

Model organisms and developmental biology

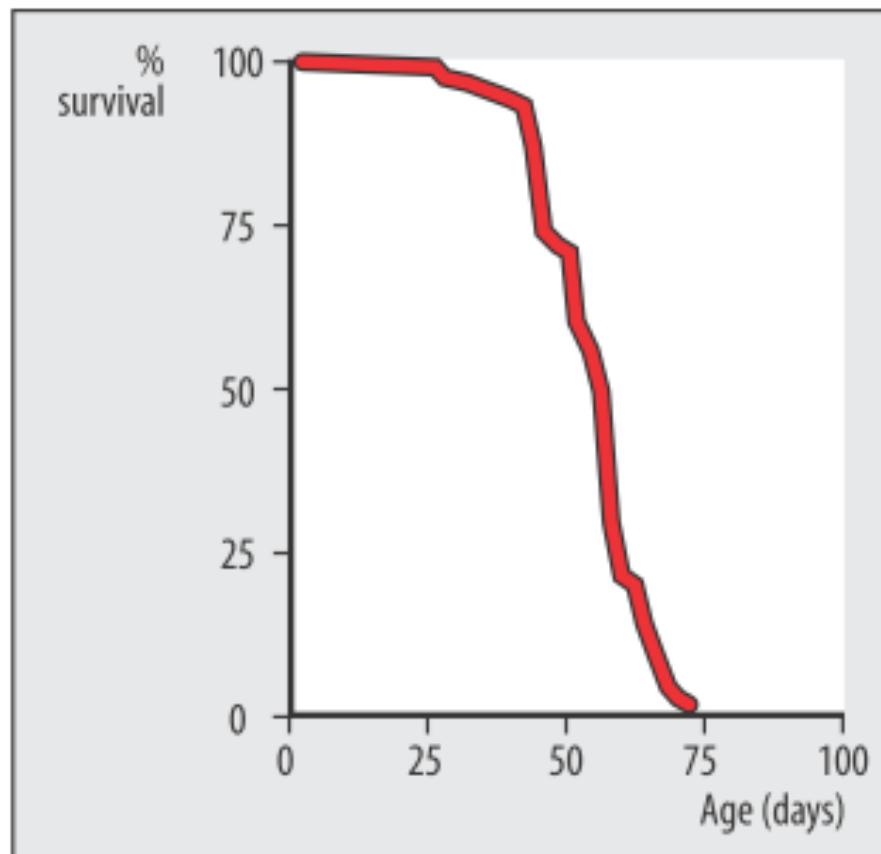
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Senescence, Aging, Lifespan

- This age-related decline in function is known as **senescence**.
- The word "**senescence**" can refer either to cellular senescence or to senescence of the whole organism. It is commonly believed that cellular senescence underlies organismal senescence. The gradual deterioration of function characteristic of most complex life forms, arguably found in all biological kingdoms, that on the level of the organism increases mortality after maturation.
- The science of biological aging is **gerontology**.

Aging in *Drosophila*



Aging

- Aging is observed in most multicellular animals, but there are notable exceptions, such as cnidarians (sea anemones, Hydra, and their relations) and planarians.
- All sexually reproducing animals age, whereas most asexual animals do not (Yeast).
- Germ cells do not age (Do you agree with this?).

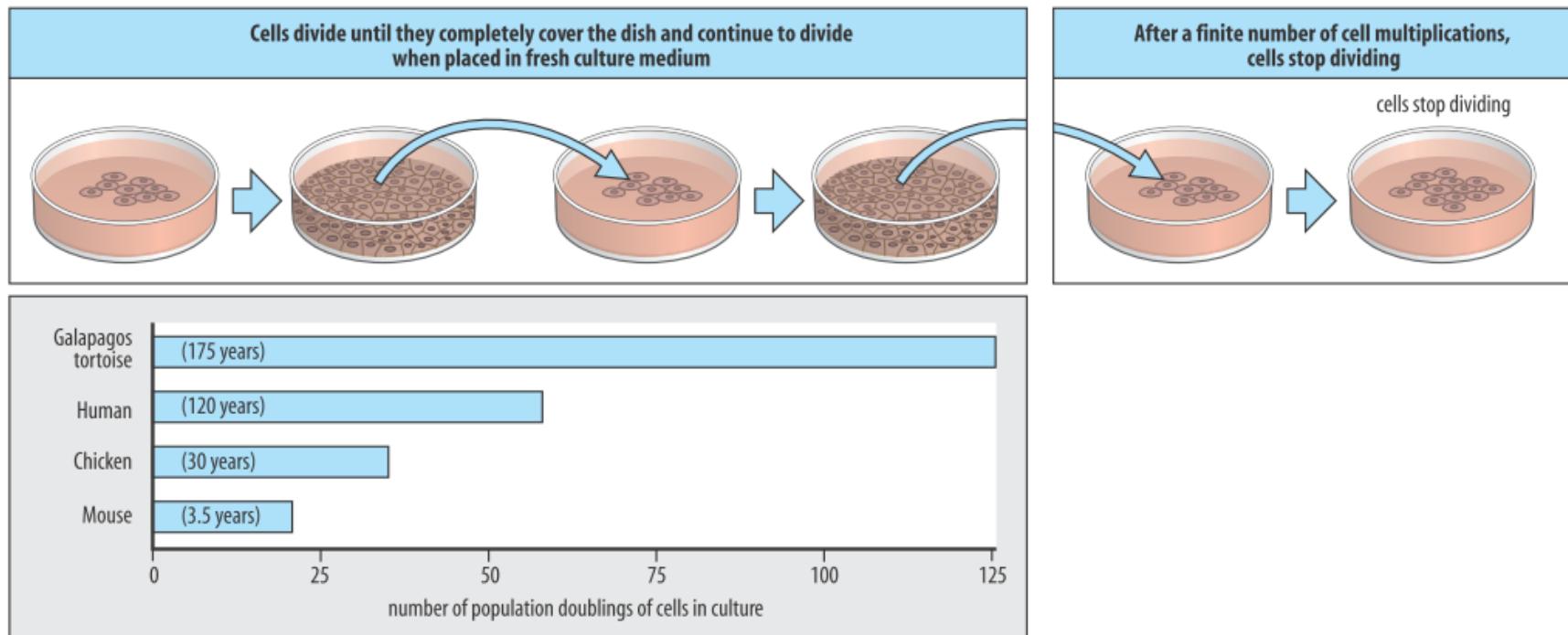
Longevity and time to attain reproductive maturity at puberty for various mammals

	Maximum lifespan (months)	Length of gestation (months)	Age at puberty (months)
Human	1440	9	144
Fin whale	960	12	~72
Indian elephant	840	21	156
Horse	744	11	15
Chimpanzee	720	8	120
Brown bear	468	7	72
Dog	348	2	7
Cattle	588	9	15
Rhesus monkey	480	5.5	36
Cat	486	2	8
Pig	276	4	5
Squirrel monkey	180	5	30
Sheep	276	5	7
Gray squirrel	180	1.5	12
European rabbit	156	1	4
Guinea-pig	90	2	2
House rat	56	0.7	2
Golden hamster	48	0.5	2
Mouse	48	0.7	1.5

The ‘disposable soma’ theory

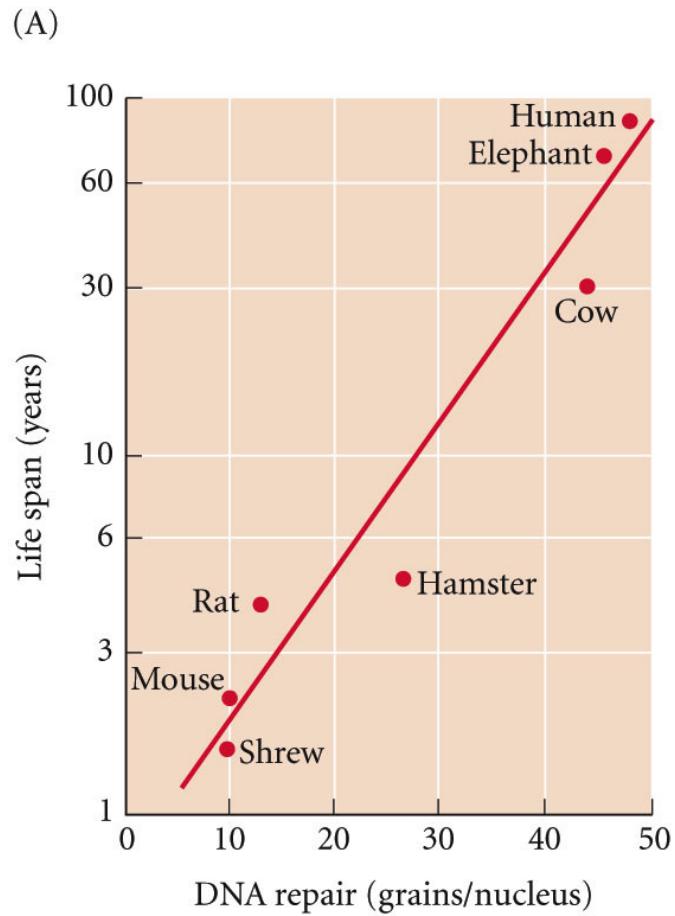
- The genetic control of aging can be understood in terms of the ‘disposable soma’ theory, which puts it into the context of evolution.
- The disposable soma theory proposes that natural selection tunes the life history of the organism so that sufficient resources are invested in maintaining the repair mechanisms that prevent aging, at least until the organism has reproduced and cared for its young.

Vertebrate fibroblasts can only go through a limited number of divisions in culture



For normal fibroblasts, the number of cell doublings depends both on the species and the age of the animal from which they are taken. Fibroblasts taken from a human fetus go through about 60 doublings, those from an 80-year-old about 30, and those from an adult mouse about 12–15 doublings.

Mutation repair deficiency



Calorie
restriction
(Sir2)

Absence
of
germline

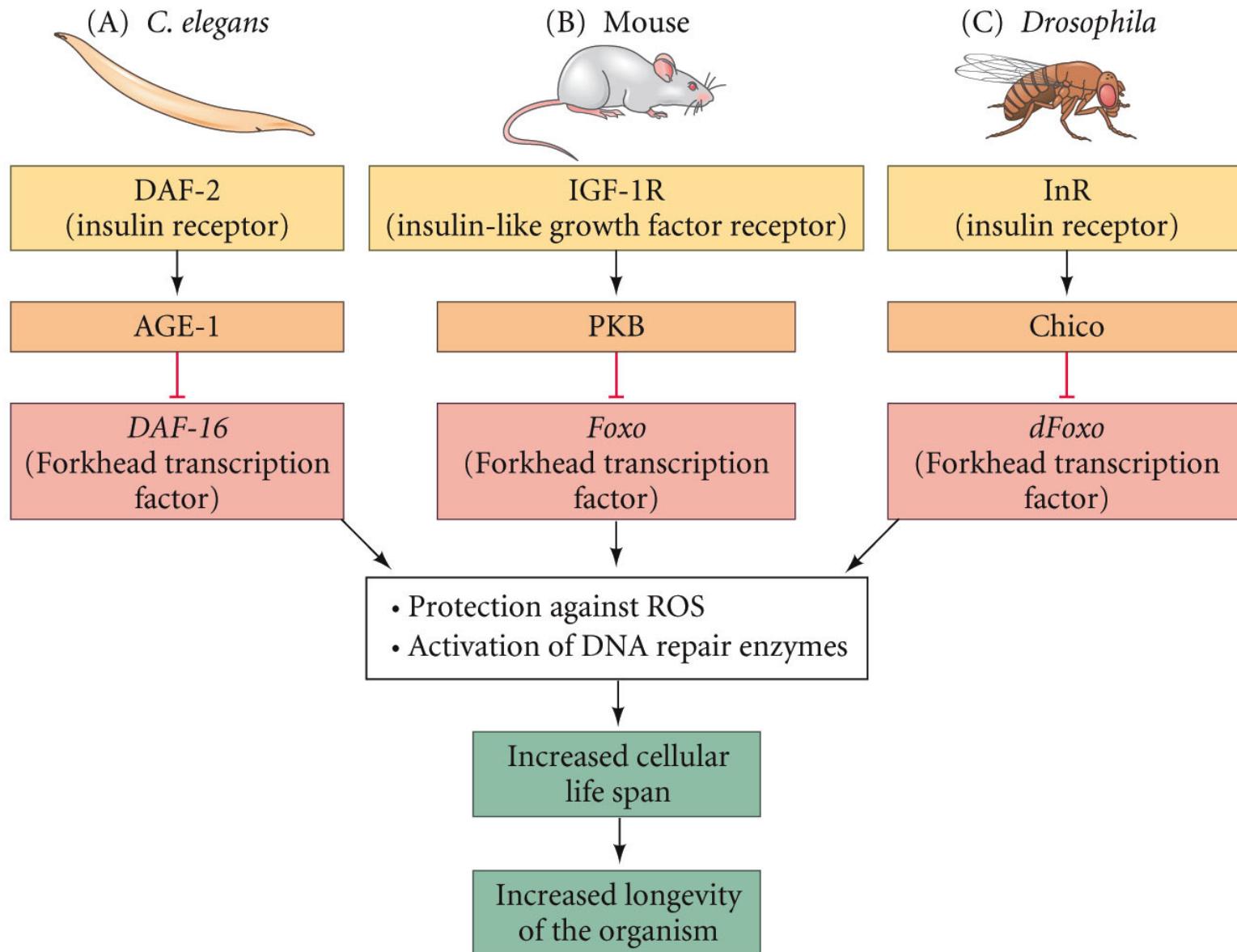


Longevity

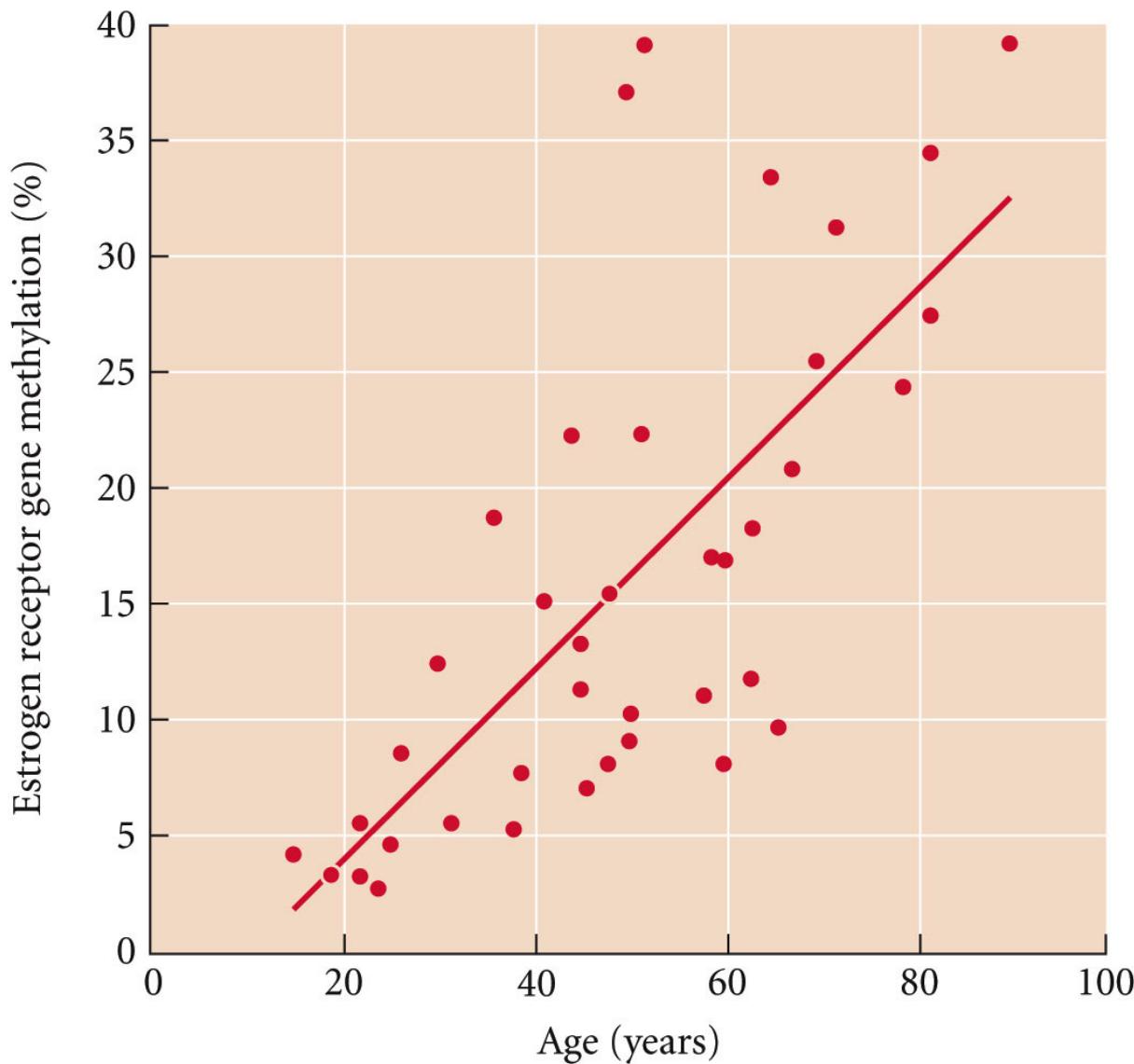


Insulin/IGF signaling via DAF-2
(inhibition of DAF-16/FoxO)

Low caloric intake is associated with long-life in all species

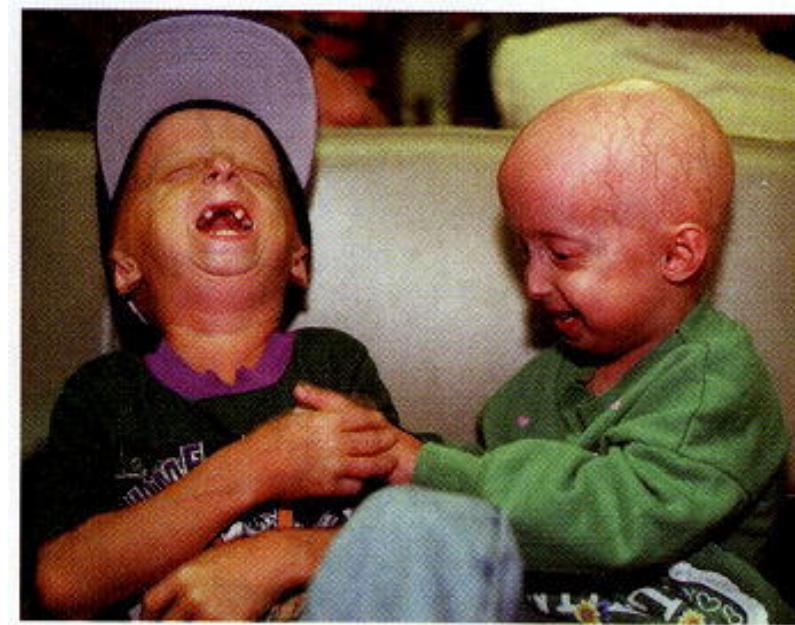


Methylation of the estrogen receptor gene occurs as a function of normal aging



How to study lifespan?

Progeria

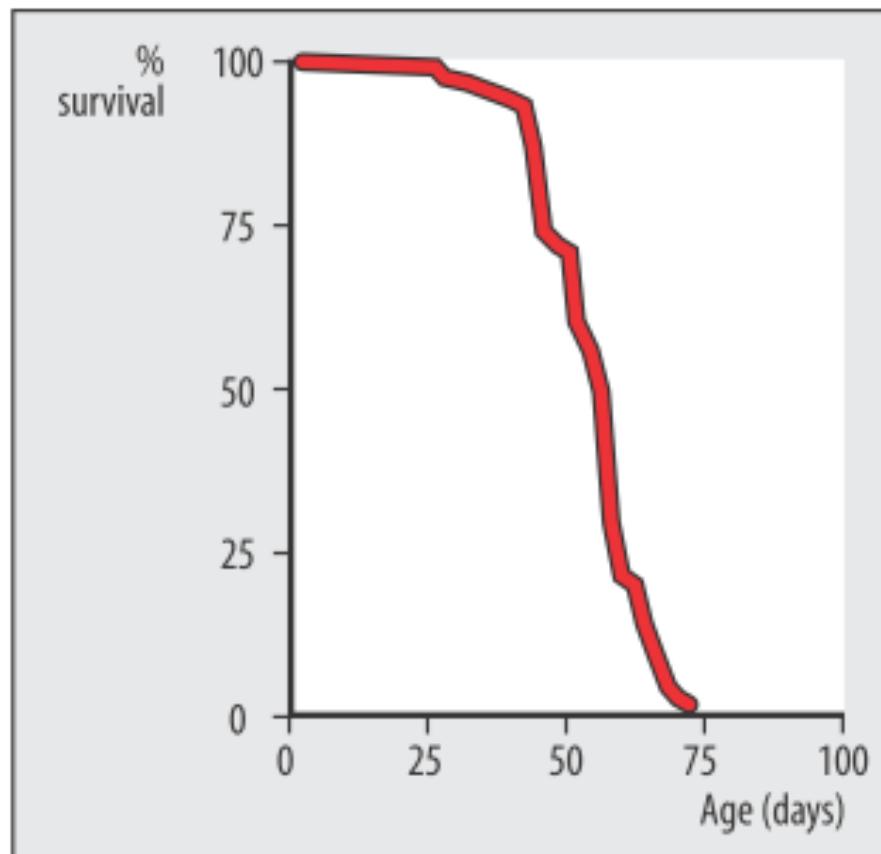


Children with progeria. Although less than 8 years old, the child on the right has a phenotype similar to that of an aged person. The hair loss, fat distribution, and transparency of the skin are characteristic of the normal human aging pattern seen in elderly adults.
(Photograph © Associated Press.)

Syndrome X

- Brooke Megan Greenberg (January 8, 1993 – October 24, 2013) was an American Syndrome X patient from Reisterstown, Baltimore County, Maryland, who remained physically and cognitively similar to a toddler, despite her increasing age. She was about 30 inches (76 cm) tall, weighed about 16 pounds (7.3 kg), and had an estimated mental age of nine months to one year. Brooke's doctors termed her condition "Syndrome X".

Aging in *Drosophila*



Calorie
restriction
(Sir2)

Absence
of
germline



Longevity



Insulin/IGF signaling via DAF-2
(inhibition of DAF-16/FoxO)

Sirtuin activators mimic caloric restriction and delay ageing in metazoans

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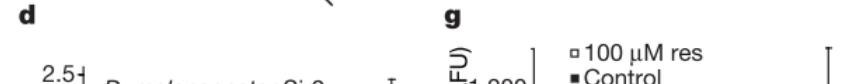
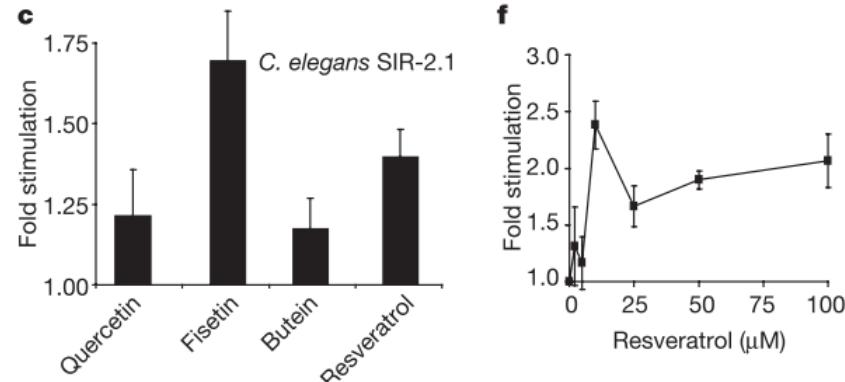
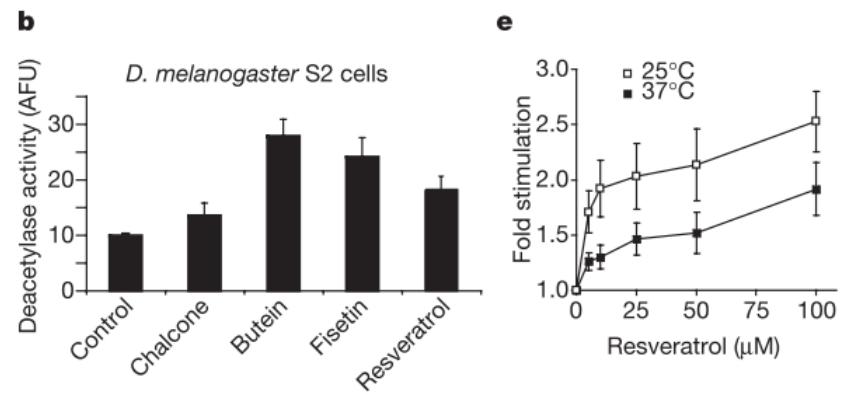
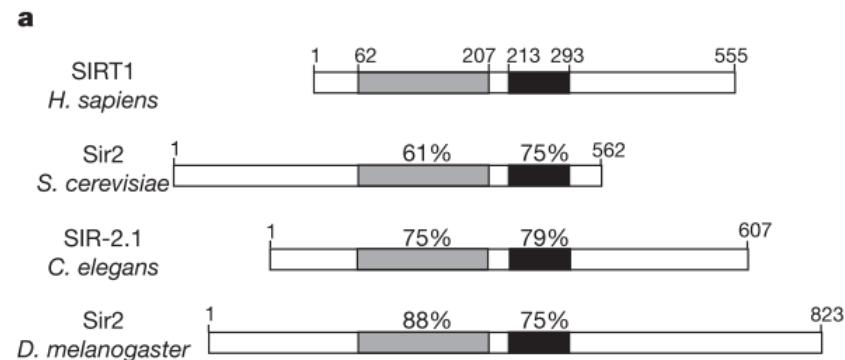
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* These authors contributed equally to this work

Caloric restriction extends lifespan in numerous species. In the budding yeast *Saccharomyces cerevisiae* this effect requires Sir2 (ref. 1), a member of the sirtuin family of NAD⁺-dependent deacetylases^{2,3}. Sirtuin activating compounds (STACs) can promote the survival of human cells and extend the replicative lifespan of yeast⁴. Here we show that resveratrol and other STACs activate sirtuins from *Caenorhabditis elegans* and *Drosophila melanogaster*, and extend the lifespan of these animals without reducing fecundity. Lifespan extension is dependent on functional Sir2, and is not observed when nutrients are restricted. Together these data indicate that STACs slow metazoan ageing by mechanisms that may be related to caloric restriction.

Sir2-like proteins (sirtuins) are a family of NAD⁺-dependent deacetylases conserved from *Escherichia coli* to humans⁵⁻⁹ (Fig. 1a)



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HEALTH CARE

Glaxo to Buy Sirtris in Bet On Antiaging Research

By Keith J. Winstein

Updated April 23, 2008 12:01 a.m. ET

GlaxoSmithKline PLC will buy Sirtris Pharmaceuticals Inc. for \$720 million, placing a substantial bet on the potential of early-stage research on drugs touted for their potential to slow the aging process.

Sirtris, of Cambridge, Mass., is working on commercializing resveratrol, a chemical found in red wine, and follow-on drugs to fight diabetes and other conditions. Advocates suspect that resveratrol may also increase lifespan, though...

TO READ THE FULL STORY

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GlaxoSmithKline Shuts Down Sirtris, Five Years After \$720M Buyout



Luke Timmerman
March 12th, 2013

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Xconomy Boston — [Updated 2:25 pm ET, 3/13/13] GlaxoSmithKline is closing down Cambridge, MA-based **Sirtris Pharmaceuticals**, almost five years after **it paid \$720 million** to acquire the hot biotech with a plan to fight diseases of aging.

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IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*. All content is Derek's own, and he does not in any way speak for his employer.



By Derek Lowe

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GSK's Response to the Sirtuin Critics

By [Derek Lowe](#) | August 25, 2010

OK, time (finally) for the latest chapter in the GSK-Sirtris saga. (This is going to get fairly geeky, so feel free to skip ahead if you're not into enzymology). You'll **recall** from previous **installments** that **Amgen** and **Pfizer**, among others, had disputed whether the reported sirtuin compounds worked the way that had originally been reported. GSK has now **published a paper** in the *Journal of Biological Chemistry* to address those questions. How well does this clear things up? Let's take things in order:

Claim 1: Resveratrol is not a direct activator of SIRT1 activity (Amgen). Building on two **2005 papers**, the **Amgen team said** that resveratrol, the prototype SIRT1 ligand, only works in that manner when the fluorescent peptide (Fluor de Lys) was used in the assay. This is due, they found, exclusively to the fluorophore on the peptide – it's an artifact of the assay conditions. Without it, no activation was seen with protein assays *in vitro*, nor in cell assays. Native substrates (p53-derived peptide and PGC-1alpha) show nothing.

GSK's response: This is true. They too, found that activation of SIRT1 depends on the structure of the substrate. Without the fluorescent label, no activation is seen.

Absence of effects of Sir2 overexpression on lifespan in *C. elegans* and *Drosophila*

Camilla Burnett^{1*}, Sara Valentini^{1*}, Filipe Cabreiro^{1*}, Martin Goss¹, Milán Somogyvári², Matthew D. Piper¹, Matthew Hoddinott¹, George L. Sutphin^{3,4}, Vid Leko⁵, Joshua J. McElwee¹, Rafael P. Vazquez-Manrique^{6,7}, Anne-Marie Orfila^{6,7}, Daniel Ackerman¹, Catherine Au¹, Giovanna Vinti¹, Michèle Riesen¹, Ken Howard⁸, Christian Neri^{6,7}, Antonio Bedalov⁵, Matt Kaeberlein^{3,4}, Csaba Sóti², Linda Partridge^{1,9} & David Gems¹

Overexpression of sirtuins (NAD⁺-dependent protein deacetylases) has been reported to increase lifespan in budding yeast (*Saccharomyces cerevisiae*), *Caenorhabditis elegans* and *Drosophila melanogaster*^{1–3}. Studies of the effects of genes on ageing are vulnerable to confounding effects of genetic background⁴. Here we re-examined the reported effects of sirtuin overexpression on ageing and found that standardization of genetic background and the use of appropriate controls abolished the apparent effects in both *C. elegans* and *Drosophila*. In *C. elegans*, outcrossing of a line with high-level *sir-2.1* overexpression¹ abrogated the longevity increase, but did not abrogate *sir-2.1* overexpression. Instead, longevity co-segregated with a second-site mutation affecting sensory neurons. Outcrossing of a line with low-copy-number *sir-2.1* overexpression² also abrogated longevity. A *Drosophila* strain with ubiquitous overexpression of *dSir2* using the UAS-GAL4 system was long-lived relative to wild-type controls, as previously reported³, but was not long-lived relative to the appropriate transgenic controls, and nor was a new line with stronger overexpression of *dSir2*. These findings underscore the importance of controlling for genetic background and for the mutagenic effects of transgene insertions in studies of genetic effects on lifespan. The life-extending effect of dietary restriction on ageing in *Drosophila* has also been reported to be *dSir2* dependent³. We found that dietary restriction increased fly lifespan independently of *dSir2*. Our findings do not rule out a role for sirtuins in determination of metazoan

exclude the possibility that the increased longevity observed in strains with overexpression of sirtuin genes is caused by differences in genetic background, or by the mutagenic effects of transgene insertion, which frequently confound studies of the genetics of ageing⁴.

We first examined a high-copy-number *sir-2.1* transgenic *C. elegans* strain (LG100) carrying the integrated transgene array *geIn3* [*sir-2.1 rol-6(su1006)*] (ref. 1). As expected, this strain was long-lived (Fig. 1a and Supplementary Table 1). However, outcrossing ($\times 5$) of *geIn3* to wild type (N2) abrogated the increase in longevity (Fig. 1a and Supplementary Table 1) without affecting SIR-2.1 protein levels (Fig. 1b). This loss of longevity upon outcrossing was verified by an independent research team (Supplementary Table 2).

LG100 showed a neuronal dye-filling (Dyf) defect²¹ that did not segregate with the transgene upon outcrossing (Supplementary Fig. 2a). Dyf mutants often show extended lifespan²². To determine whether the longevity of LG100 might be attributable to a *dyf* mutation, we derived from this strain three Dyf, non-Rol lines (lacking *geIn3*) and three non-Dyf, Rol lines (carrying *geIn3*). Dyf, non-Rol lines were long-lived and showed wild-type SIR-2.1 protein levels (Fig. 1c, d and Supplementary Table 3). Non-Dyf, Rol lines showed elevated SIR-2.1 protein levels but had wild-type lifespans. Dyf mutant longevity seemed to be partially dependent on *daf-16* (Supplementary Fig. 2b), as seen previously for other Dyf mutants²². The co-segregation of longevity with this *dyf* mutation, but not with *geIn3*, was previously noted by another research



Aging Genes: The Sirtuin Story Unravels

Work that pinpointed the control of aging in a handful of genes is being taken apart by some of the scientists who made early discoveries. Efforts to replicate studies are producing conflicting results

SEATTLE, WASHINGTON—The lush, drizzly campus here at the University of Washington (UW) is 4000 kilometers from the concrete jungle of the Massachusetts Institute of Technology (MIT) in Cambridge, but Matt Kaeberlein keeps finding himself pulled back to the East Coast institution where his unusual scientific career began. Thirteen years ago, as a graduate student from a little-known western school, he stepped into a highly competitive lab and helped launch a new field in the biology of aging. For the past 7 years, he's been systematically dismantling the building blocks he laid, arguing that some of those early discoveries—and many since then—are wrong.

"It's been an adventure," says Kaeberlein, who turned 40 this year. Wearing jeans and glasses with square metal frames, he comes across as a mix of science nerd and Seattle cool. His fifth-floor office is as neat as they come. "I don't think that I could have ever predicted that things would happen the way they happened," he says.

Kaeberlein's journey began in the lab of MIT professor Leonard Guarente back in

1998, chasing a then-heretical idea in science: that certain genes can prolong life. The work started slowly but captured the attention of nearly everyone in the lab, particularly Guarente, an intense, brilliant biologist. The group churned out a series of influential papers that transformed how scientists and the public think about aging. The idea that life span was a malleable part of biology was no longer science fiction. Discoveries from Guarente's lab linked a set of genes to calorie restriction, which had been known for years to stretch life span in animals. This suggested that drugs to mimic the effects of calorie restriction might not be far behind.

About 10 years ago, Kaeberlein and his cohort of Guarente lab members wrapped up their Ph.D.s and postdocs and scattered. Most went on to start labs of their own at top institutions. From there, the story gets peculiar.

Guarente and some former lab members pushed forward with the new aging genes and vigorously promoted their findings. Others, such as Kaeberlein, experi-

enced nagging doubts that grew with time. Kaeberlein wasn't finding what others were reporting in recent experiments. Outside the Guarente circle, some scientists had similar problems while others reported success.

The result is mass confusion over who's right and who's wrong, and a high-stakes effort to protect reputations, research money, and one of the premier theories in the biology of aging. It's also a story of science gone sour: Several principals have dug in their heels, declined to communicate, and bitterly derided one another. Tensions reached a crescendo in September, when Kaeberlein and colleagues in the United Kingdom published one of their most damning papers yet, finding no effects from a key aging gene in worms and flies.

Almost everyone "is from the same place," the MIT lab run by Guarente, says Stephen Helfand, a fly biologist at Brown University who studies aging and who did not start his career there. What's happening now, he says, is "either Shakespearean or Freudian." Or maybe both.

Hooked

Kaeberlein was not programmed for a career in science. His father was a postal worker and his mother a homemaker, then an office

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“Rumors of the death of sirtuins and aging are greatly exaggerated.”

DAVID SINCLAIR,
Harvard



“There's a view that seems to be current, that somehow one doesn't engage in quarrels. Sometimes, you have to.”

DAVID GEMS, University College London



“I'd believe the positive result. There's lots of reasons why you can do an experiment and have it not work.”

LEONARD GUARENTE,
MIT

The Sinclair Lab



Harvard Medical School

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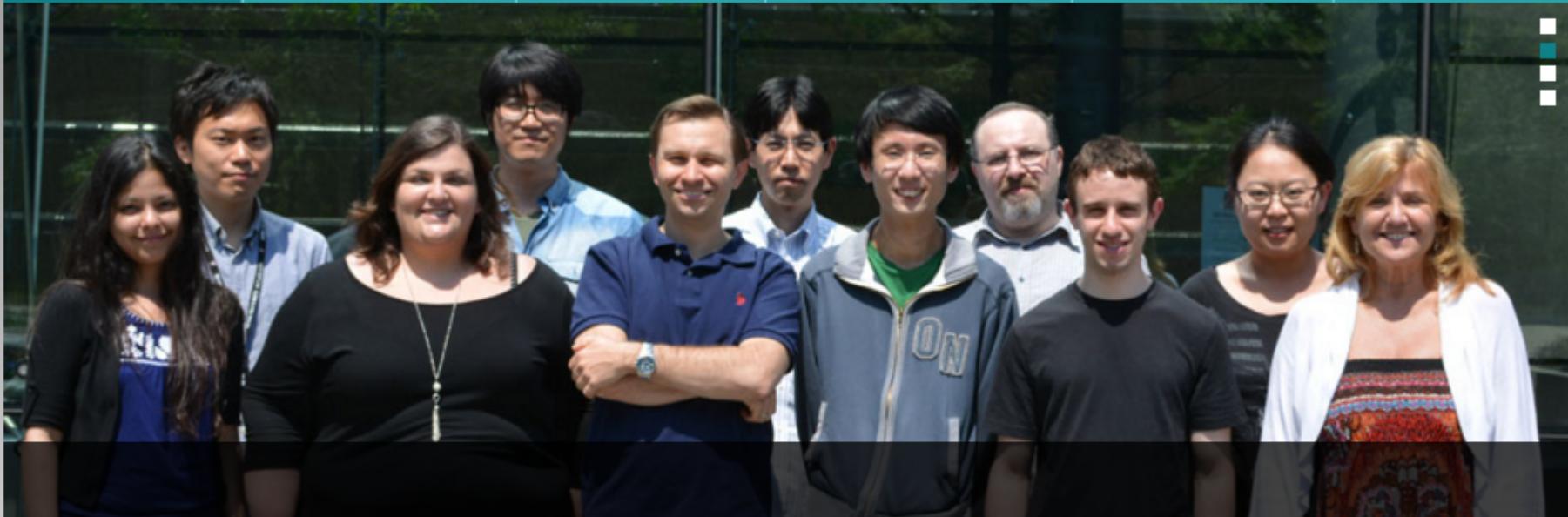
Research

People

Publications

Contact

Links



Welcome

The Sinclair Lab studies genes that slow the pace of aging. Work ranges from the isolation of novel stem cells from mouse and humans, to assessing small molecules that slow the pace of aging when fed to mice. Our goal is to uncover new biological processes that can be translated into radically different medicines to promote longer, more productive lives. A focus is on the Sirtuin genes and how they protect

David Sinclair



People



Research



C. elegans Ageing Laboratory (David Gems)

Understanding the biology of longevity and ageing using a nematode model

The nature of the biological mechanisms at the heart of the ageing process is one of the greatest unsolved mysteries in science. An ideal model organism in which to study ageing is the free-living nematode *Caenorhabditis elegans*. This species has well-developed genetics, its ~100 million base pair genome is fully sequenced, and its life span is a mere 2-3 weeks. Importantly, numerous mutations have been identified in *C. elegans* which alter the rate of ageing, with some mutants living up to 10-times longer than wild-type worms. By understanding ageing in a simple animal like *C. elegans* we hope to begin to unravel the mystery of human ageing, and the wide range of diseases that it causes, from cardiovascular disease and type II diabetes, to Alzheimer's disease and cancer.

A focus of current work in this laboratory is understanding the biological mechanisms that cause pathologies of ageing, and how such pathologies lead to mortality; and how reduced insulin/IGF-1 signalling and dietary restriction suppress ageing and increase lifespan. Other interests include the mechanisms of organismal death, sex differences in the biology of ageing, the role of the microbiome in ageing, evolutionary conservation of mechanisms of ageing, and bioethical implications of ageing research. Our work is largely funded by the European Union and the Wellcome Trust.

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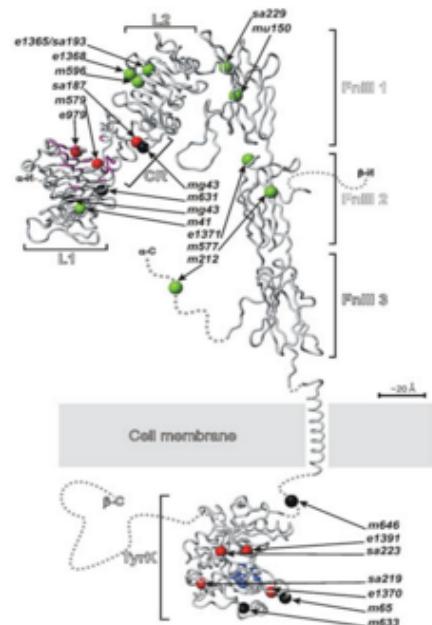
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Homology model of DAF-2 receptor showing mutant lesions. Green = class 1, red = class 2, black= non-conditional alleles (*Genetics*, 2008)

Links

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C. elegans Links

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PAUL F. GLENN CENTER FOR SCIENCE OF AGING RESEARCH AT MIT

Director: Dr. Leonard Guarente, Novartis Professor of Biology

We work on mechanisms of aging so that people may lead healthier lives.



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Welcome to the Glenn Laboratory for the Science of Aging at MIT! In operation since 1982, the lab is currently located in MIT's Koch Biology Building (Building

Keeps laboratory running by walking around and asking? "So what are the new discoveries you have made today?"



The free-living roundworm *Caenorhabditis elegans* is about 1 millimetre long.

A long journey to reproducible results

Replicating our work took four years and 100,000 worms but brought surprising discoveries, explain **Gordon J. Lithgow, Monica Driscoll and Patrick Phillips**.

About 15 years ago, one of us (G.J.L.) got an uncomfortable phone call from a colleague and collaborator. After nearly a year of frustrating experiments, this colleague was about to publish a paper¹ chronicling his team's inability to reproduce the results of our high-profile paper² in a mainstream journal. Our study was the first to show clearly that a drug-like molecule could extend an animal's lifespan. We had found over and over again that the treatment lengthened the life of a roundworm by

as much as 67%. Numerous phone calls and e-mails failed to identify why this apparently simple experiment produced different results between the labs. Then another lab failed to replicate our study. Despite more experiments and additional publications, we couldn't work out why the labs were getting different lifespan results. To this day, we still don't know.

A few years later, the same scenario played out with different compounds in other labs^{3,4}. Around the same time, there was a roiling debate about whether resveratrol — a

compound found in red wine — could extend lifespan in lab animals.

The possibility of drugs that stall ageing launched companies and a scientific subfield, but work in the field brought the realization that robust longevity outcomes could be challenging to replicate. Ageing research has long battled to distance itself from pseudoscientific claims. Irreproducible results from respected labs raised the spectre of yet more false promises. This had a chilling effect: some researchers (including G.J.L.) paused work on pharmacological compounds for years.

Nonetheless, scores of publications continued to appear with claims about compounds that slow ageing. There was little effort at replication. In 2013, the three of us were charged with that unglamorous task.

We have certainly not resolved discrepancies in the literature. But, by tracking the individual lifespans of more than 100,000 worms, we have found how crucial it is to understand sources of variability between labs and experiments. We even see hints of new biology that may explain discrepancies.

BROADER PROBLEM

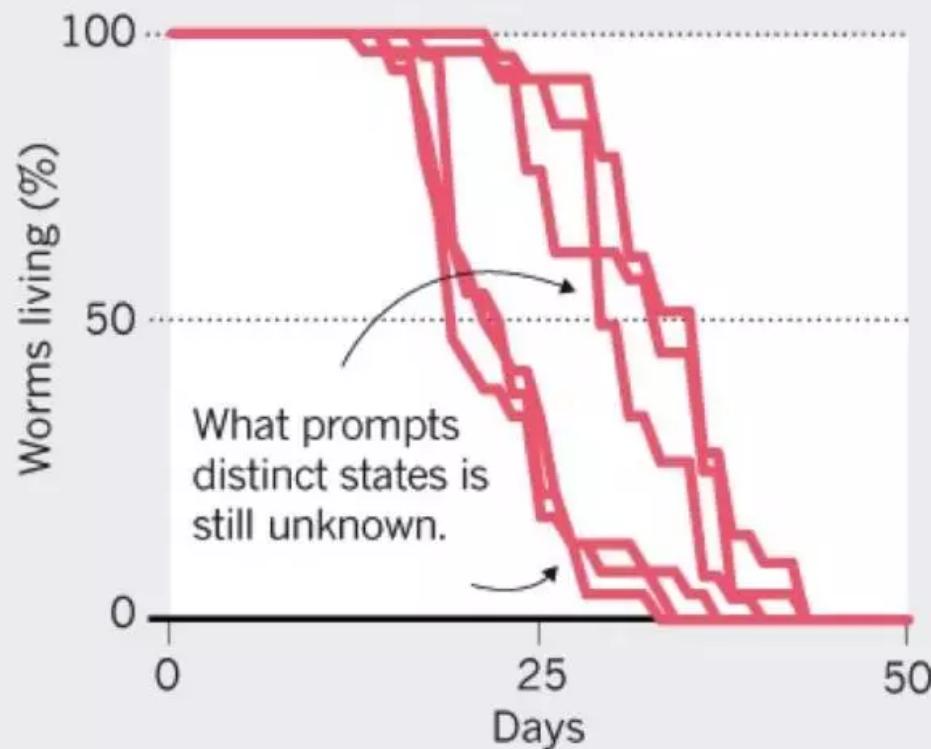
Improved reproducibility often comes from pinning down methods. Scientists studying autophagy — the process by which cells remove degraded components — have coordinated efforts to craft and update extensive guidelines on, for instance, how to quantify that a component has been engulfed or how to verify that a gene is involved in the process⁵. In another, now-famous example, two cancer labs spent more than a year trying to understand inconsistencies⁶. It took scientists working side by side on the same tumour biopsy to reveal that small differences in how they isolated cells — vigorous stirring versus prolonged gentle rocking — produced different results.

Subtle tinkering has long been important in getting biology experiments to work. Before researchers purchased kits of reagents for common experiments, it wasn't unheard of for a team to cart distilled water from one institution when it moved to another. Lab members would spend months tweaking conditions until experiments with the new institution's water worked as well as before.

Sources of variation include the quality and purity of reagents, daily ►

B Same strain, different lifespans

Each line represents an experimental run of 35 worms — in this case, *Caenorhabditis briggsae* strain ED3092.



Nothobranchius furzeri, an annual killifish

Aging Cell (2005) **4**, pp223–233

Doi: 10.1111/j.1474-9726.2005.00165.x

REVIEW

Annual fishes of the genus *Nothobranchius* as a model system for aging research

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Summary

Aging research in vertebrates is hampered by the lack of short-lived models. Annual fishes of the genus *Nothobranchius* live in East African seasonal ponds. Their life expectancy in the wild is limited by the duration of the wet season and their lifespan in captivity is also short. *Nothobranchius* are popular

Introduction

Annual fishes are a group of teleosts that successfully colonized seasonal bodies of water by producing desiccation-resistant eggs which survive the dry season (Jubb, 1981). Their life expectancy in the wild cannot exceed the seasonal duration of their habitat and their extrinsic mortality probability is basically rectangular. They therefore represent an excellent model to study the effects of extrinsic mortality rate on the evolution of senescence.

American annual fishes of the genus *Cynolebias* (now *Austrolebias*) were studied by Walford and colleagues in the 1960s and 1970s (Walford *et al.*, 1969; Liu & Walford, 1970; Liu *et al.*, 1975). The African annual fish *Nothobranchius guentheri* was studied by Markofsky and colleagues in the 1970s (Markofsky & Perlmutter, 1972; Markofsky, 1976; Markofsky & Matias, 1977; Markofsky & Milstoc, 1979a,b). These researchers reported

Summary

Aging research in vertebrates is hampered by the lack of short-lived models. Annual fishes of the genus *Nothobranchius* live in East African seasonal ponds. Their life expectancy in the wild is limited by the duration of the wet season and their lifespan in captivity is also short. *Nothobranchius* are popular aquarium fishes and many different species are kept as captive strains, providing rich material for comparative studies. The present paper aims at reviving the interest in these fishes by reporting that: (1) *Nothobranchius* can be cultured, and their eggs stored dry at room temperature for months or years, offering inexpensive methods of embryo storage; (2) *Nothobranchius* show accelerated growth and expression of aging biomarkers at the level of histology and behaviour; (3) the species *Nothobranchius furzeri* has a maximum lifespan of only 3 months and offers the possibility to perform investigations thus far unthinkable in a vertebrate, such as drug screening with life-long pharmacological treatments and experimental evolution; (4) when the lifespan of different species is compared, a general correlation is found between wet season duration in their natural habitat and longevity in captivity; and (5) vertebrate aging-related genes, such as *p66Shc* and *MTP*, can be easily isolated in *Nothobranchius* by homology cloning. These fishes can become excellent models for aging studies. They can be employed to test the effects of experimental manipulation on aging at a pace comparable with that of *Drosophila* and to probe the effects of natural selection on the evolution of aging-related genes.



New Results

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Regulation of Life Span by the Gut Microbiota in The Short-Lived African Turquoise Killifish

Patrick Smith, David Willemsen, Miriam Lea Popkes, Franziska Metge, Edson Gandiwa, Martin Reichard,
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doi: <https://doi.org/10.1101/120980>

Now published in eLife doi: [10.7554/eLife.27014](https://doi.org/10.7554/eLife.27014)

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Abstract

Gut bacteria occupy the interface between the organism and the external environment, contributing to homeostasis and disease. Yet, the causal role of the gut microbiota during host aging is largely unexplored. Here, using the African turquoise killifish (*Nothobranchius furzeri*), a naturally short-lived vertebrate, we show that the gut microbiota plays a key role in modulating vertebrate life span. Recolonizing the gut of middle-age individuals with bacteria from young donors resulted in life span extension and delayed behavioral decline. This intervention prevented the decrease in microbial diversity associated with host aging and maintained a young-like gut bacterial community, characterized by overrepresentation of the key genera *Exiguobacterium*, *Planococcus*, *Propionigenium* and *Psychrobacter*. Our findings demonstrate that the natural microbial gut community of young individuals can causally induce long-lasting beneficial systemic effects that lead to life span extension in a vertebrate model.



GENOMICS AND EVOLUTIONARY BIOLOGY, MICROBIOLOGY AND INFECTIOUS DISEASE



Regulation of life span by the gut microbiota in the short-lived African turquoise killifish

Patrick Smith, David Willemsen, Miriam Popkes, Franziska Metge, Edson Gandiwa, Martin Reichard, Dario Riccardo Valenzano 

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RESEARCH ARTICLE Aug 22, 2017

CITED 1 VIEWS 3,452 COMMENTS 0

CITE AS: eLife 2017;6:e27014 DOI: 10.7554/eLife.27014

Article

Figures and data

Side by side

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Abstract

Gut bacteria occupy the interface between the organism and the external environment, contributing to homeostasis and disease. Yet, the causal role of the gut microbiota during host aging is largely unexplored. Here, using the African turquoise killifish (*Nothobranchius furzeri*), a naturally short-lived vertebrate, we show that the gut microbiota plays a key role in modulating vertebrate life span. Recolonizing the gut of middle-age individuals with bacteria from young donors resulted in life span extension and delayed behavioral decline. This intervention prevented the decrease in microbial diversity associated with host aging and maintained a young-like gut bacterial community, characterized by overrepresentation of the key genera *Exiguobacterium*, *Planococcus*, *Propionigenium* and *Psychrobacter*. Our findings demonstrate that the natural microbial gut community of young individuals can causally induce long-lasting beneficial systemic effects that lead to life span extension in a vertebrate model.

OF INTEREST

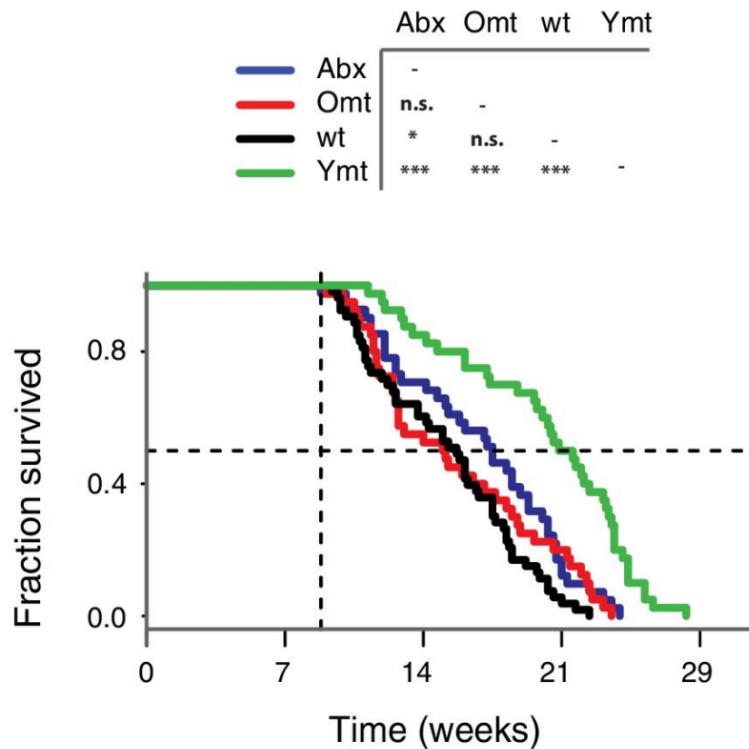
Functional divergence of paralogous transcription factors supported the evolution of biomineralization in echinoderms

Jian Ming Khor, Charles A Ettensohn

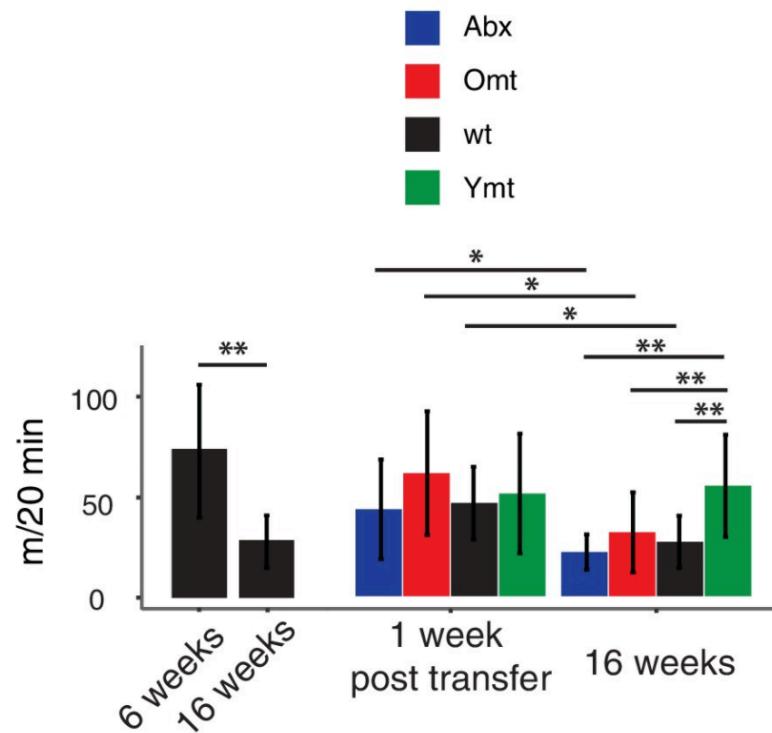
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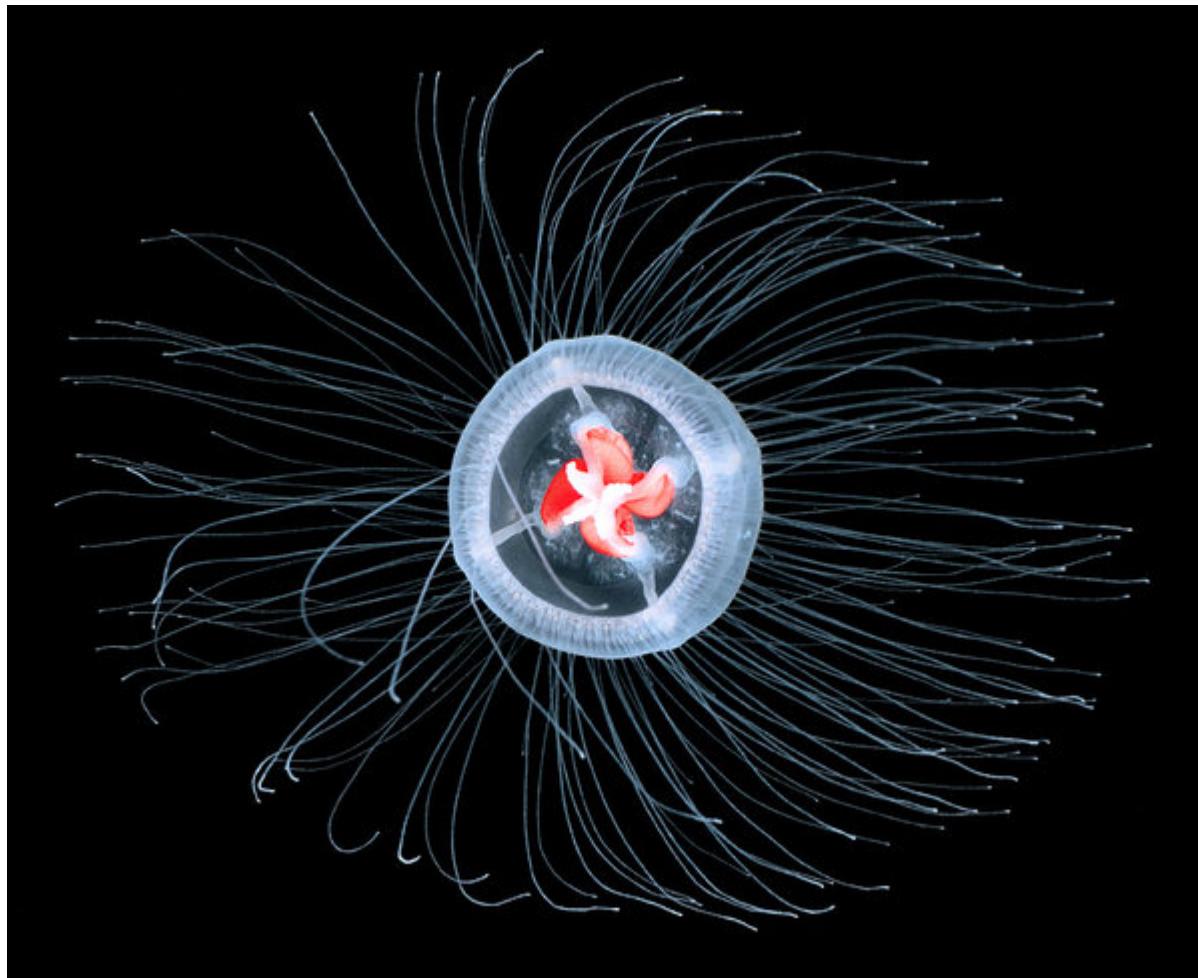
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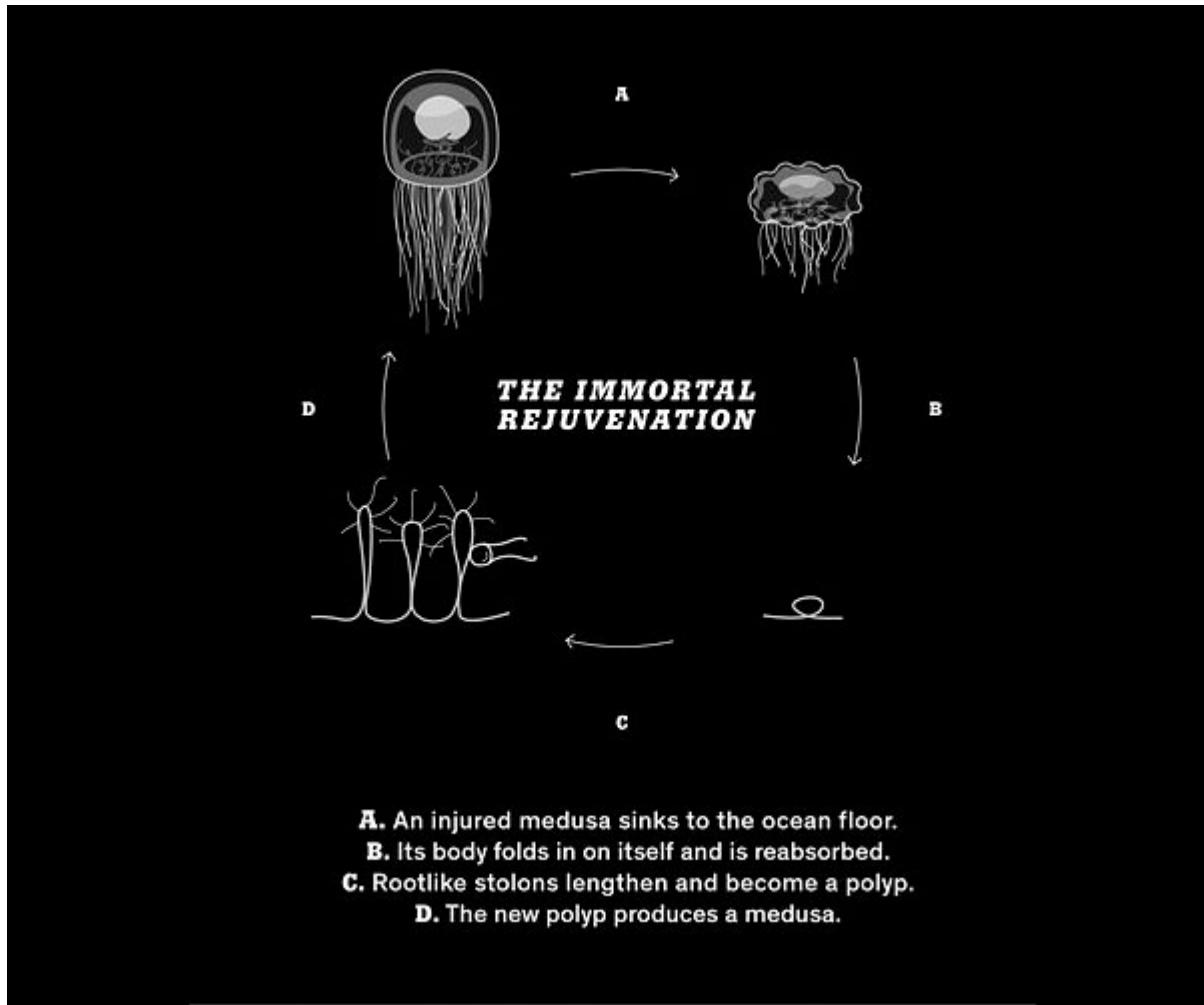


Transferring young GM to adult fish prolongs life span and delays motor decline.

(A) Schematic representation of the microbial transfer experiment (Materials and methods). Experimental group legend, Abx: fish receiving only antibiotic treatment at 9.5 weeks without direct recolonization. Omt: fish receiving same-age GM transfer after antibiotic treatment at 9.5 weeks. Wt: wild-type, untreated fish. Ymt: fish receiving 6-week-old fish GM transfer after antibiotic treatment at 9.5 weeks. VMNA: antibiotic cocktail of vancomycin, metronidazole, neomycin and ampicillin. **(B)** Survival analysis. Statistical significance is calculated by Logrank test. * indicates a p value < 0.05; *** indicates a p value < 0.001. **(C)** Exploratory behavior in different treatments. Y-axis indicates average distance (in meters) covered in 20 min. Young and old wild-types are compared with a Kruskal-Wallis test (left), the remaining groups are compared using a Dunn Kruskal-Wallis test for multiple comparisons, and the p values are adjusted based on BH correction. Statistical significance: * indicates a p value < 0.05; ** indicates a p value < 0.01; *** indicates a p value < 0.001.

Turritopsis dohrnii (灯塔水母), the immortal jellyfish





Regeneration of the aged thymus

© 2014. Published by The Company of Biologists Ltd | Development (2014) 141, 1627-1637 doi:10.1242/dev.103614



RESEARCH ARTICLE

STEM CELLS AND REGENERATION

Regeneration of the aged thymus by a single transcription factor

Nicholas Bredenkamp*, Craig S. Nowell† and C. Clare Blackburn§

ABSTRACT

Thymic involution is central to the decline in immune system function that occurs with age. By regenerating the thymus, it may therefore be possible to improve the ability of the aged immune system to respond to novel antigens. Recently, diminished expression of the thymic epithelial cell (TEC)-specific transcription factor Forkhead box N1 (FOXN1) has been implicated as a component of the mechanism regulating age-related involution. The effects of upregulating FOXN1 function in the aged thymus are, however, unknown. Here, we show that forced, TEC-specific upregulation of FOXN1 in the fully involuted thymus of aged mice results in robust thymus regeneration characterized by increased thymopoiesis and increased naïve T cell output. We demonstrate that the regenerated organ closely resembles the juvenile thymus in terms of architecture and gene expression profile, and further show that this FOXN1-mediated regeneration stems from an enlarged TEC compartment, rebuilt from progenitor TECs. Collectively, our data establish that upregulation of a single transcription factor can substantially reverse age-related thymic involution, identifying FOXN1 as a specific target for improving thymus function and, thus, immune competence in patients. More widely, they demonstrate that organ regeneration in an aged mammal can be directed by manipulation of a single transcription factor, providing a provocative paradigm that may be of broad impact for regenerative biology.

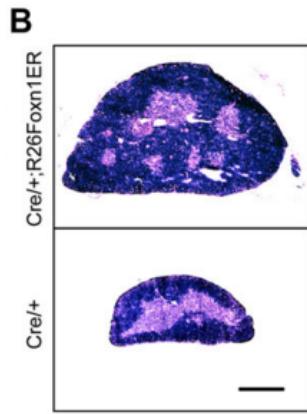
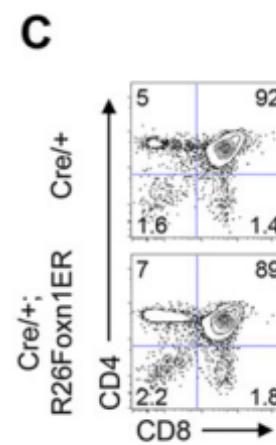
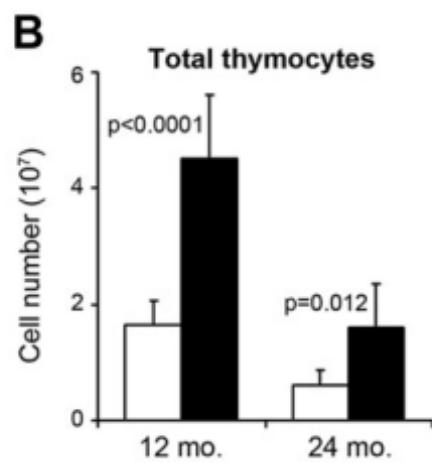
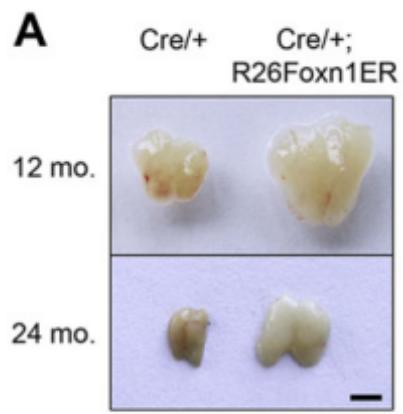
KEY WORDS: Thymic involution, FOXN1, Organ regeneration, Mouse

in a wide variety of clinical settings, and consequently a number of strategies aimed at regenerating the aged thymus are currently under investigation (van den Brink et al., 2004; Holland and van den Brink, 2009; Markert et al., 2009).

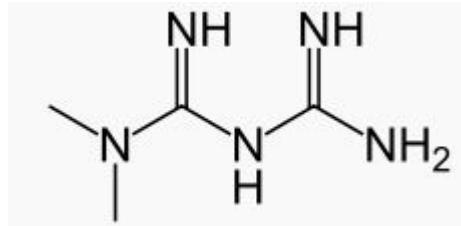
The epithelial component of the thymic stroma is essential for intrathymic T cell development and undergoes a stereotypical age-related degeneration that is strongly implicated as a cause of age-related thymic involution (Mackall et al., 1998; Gray et al., 2006; Williams et al., 2008). The key transcription factor FOXN1 (Nehls et al., 1996) is crucially required throughout thymic epithelial cell (TEC) differentiation in the fetal and postnatal thymus (Chen et al., 2009; Nowell et al., 2011) and is downregulated with age in the thymic stroma (Ortmann et al., 2002; Chen et al., 2009; Zook et al., 2011). Forced downregulation of *Foxn1* in the perinatal thymic epithelium results in loss of thymus homeostasis (Chen et al., 2009), while overexpression in young mice delays thymus degeneration (Zook et al., 2011). FOXN1 is thus implicated as one of the primary targets in age-related thymic involution.

Sex-steroid signaling is also thought to be an important regulator of involution. However, castration-induced thymic rebound was recently demonstrated to reflect enlargement of a thymus with an aged phenotype rather than restoration of the functionality and architecture of the young organ (Griffith et al., 2012). Therefore, the clinically important question of whether the effects of established age-related thymic involution can be reversed to drive rejuvenation of the fully involuted, aged thymus remains unanswered.

Induction of FOXN1 drives thymus regeneration in aged mice



Metfomin (二甲双胍)



BY T. NIKOLAEVGETTY

"We are going to dance in the streets."

The AKP's grip on science extends beyond YÖK. In 2005, Erdogan began to place political loyalists in top posts at Turkey's research-funding agency TÜBİTAK, which had previously enjoyed a degree of autonomy. Many of them were from the Gülen movement — a transnational religious and social organization. Scientists say that research funds were no longer distributed according to merit and that the agency has seemed to be anti-evolution. In 2009, TÜBİTAK removed a portrait of Charles Darwin from a cover of a government-backed science magazine and sacked the editor (see *Nature* 458, 259; 2009). Under the AKP, which turned Turkey from a constitutionally secular nation to one where religion is state-sponsored, creationism is often taught in schools and debated in universities. (The AKP fell out with the Gülenists in 2013 and purged them from TÜBİTAK, leaving it in chaos.)

In 2011, the science ministry assumed control of the Turkish Academy of Sciences, TÜBA. It decreed that TÜBİTAK and YÖK would appoint two-thirds of TÜBA's members, who would then elect the remaining one-third. Most of TÜBA's original members resigned in protest and launched another national academy, Bilim Akademisi, which has regularly challenged science standards.

Earlier this month, the academy, of which Alpar is president, identified two universities that had approved theses and certificates in astrology, and called on YÖK not to allow such unscientific practices. It also contested a government order forbidding university researchers from interviewing refugees without government supervision. The academy argued that the government's claim that the interviews would infringe data-protection laws was invalid.

Until a new government forms, the AKP remains in charge. It irked scientists further on 11 June by appointing Ahmet Arif Ergin as head of TÜBİTAK. "It is extremely undemocratic and inappropriate for a caretaker government to make such an important political appointment," says Mungan.

But the election results have brought hope.



Researchers hope to find drugs that extend a person's healthy years.

CLINICAL RESEARCH

Ageing pushed as treatable condition

Regulators asked to consider innovative trial design.

BY ERIKA CHECK HAYDEN

Doctors and scientists want drug regulators and research funding agencies to consider medicines that delay ageing-related disease as legitimate drugs. Such treatments have a physiological basis, researchers say, and could extend a person's healthy years by slowing down the processes that underlie common diseases of ageing — making them worthy of government approval. On 24 June, researchers will meet with regulators from the US Food and Drug Administration (FDA) to make the case for

them. People with type 2 diabetes cannot be enrolled because metformin is already used to treat that disease. The participants will then be monitored to see whether the medication forestalls the illnesses they do not already have, as well as diabetes and death.

On 24 June, researchers will try to convince FDA officials that if the trial succeeds, they will have proved that a drug can delay ageing. That would set a precedent that ageing is a disorder that can be treated with medicines, and perhaps spur progress and funding for ageing research.

"What we're

During a meeting

An Ancient, Unified Mechanism for Metformin Growth Inhibition in *C. elegans* and Cancer

Lianfeng Wu,^{1,2,3,4} Ben Zhou,^{1,2,3,4} Noriko Oshiro-Rapley,⁵ Man Li,⁶ Joao A. Paulo,⁷ Christopher M. Webster,^{1,2,3,4} Fan Mou,⁶ Michael C. Kacergis,^{1,2} Michael E. Talkowski,^{2,8} Christopher E. Carr,^{5,9} Steven P. Gygi,⁷ Bin Zheng,⁶ and Alexander A. Soukas^{1,2,3,4,10,*}

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<http://dx.doi.org/10.1016/j.cell.2016.11.055>

SUMMARY

Metformin has utility in cancer prevention and treatment, though the mechanisms for these effects remain elusive. Through genetic screening in *C. elegans*, we uncover two metformin response elements: the nuclear pore complex (NPC) and acetyl-CoA dehydrogenase family member-10 (ACAD10). We demonstrate that biguanides inhibit growth by inhibiting mitochondrial respiratory capacity, which restrains transit of the RagA-RagC GTPase heterodimer through the NPC. Nuclear exclusion renders RagC incapable of gaining the GDP-bound state necessary to stimulate mTORC1. Biguanide-induced inactivation of mTORC1 subsequently inhibits growth through transcriptional induction of

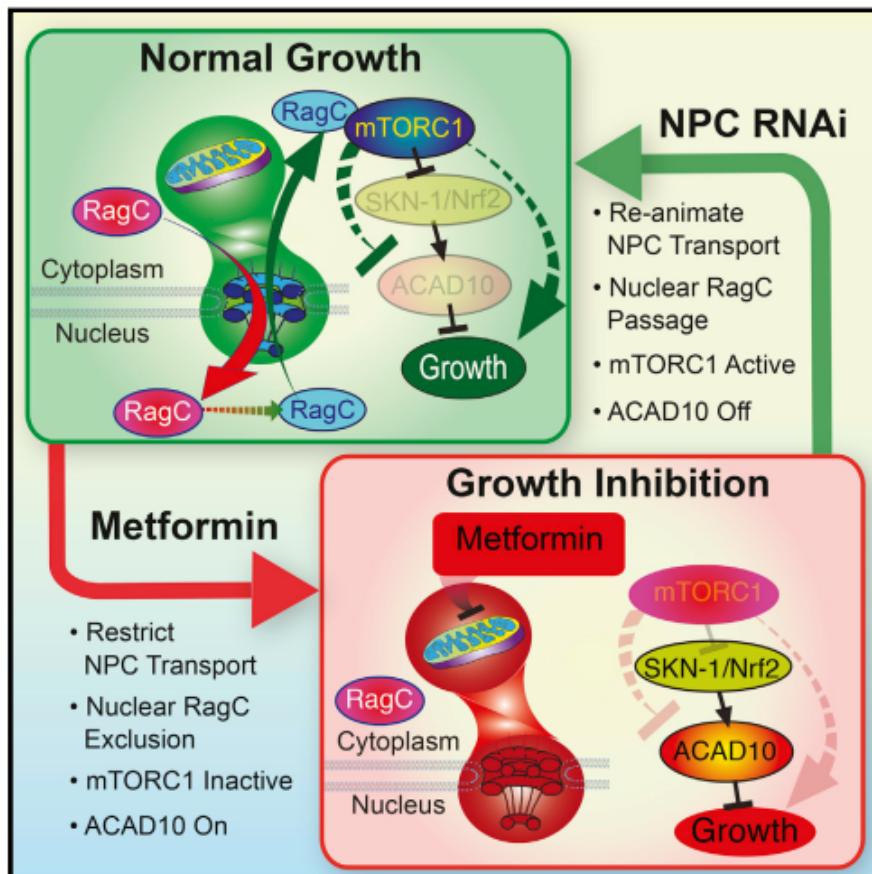
cellular growth in a variety of cancer cell lines, particularly in melanoma (Yuan et al., 2013) and pancreatic cancer cells (Kordes et al., 2015). While it is widely accepted that the mitochondrion is a primary target of metformin (Griss et al., 2015; Owen et al., 2000; Wheaton et al., 2014), exactly how mitochondrial inhibition by metformin is transduced to the drug's other health-promoting effects, including its anticancer properties, remains unclear.

Mitochondrial inhibition by metformin causes energetic stress, which results in activation of the energy sensor adenosine monophosphate-activated protein kinase (AMPK) (Zhou et al., 2001). However, multiple lines of evidence indicate that AMPK is dispensable for metformin's beneficial effects (Foretz et al., 2010; Griss et al., 2015; Kalender et al., 2010), invoking other major metformin effectors downstream of mitochondria.

The protein kinase mechanistic target of rapamycin complex 1 (mTORC1), which also serves as an energy and nutrient sensor, plays a central role in regulating cell growth, proliferation and

An Ancient, Unified Mechanism for Metformin Growth Inhibition in *C. elegans* and Cancer

Graphical Abstract



Authors

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Noriko Oshiro-Rapley, ..., Steven P. Gygi,
Bin Zheng, Alexander A. Soukas

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In Brief

Metformin both suppresses cancer cell growth and promotes organismal longevity through a key transcriptional target that is induced through inhibition of mitochondrial respiration and modulation of mTOR signaling.



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Faculty Profile

Nir Barzilai, M.D.



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Dr. Barzilai's expert
profile



Professional Interests

Dr. Nir Barzilai is the director of the Institute for Aging Research at the Albert Einstein College of Medicine and the Director of the Paul F. Glenn Center for the Biology of Human Aging Research and of the National Institutes of Health's (NIH) Nathan Shock Centers of Excellence in the Basic Biology of Aging. He is the Ingeborg and Ira Leon Rennert Chair of Aging Research, professor in the Departments of Medicine and Genetics, and member of the Diabetes Research Center and of the Divisions of Endocrinology & Diabetes and Geriatrics.

Media Coverage

In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming

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<http://dx.doi.org/10.1016/j.cell.2016.11.052>

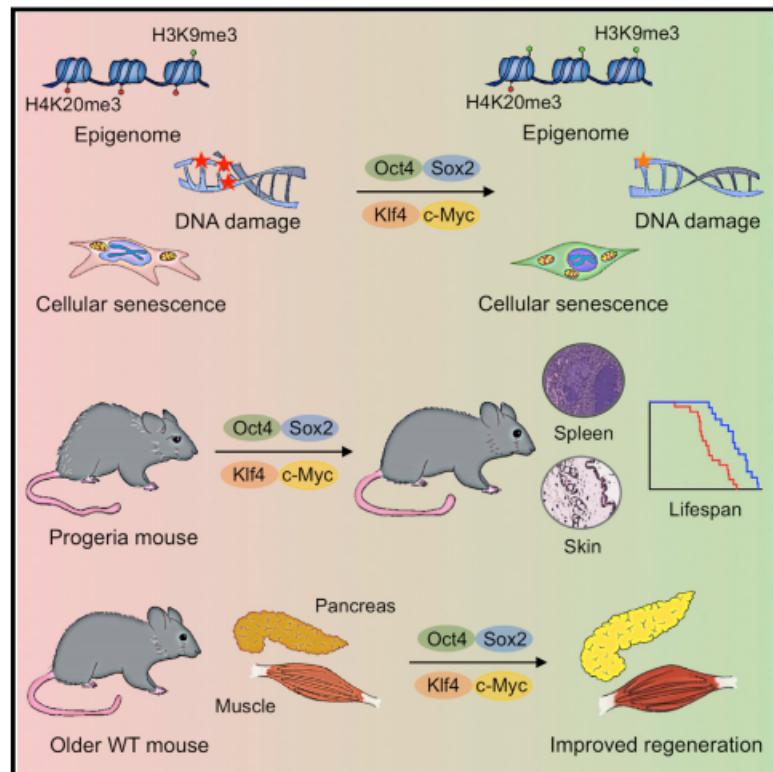
SUMMARY

Aging is the major risk factor for many human diseases. In vitro studies have demonstrated that cellular reprogramming to pluripotency reverses cellular age, but alteration of the aging process through reprogramming has not been directly demonstrated *in vivo*. Here, we report that partial reprogramming by short-term cyclic expression of Oct4, Sox2, Klf4, and c-Myc (OSKM) ameliorates cellular and physiological hallmarks of aging and prolongs lifespan in a mouse model of premature aging. Similarly, expression of OSKM *in vivo* improves recovery from metabolic disease and muscle injury in older wild-type mice. The amelioration of age-associated phenotypes by epigenetic remodeling during cellular reprogramming highlights the role of epigenetic dysregulation as a driver of mammalian aging. Establishing *in vivo* platforms to modulate age-associated epigenetic marks may provide

et al., 2013; Kenyon, 2010; Riera et al., 2016). The notion that cells undergo a unidirectional differentiation process during development was proved wrong by the experimental demonstration that a terminally differentiated cell can be reprogrammed into a pluripotent embryonic-like state (Gurdon, 1962; Takahashi and Yamanaka, 2006). Cellular reprogramming to pluripotency by forced expression of the Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc [OSKM]) occurs through the global remodeling of epigenetic marks (Buganim et al., 2012, 2013; Hansson et al., 2012; Polo et al., 2012). Importantly, many of the epigenetic marks that are remodeled during reprogramming (e.g., DNA methylation, post-translational modification of histones, and chromatin remodeling) are dysregulated during aging (Benayoun et al., 2015; Liu et al., 2013b; Pollina and Brunet, 2011). In fact, epigenetic dysregulation has emerged as a key hallmark of the aging process (Sen et al., 2016). Several groups, including ours, have observed an amelioration of age-associated cellular phenotypes during *in vitro* cellular reprogramming (Lapasset et al., 2011; Liu et al., 2011; Mahmoudi and Brunet, 2012; Rando and Chang, 2012). Reprogramming of cells from centenarians or patients with Hutchinson-Gilford progeria syn-

In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming

Graphical Abstract



Authors

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In Brief

Cellular reprogramming by transient expression of Yamanaka factors ameliorates age-associated symptoms, prolongs lifespan in progeroid mice, and improves tissue homeostasis in older mice.

Highlights

- Partial reprogramming erases cellular markers of aging in mouse and human cells
- Induction of OSKM in progeria mice ameliorates signs of aging and extends lifespan
- In vivo reprogramming improves regeneration in 12-month-old wild-type mice

Targeting cellular senescence prevents age-related bone loss in mice

Joshua N Farr^{1,2}, Ming Xu^{1,2}, Megan M Weivoda^{1,2}, David G Monroe¹, Daniel G Fraser¹, Jennifer L Onken¹, Brittany A Negley¹, Jad G Sfeir¹ , Mikolaj B Ogrodnik¹, Christine M Hachfeld¹, Nathan K LeBrasseur¹, Matthew T Drake¹, Robert J Pignolo¹, Tamar Pirtskhala¹, Tamara Tchkonia¹, Merry Jo Oursler¹, James L Kirkland¹ & Sundeep Khosla¹ 

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Aging is associated with increased cellular senescence, which is hypothesized to drive the eventual development of multiple comorbidities¹. Here we investigate a role for senescent cells in age-related bone loss through multiple approaches. In particular, we used either genetic (i.e., the *INK-ATTAC* 'suicide' transgene encoding an inducible caspase 8 expressed specifically in senescent cells^{2–4}) or pharmacological (i.e., 'senolytic' compounds^{5,6}) means to eliminate senescent cells. We also inhibited the production of the proinflammatory secretome of senescent cells using a JAK inhibitor (JAKi)^{3,7}. In aged (20- to 22-month-old) mice with established bone loss, activation of the *INK-ATTAC* caspase 8 in senescent cells or treatment with senolytics or the JAKi for 2–4 months resulted in higher bone mass and strength and better bone microarchitecture than in vehicle-treated mice. The beneficial effects of targeting senescent cells were due to lower bone resorption with either maintained (trabecular) or higher (cortical) bone formation as compared to vehicle-treated mice. *In vitro* studies demonstrated that senescent-cell conditioned medium impaired osteoblast mineralization and enhanced osteoclast-progenitor survival, leading to increased osteoclastogenesis. Collectively, these data establish a causal role for senescent cells in bone loss with aging, and demonstrate that targeting these cells has both anti-resorptive and anabolic effects on bone. Given that eliminating senescent cells and/or inhibiting their proinflammatory secretome also improves cardiovascular function⁴, enhances insulin sensitivity³, and reduces frailty⁷, targeting this fundamental mechanism to prevent age-related bone loss suggests a novel treatment strategy not only for osteoporosis, but also for multiple age-related comorbidities.

characterized by profound chromatin and secretome changes. Cellular senescence is also associated with increased expression of the senescence biomarker *p16^{Ink4a}* (also known as *Cdkn2a*) and resistance to apoptosis^{1,17}. In addition, senescent cells can develop the senescence-associated secretory phenotype (SASP), consisting of proinflammatory cytokines, chemokines, and extracellular matrix-degrading proteins, which have deleterious paracrine and systemic effects^{3,18–20}. Indeed, even a relatively low abundance of senescent cells (for example, ~10–15% in aged primates²¹) is sufficient to cause tissue dysfunction. We recently demonstrated that with aging, multiple cell types in the bone microenvironment become senescent, although senescent myeloid cells and senescent osteocytes predominantly develop the SASP¹⁶. Consistent with this, further characterization revealed that *p16^{Ink4a}* expression in mouse osteocytes increases markedly after ~18 months of age in both sexes (**Supplementary Fig. 1a,b**), coinciding with the timing of accelerated age-related bone loss in both female and male mice (**Supplementary Fig. 1c–j**)^{22,23}.

Eliminating a relatively small proportion (~30%) of senescent cells using a 'suicide' transgene, *INK-ATTAC*, that permits inducible elimination of *p16^{Ink4a}*-expressing senescent cells upon the administration of a drug (AP20187; **Supplementary Fig. 2**) extends health span and prevents the development of multiple age-related morbidities in both progeroid and normal, chronologically aged mice^{2–4}. However, the skeletal phenotype of these animals has not been characterized, and the potential role of senescent cells in age-related bone loss has not been investigated. To test the hypothesis that senescent cells mediate age-related bone loss, female *INK-ATTAC* transgenic mice^{2–4} were randomized to either vehicle or AP20187 treatment twice weekly for 4 months, starting at 20 months of age (**Fig. 1a**). As anticipated, AP20187 treatment resulted in markedly lower *p16^{Ink4a}* mRNA expression (by ~59%) in bone relative to that in vehicle-treated mice

Clinical Management of the Older Adult

The Clinical Potential of Senolytic Drugs

James L. Kirkland MD, PhD , Tamara Tchkonia PhD, Yi Zhu PhD,

Laura J. Niedernhofer MD, PhD, Paul D. Robbins PhD

First published: 4 September 2017 [Full publication history](#)

DOI: 10.1111/jgs.14969 [View/save citation](#)

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Funding Information



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Volume 65, Issue 10

October 2017

Pages 2297-2301

Abstract

Senolytic drugs are agents that selectively induce apoptosis of senescent cells. These cells accumulate in many tissues with aging and at sites of pathology in multiple chronic diseases. In studies in animals, targeting senescent cells using genetic or pharmacological approaches delays, prevents, or alleviates multiple age-related phenotypes, chronic diseases, geriatric syndromes, and loss of physiological resilience. Among the chronic conditions successfully treated by depleting senescent cells in preclinical studies are frailty, cardiac dysfunction, vascular hyporeactivity and calcification, diabetes mellitus, liver steatosis, osteoporosis, vertebral disk degeneration, pulmonary fibrosis, and radiation-induced damage. Senolytic agents are being tested in proof-of-concept clinical trials. To do so, new clinical trial paradigms for testing senolytics and other agents that target fundamental aging mechanisms are being developed, because use of long-term endpoints such as lifespan or healthspan is not feasible. These strategies include testing effects on multimorbidity, accelerated aging-like conditions, diseases with localized accumulation of senescent cells, potentially fatal diseases associated with senescent cell accumulation, age-related loss of physiological resilience, and frailty. If senolytics or other interventions that target fundamental aging processes prove to be effective and safe in clinical trials, they could transform geriatric medicine by enabling prevention or treatment of multiple diseases and functional deficits in parallel, instead of one at a time.

Thanks!

Cell里程碑！新分子逆转“衰老”，未发现任何明显副作用

原创 2017-03-25 Chen 生物探索

生物探索 编者按

抗衰老研究一直是一个热门领域。科学家们试图通过各种方式找到“青春之泉”。日前，发表在Cell杂志上的一项研究再次获得了里程碑式的进展。来自荷兰的一个科学家小组发现了一种分子能够选择性地破坏衰老细胞，逆转衰老的影响。值得一提的是，用该分子处理小鼠超过10个月的时间，没有发现任何明显的副作用。



Nature趣闻：吃年轻鱼的便便，让老年鱼更长寿！

原创 2017-04-06 漱石 生物探索

生物探索 编者按

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