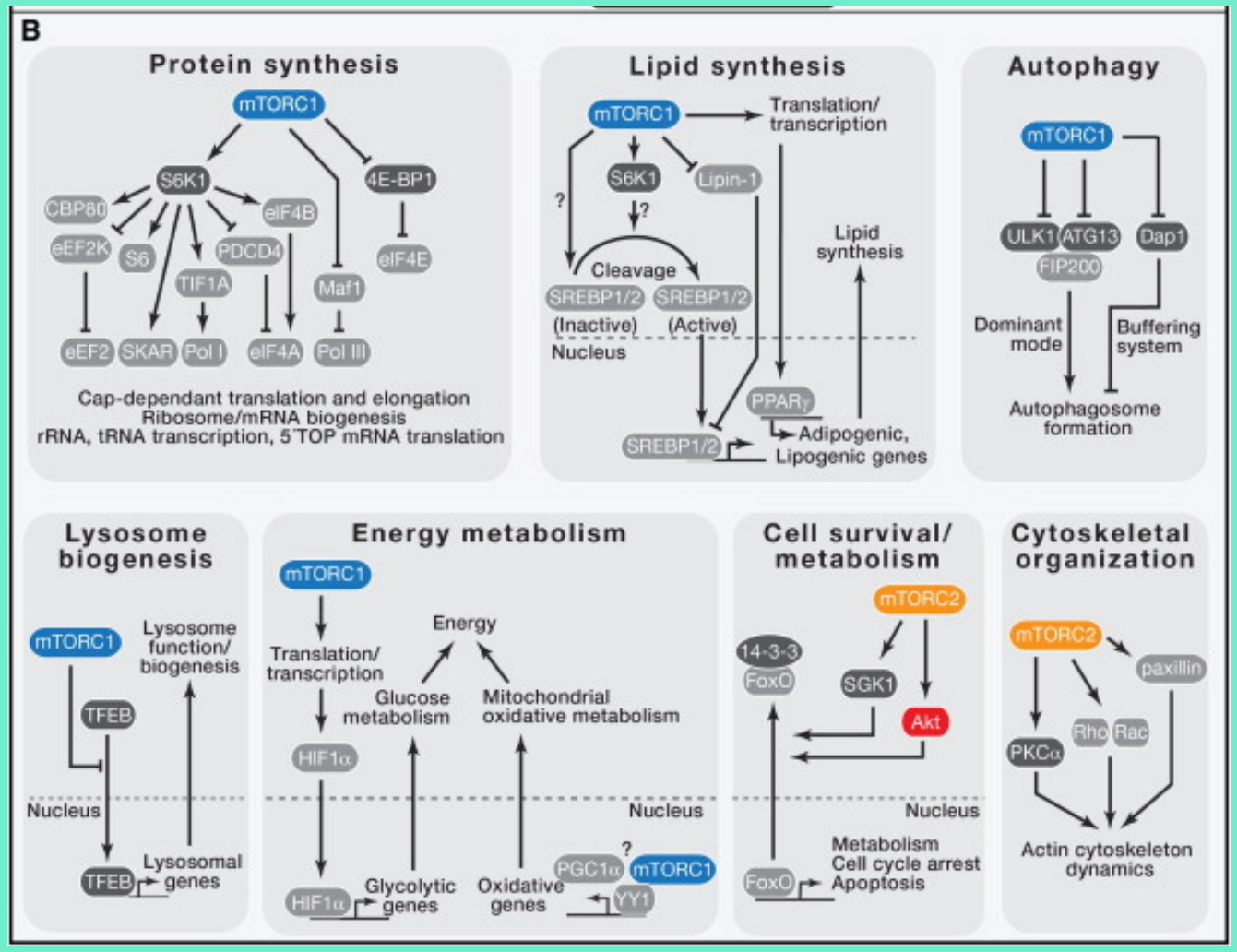
-Decreased protein synthesis

-Decreased lipid synthesis

-Increased lysosome and autophagosome production

-Reduced energy use

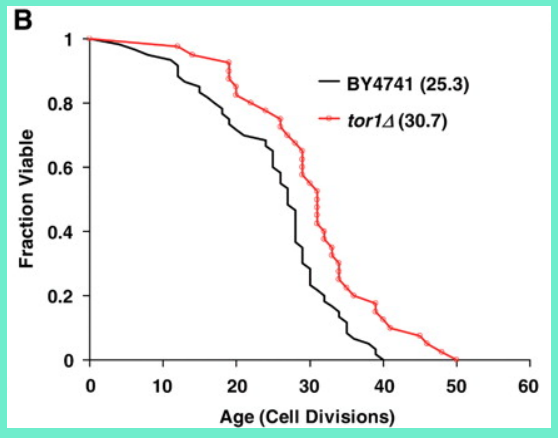
- And likely many other effects!

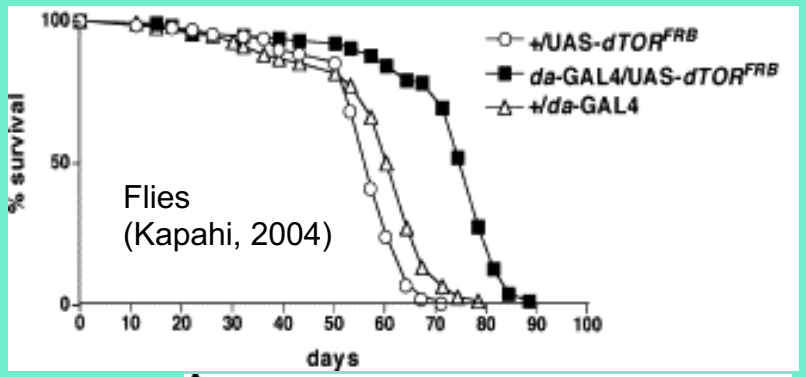


Why Was Rapamycin Studied in Aging?

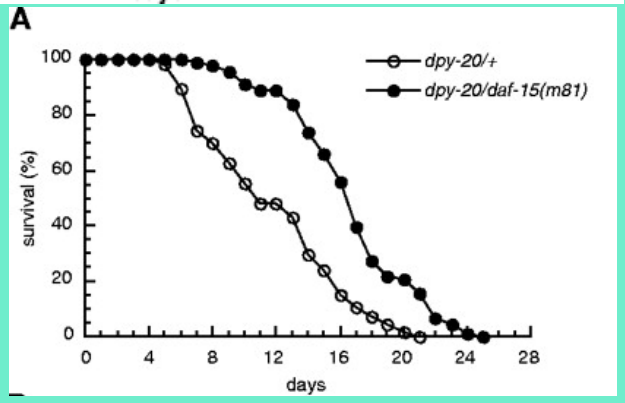
- TOR signaling is conserved from fungi to vertebrates
- Reducing TOR signaling increases lifespan in multiple species
- Caloric Restriction and Dwarf Mice have reduced TOR signaling

Yeast
(Kaeberlein, 2005)





Flies
(Kapahi, 2004)

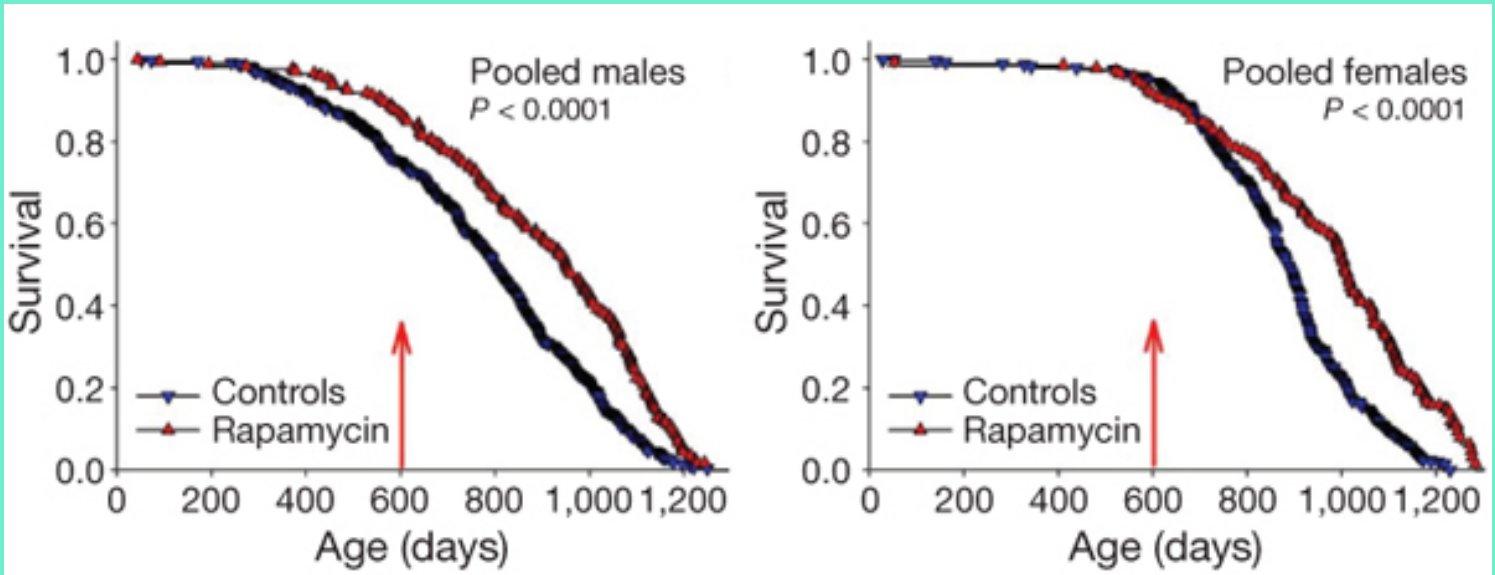


Worms
(Jia, 2004)

What does Rapamycin do to Mice?

Males

Females

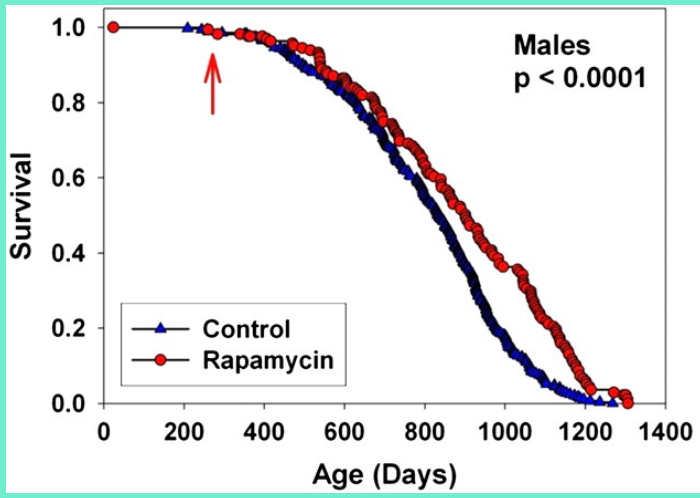


- Rapamycin treated was started at 600 days (~ 60 yo for humans)
- Increased total life expectancy 9 (male) -13 (female)%
- Increased remaining life expectancy 28 (male) – 38 (female)%
- “No change in causes of death”

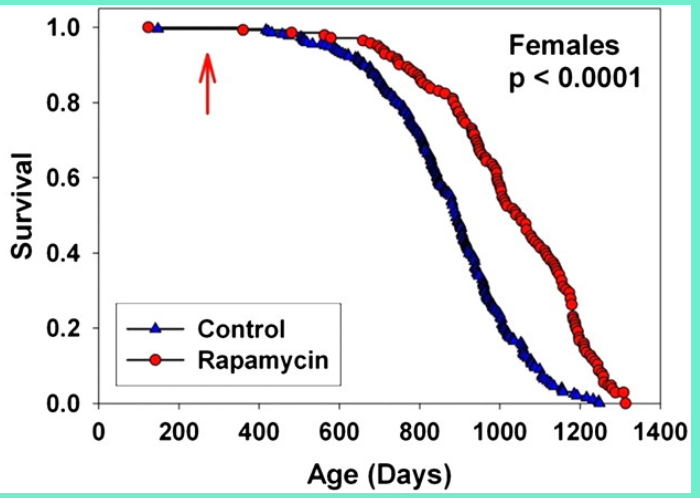
Harrison, *Nature* 2009

How About Treating Younger Mice?

Males

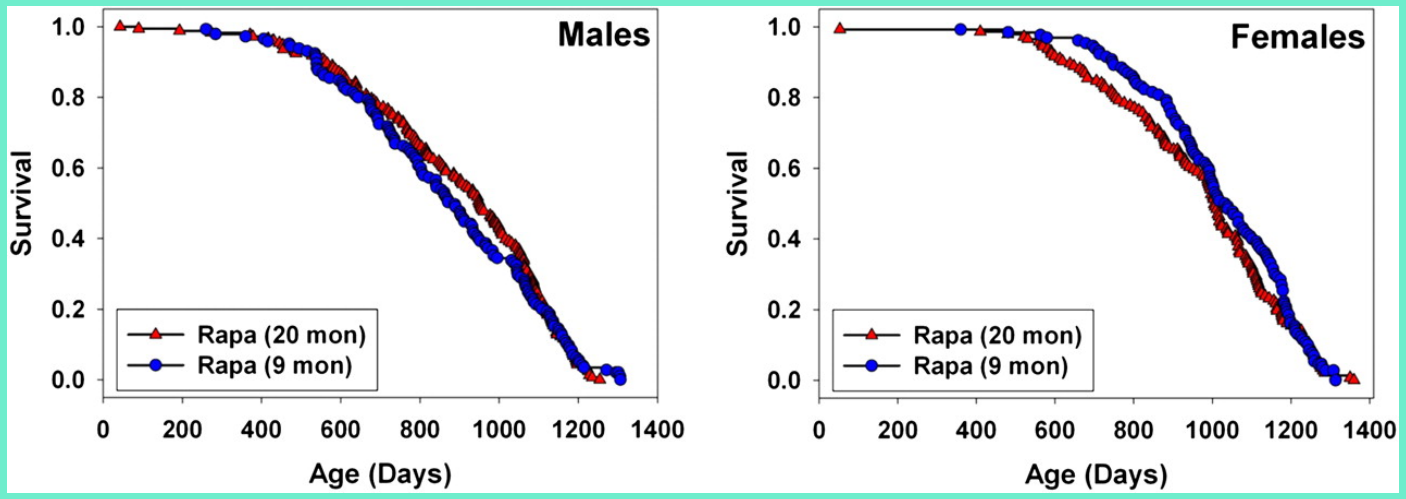


Females



- Rapamycin treated was started at 270 days (~ 27 yo for humans)
- Increased total life expectancy 10 (male) -18 (female)%
- Increased 90% percentile longevity 16 (male) – 13 (female)%
- “No dramatic change in the range of lethal or nonlethal illnesses ”

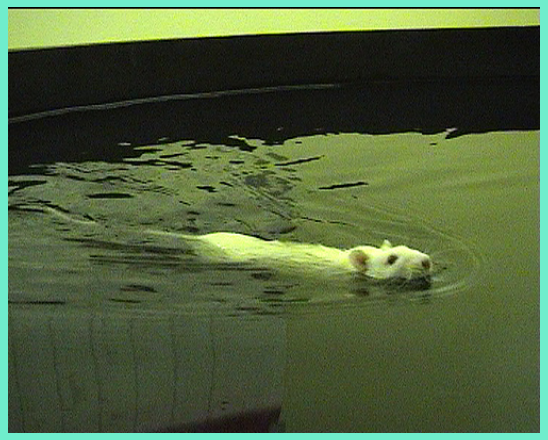
But Don’t We Expect to See More Benefit Starting Early?

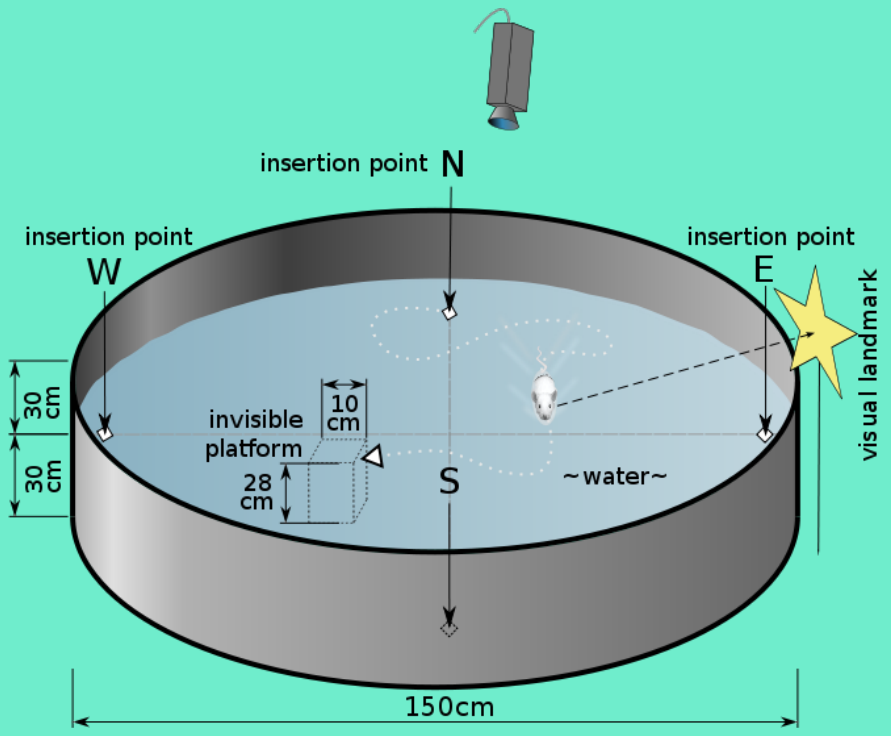


- Survival curves for early vs late start are essential the same
- ? Affects something happening later in life
- Might actually be useful in practice

Rapamycin Improves Memory in an Alzheimer's Disease Model

How do you study memory in mice?



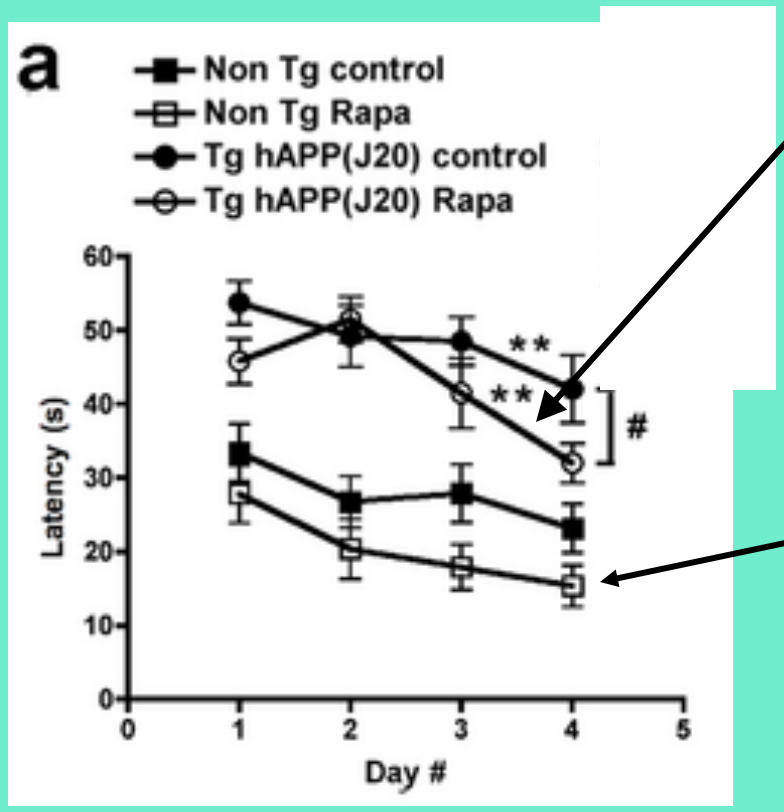


Morris Water Maze

- Measures spatial memory
- Less influenced by motivation

Rapamycin Improves Memory in an Alzheimer's Disease Model

- Treated APP transgenic mice for 13 weeks starting at 4 months of age.
- Went on 6 swims/day for 4 days for training
- Measured time to find platform
- Tests learning



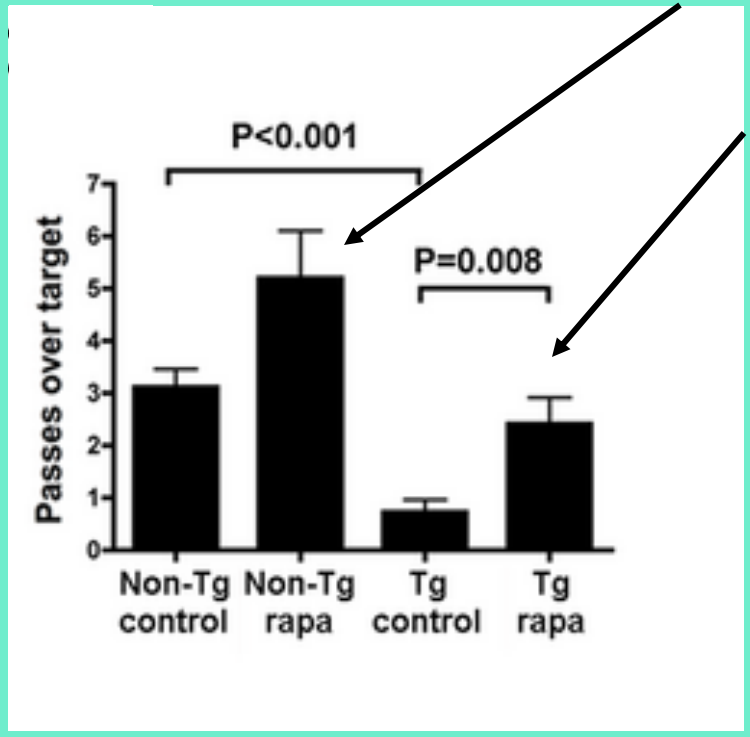
Treatment reduces time to find platform

Improves normal mice too?

Spilman, *PLOS One*, 2010

Rapamycin Improves Memory in an Alzheimer's Disease Model

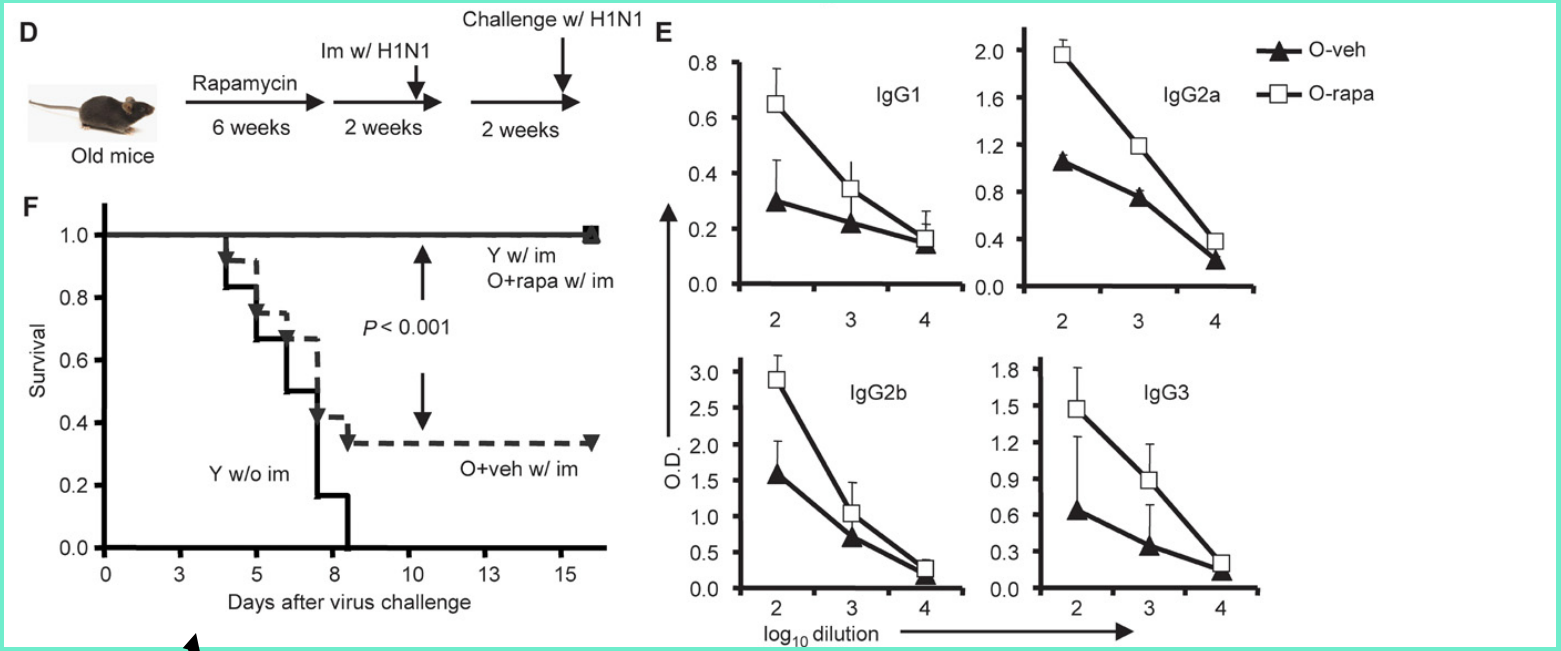
- After last trial, maze was removed and mouse put back in tank
- Looked for searching for platform in the old location
- Tests spatial memory



Improved both AD and normal mice!

Spilman, *PLOS One*, 2010

Improves Immune Function and Response to Flu Vaccination



Treatment for 6 weeks (4 mg/kg QOD):

- Produces more immature B-cells
- Gives higher titer response to flu vaccine
- Makes vaccine more effective against infection

Chen, *Sci. Signaling,* 2009

Summary

• Aging is a universal process that impacts on human health and function

• Biology focused research has taught us that aging is malleable and involves specific mechanisms

• Uncovering mechanisms has lead to the use of drugs to modify aging both as a research tool and as a potential therapeutic

• Benefits for people are unknown but many avenues/opportunities exist for translation to the clinic