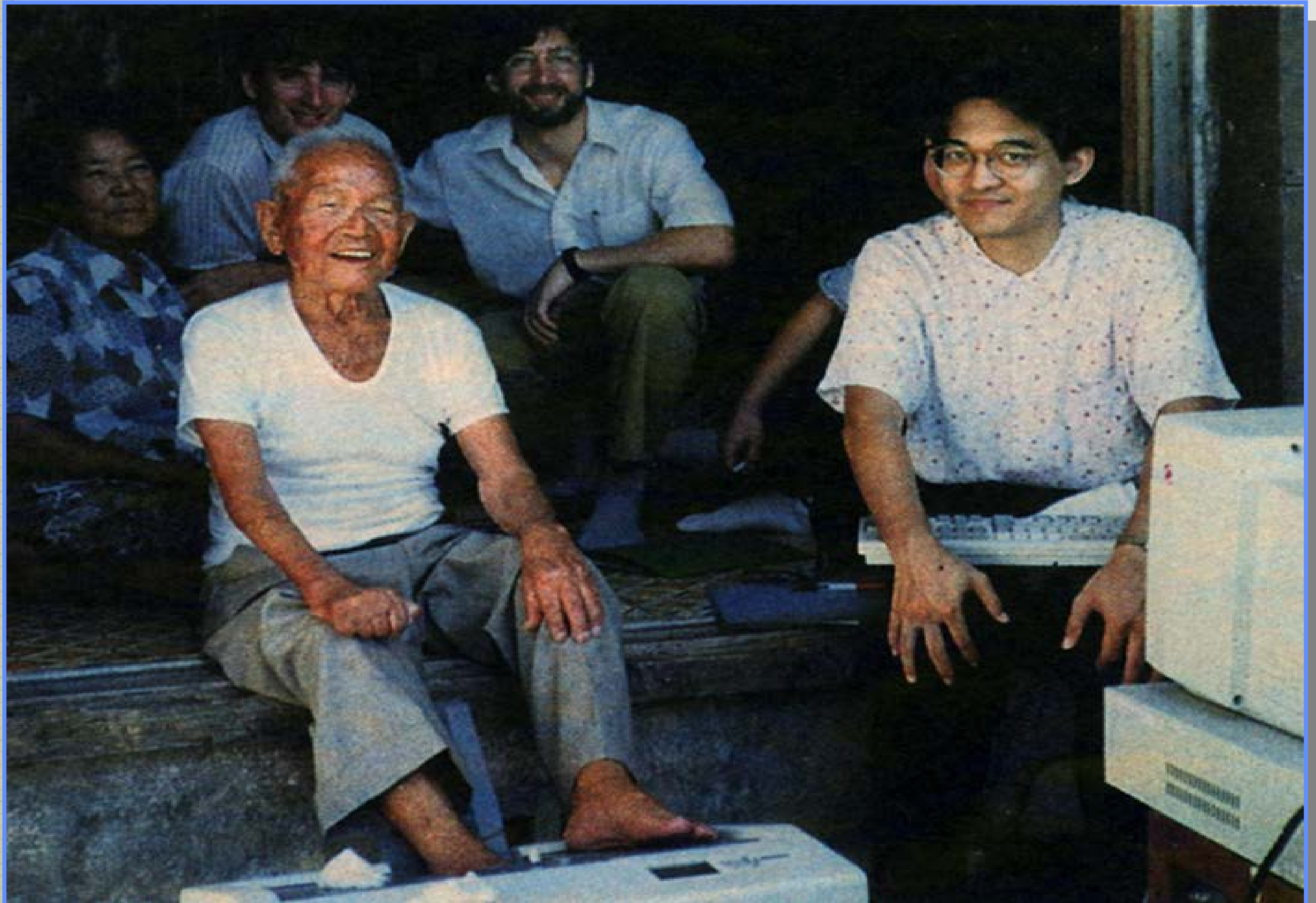


# Beneficial Dietary Patterns: Impact on Longevity & Lifespan



D. Craig Willcox & the Kuakini Hawaii LIFESPAN Study Research Group  
Dept. of Research, Kuakini Medical Center & Dept of Geriatric Medicine,  
University of Hawaii & Dept. of Human Welfare, Okinawa International Univ.

# Healthy and Independent at 100 years old is Possible





# *Okinawa Centenarian Study : Methods*

- ❖ Population-based study  
(1000+ cases 1976- present)
- ❖ Cross-sectional, longitudinal, case-control
- ❖ Age validation
- ❖ Geriatric exam; past medical & social history; health habits, anthropometry, ECG
- ❖ Family pedigree
- ❖ Activities of Daily Living (ADLs/IADLs)
- ❖ Psychosocial/cognitive tests
- ❖ Biobanking: Blood and saliva







Japanese-  
American  
centenarian, age  
101 years

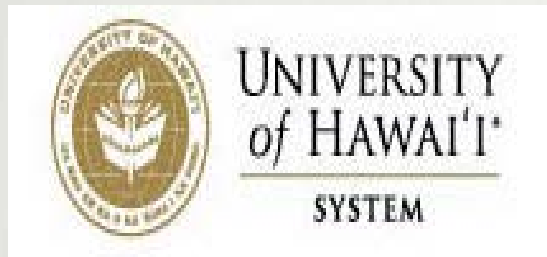
# Kuakini Honolulu Heart Program Aging Studies

## POPULATION

- 8,006 middle-aged American men of Japanese ancestry from the Honolulu Heart Program, studied with 13 full exams since 1965
  - > now over 1200 nonagenarians and centenarians
- 
- **Kuakini Honolulu Asia Aging Study**
    - dementia, Parkinson's disease, brain autopsy study
  - **Kuakini Hawaii LIFESPAN Study**
    - quantify aging , understand genetic and non-genetic factors for healthy aging and longevity
  - **Kuakini Hawaii HEALTHSPAN Study**
    - understand gene pathways and networks for healthy aging
  - **Kuakini Honolulu Heart Program Offspring Study**
    - next generation study of aging in men and women
  - **Kuakini Hawaii Healthspan Program Project Grant Proposal**
    - from molecular, cellular, tissue, mouse →→ human (body, brain)



# Honolulu Heart Program and OCS Team



**LIFESPAN/HEALTHSPAN Studies PI:** B. Willcox, MD

**Genetics Lab:** T. Donlon, PhD; A. Elliot, BS

**Biostatistics/Bioinformatics:** J. Grove, PhD

Q. He, PhD

**Programmers:** R. Chen, MS; K. Fong, MS, E. Ardo, MS

**Medical Exams/Autopsy/Phenotyping:** K. Masaki, MD; The “A” Team  
(Ruth Medcalf, Taryn Phan, Angie Moong, Vanessa Cunanan)

**Biorepository:** E. Ardo, MS

**Study Coordinators:** C. Imamura; H. Nakada

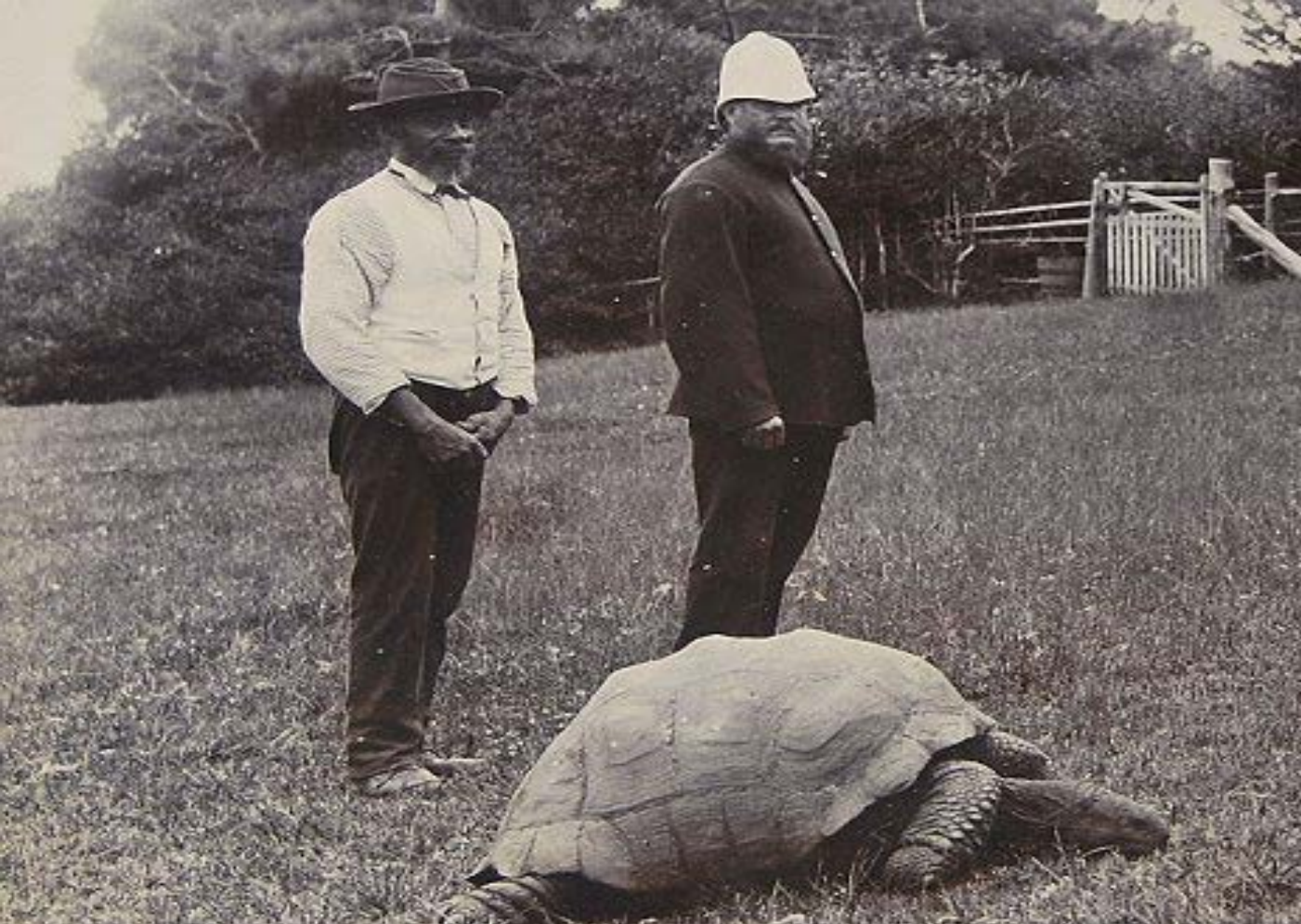
**Recruiter:** Atsuko Pritchard

**Okinawa Team:** DC Willcox, PhD; M. Suzuki, MD



***Is there a Common  
Mechanism  
for Aging? Is it  
Malleable?***





Permission: NOAA Photo Library by Creative Commons



Permission: BNPS.CO.UK



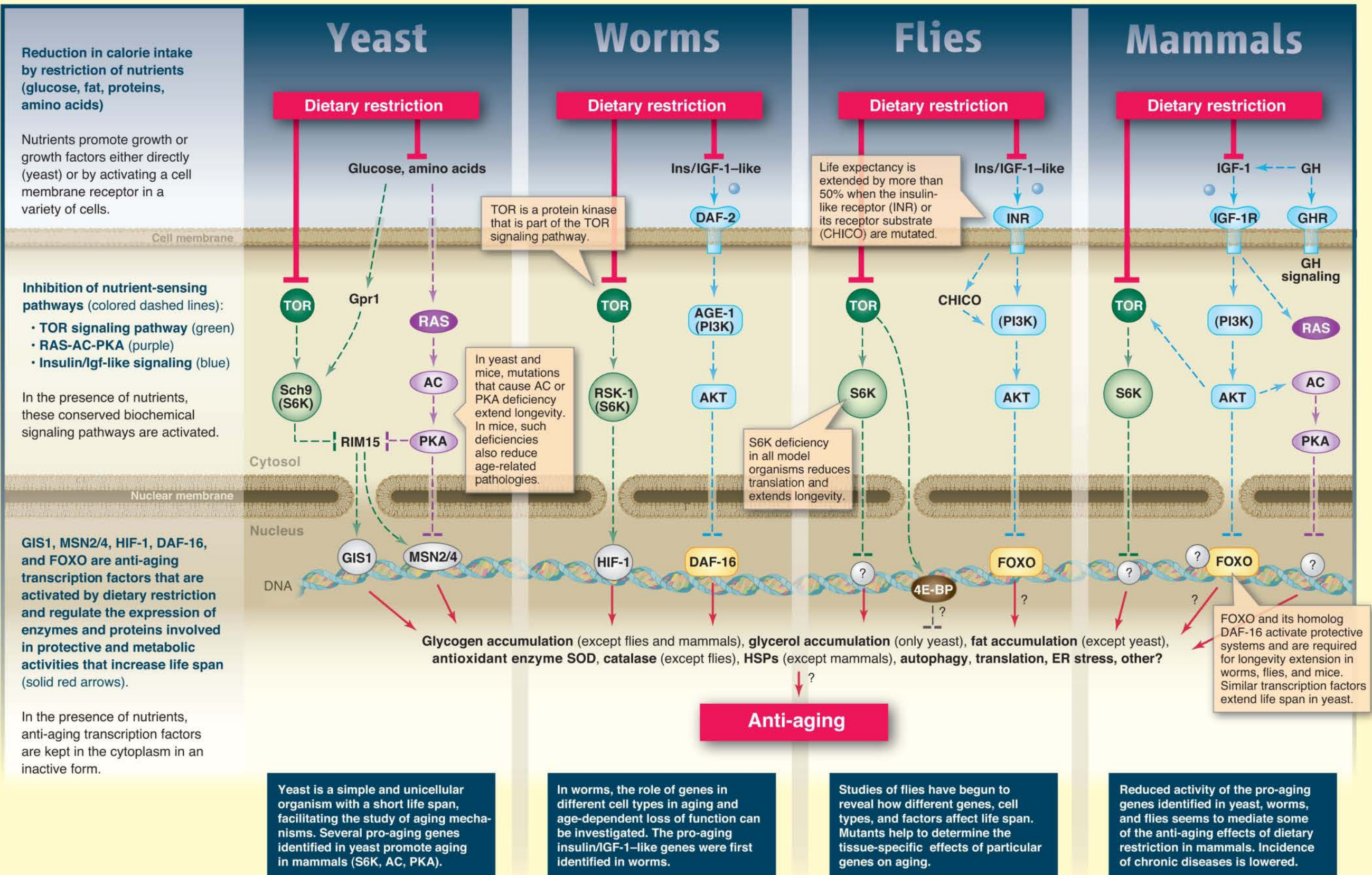
Permission: Karl Brodowsky by Creative Commons







# Conserved Nutrient Signaling Pathways Regulating Longevity





# Genetic animal models of longevity

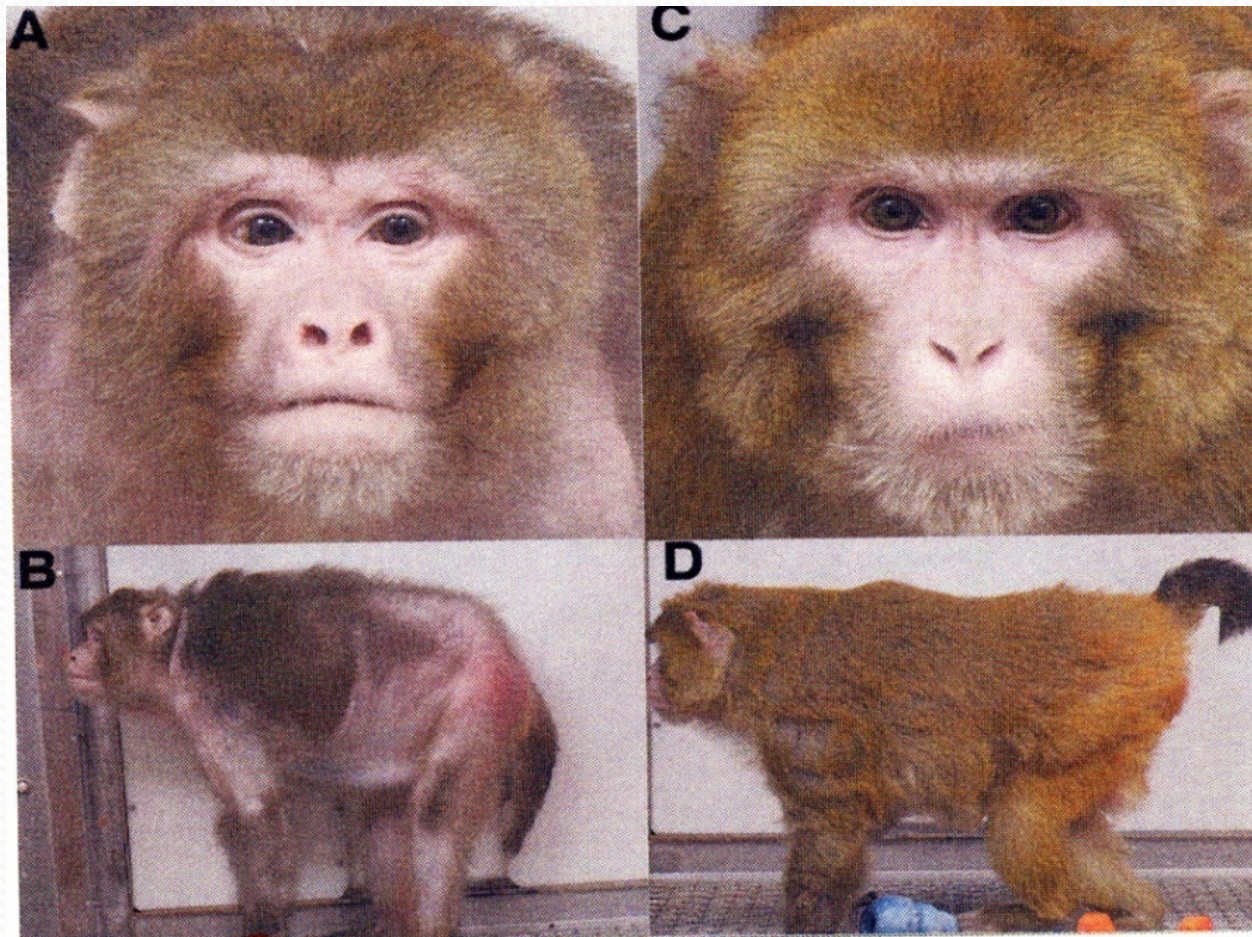
- Ames and Snell dwarf mice
- Growth hormone receptor KO mice
- IGF-1 receptor deficient mice
- Klotho overexpressing mice
- Fat Insulin Receptor KO (FIRKO) mice
- Insulin Receptor Substrate 1 KO mice
- Brain IRS-2 KO mice
- Ribosomal S6 protein kinase-1 KO mice
- p66shc KO mice
- Type 5 Adenylyl Cyclase KO mice
- Angiotensin II type 1 receptor KO mice
- Mice overexpressing catalase targeted to mitochondria

**Downregulation  
Insulin/IGF-1  
and  
mTOR  
pathways  
=  
Nutrient –sensing  
signalling  
pathways**



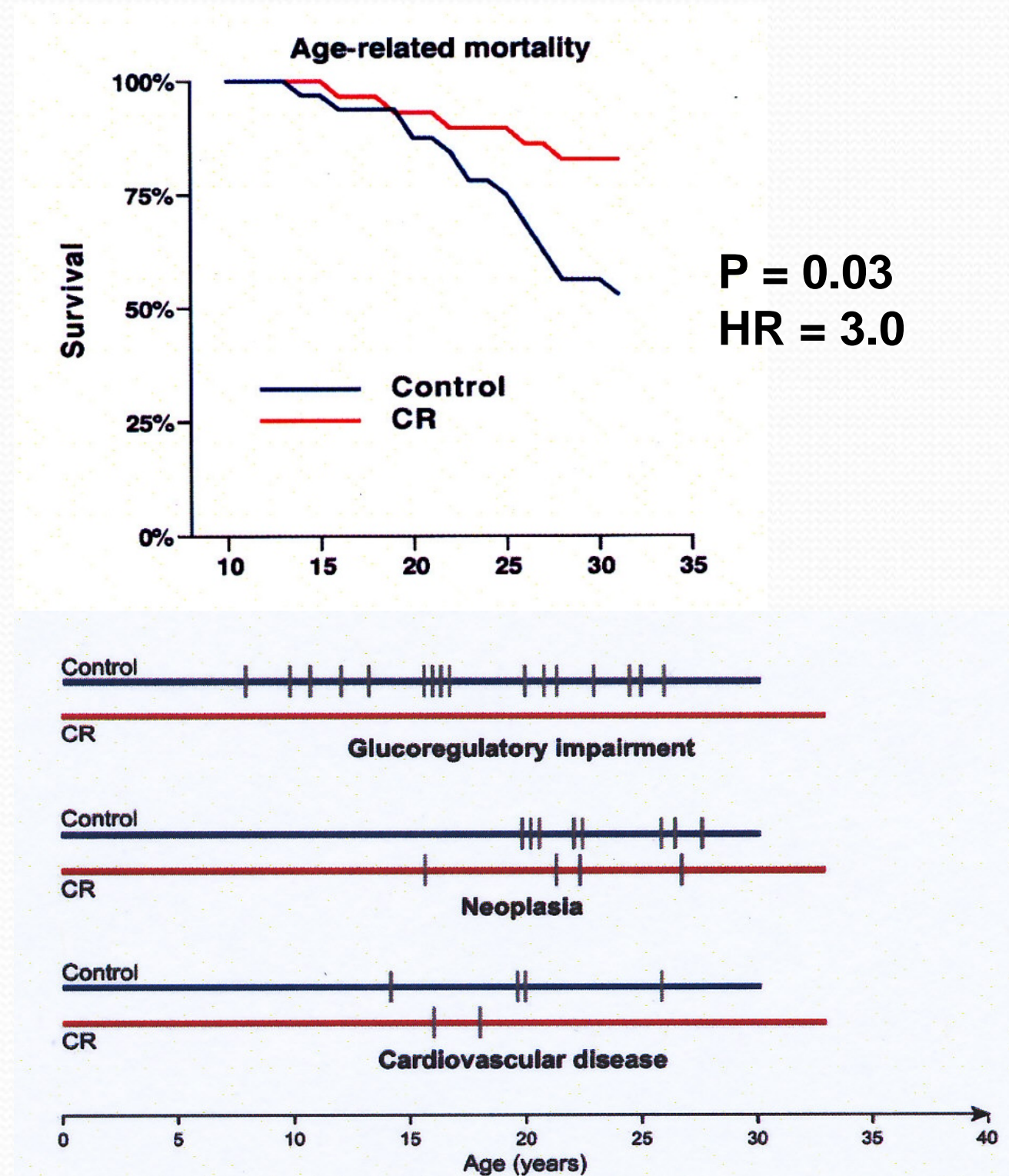
# Caloric Restriction : Most Powerful Anti-Aging Intervention

Calorie Restriction (CR) Reduces Cardiovascular and Cancer Mortality by 50% in Non-human Primates



**Ad libitum**

**CR**



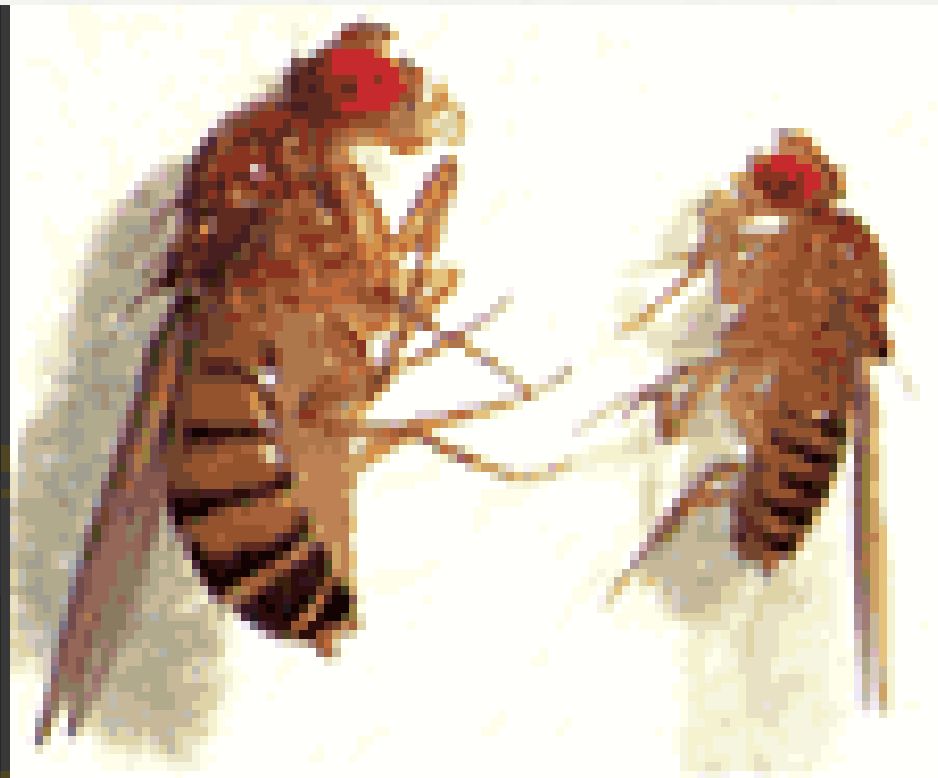


# Gene Variants in the Insulin Signaling Pathway and Healthy Aging

## *Genes, Body Size and Longevity*



yeast



flies

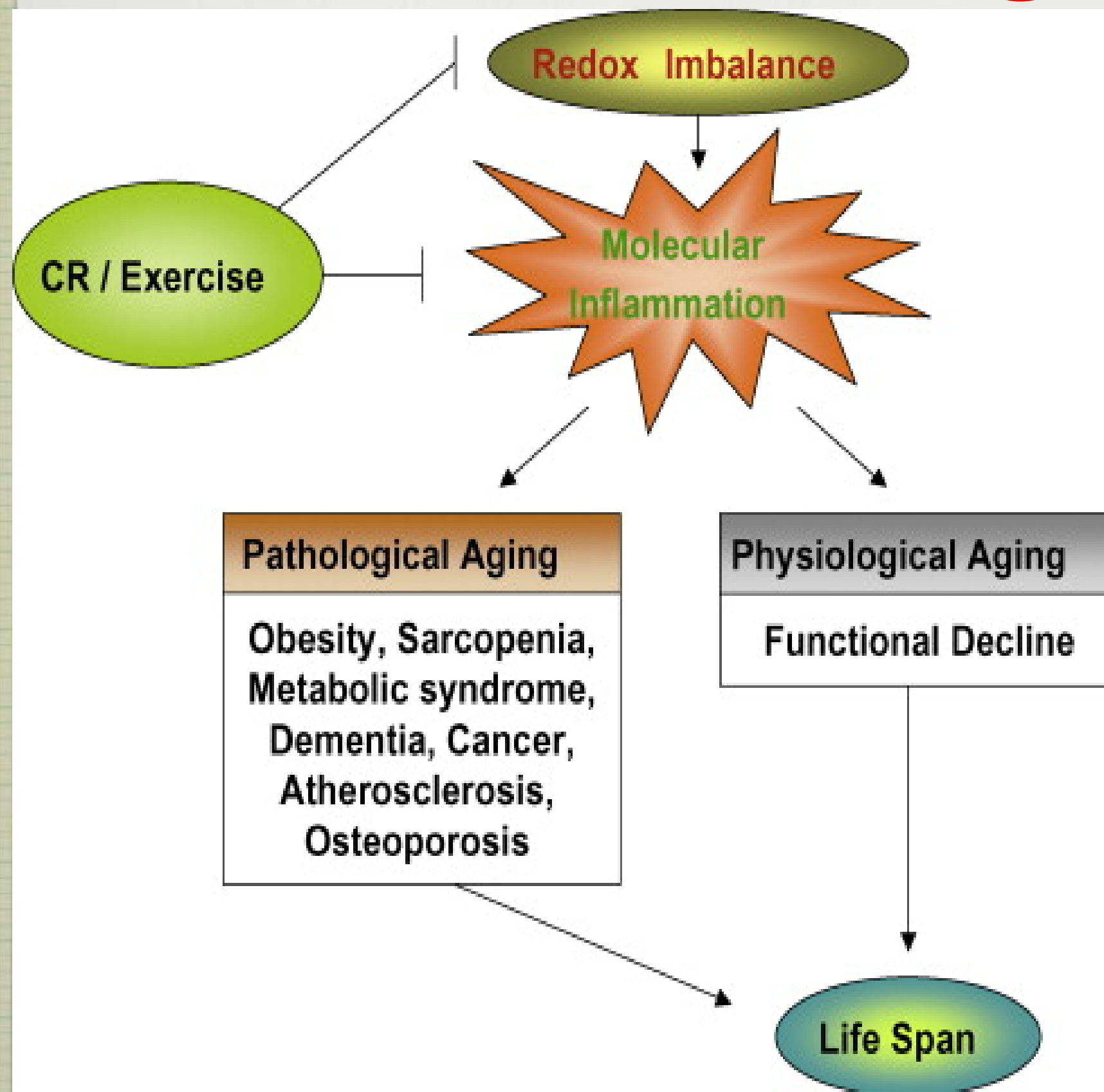


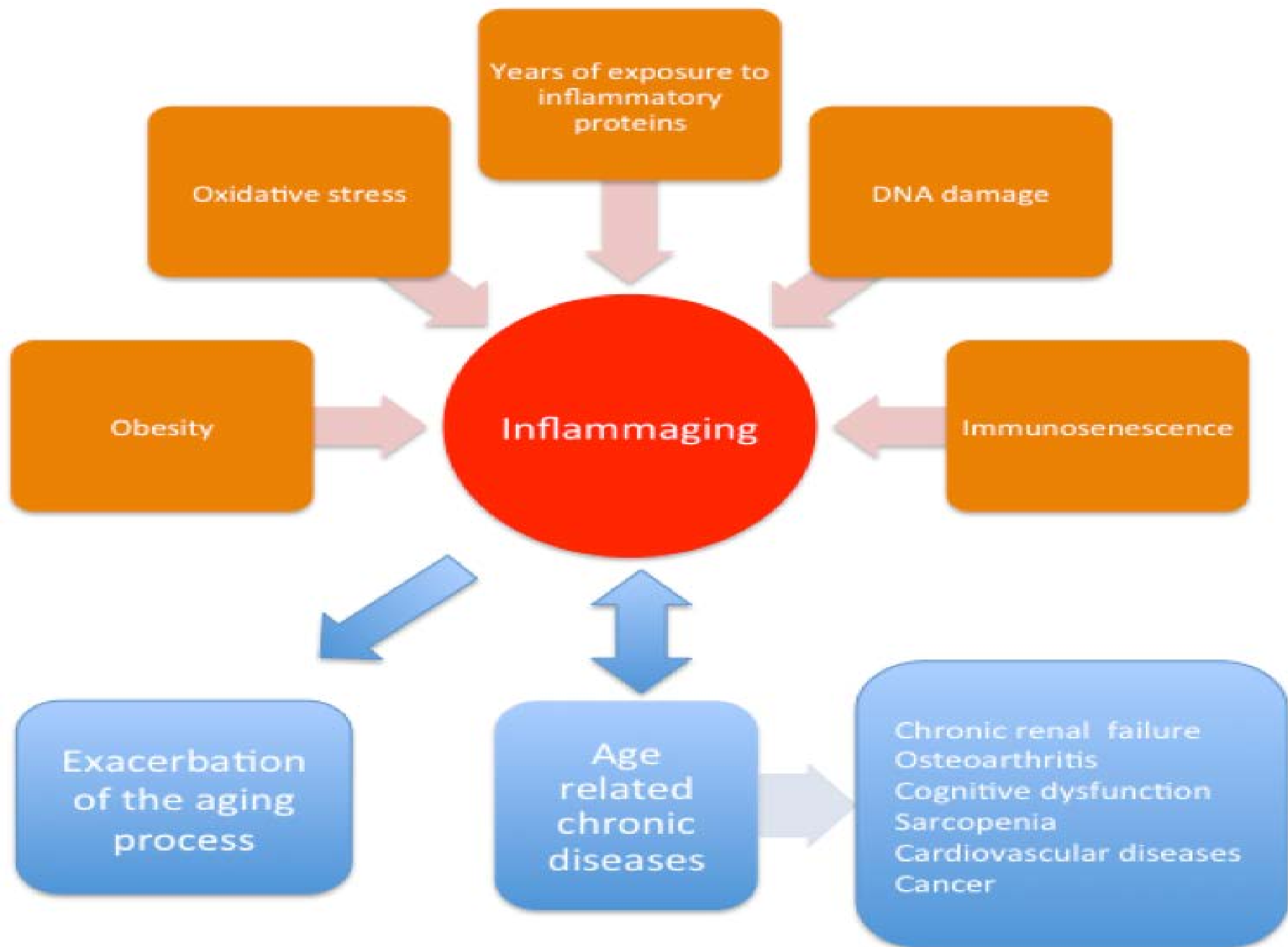
mice

**Mutations that slow aging also postpone age-related disease. Gene variants that result in lower blood sugar and blood insulin result in long-lived animals with increased resistance to oxidative stress and inflammation.....**



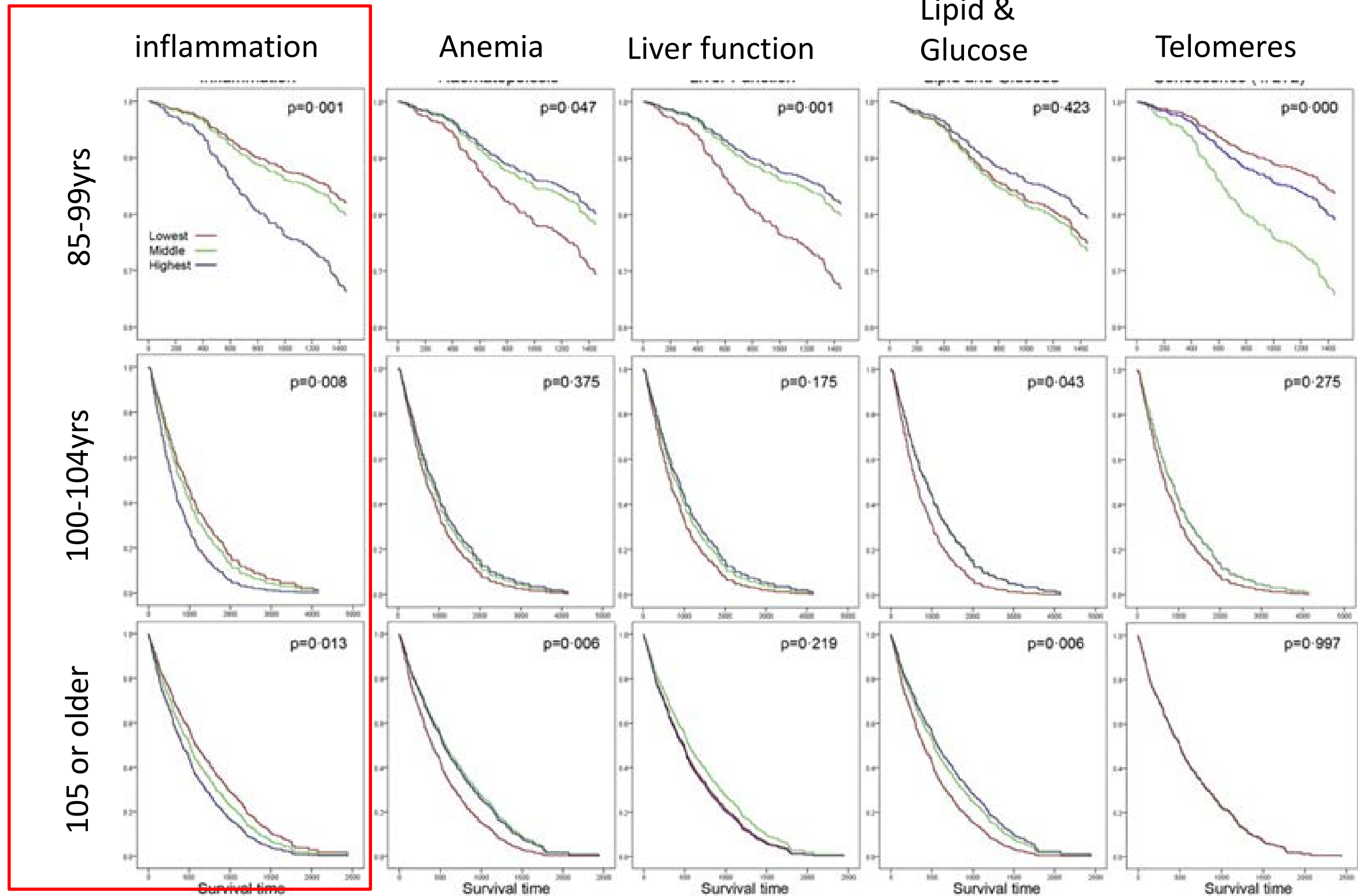
# Inflammaging







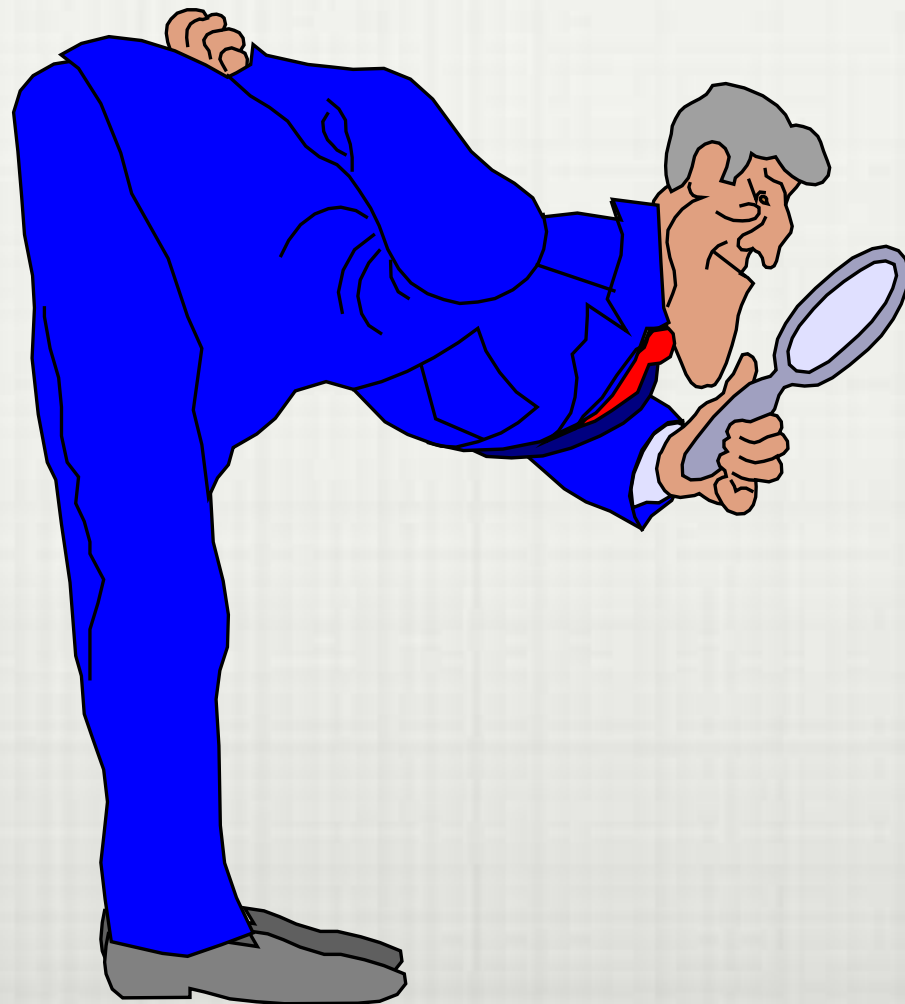
# Inflammation consistently predicts all-cause mortality in very late life



Arai Y, et al. EBioMedicine 2015



# *Do Longevity Genes Exist that Influence Human Aging?*





# Star Bulletin



TUESDAY SEPTEMBER 2, 2008 • HAWAII'S OLDEST DAILY NEWSPAPER, SINCE 1882 • 50¢

STARBULLETIN.COM

"Most people my age would get into the starting block and never be able to get up," says Chuck Yogi, 89. A lifelong runner of Okinawan decent, Yogi's mother lived to 102 and his father to 98. "If worrying made you live longer, I would do it, but it doesn't help so I never do," he says. Here, Yogi runs on a high school track



## LONGEVITY GENE FOUND

*Isle scientists isolate the gene using decades of data*

Hawaii scientists say they have identified a human "longevity" gene prevalent in men who have led long, healthy lives.

The gene, labeled FOXO3A, was identified by Kuakini Medical Center and Pacific Health Research Institute investigators. They studied biological specimens and clinical data collected and maintained at Kuakini since 1965 on 8,000

Discovery of the FOXO3A gene is part of a Hawaii Lifespan Study that is continuing to mine information from the cohort to increase understanding of diseases and aging.

Findings of the team, led by Dr. Bradley Willcox, were published yesterday in the National Academy of Sciences' journal.

"Some humans are just built stronger built to last and others

MORNING DIGEST

HAWAII



# Genes that *Strongly* Influence Human Longevity are Rare

The A Team (15+ replications)

ONLY *APOE*, *FOXO3*

The B Team (4-6 replications)

... a half-dozen genes (e.g. *ACE*, *APOC3*, *CETP*)

The C Team (1-3 replications)

... a dozen or so genes (e.g. *FOXO1*, *HLA-DR1*, *SIRT1*)

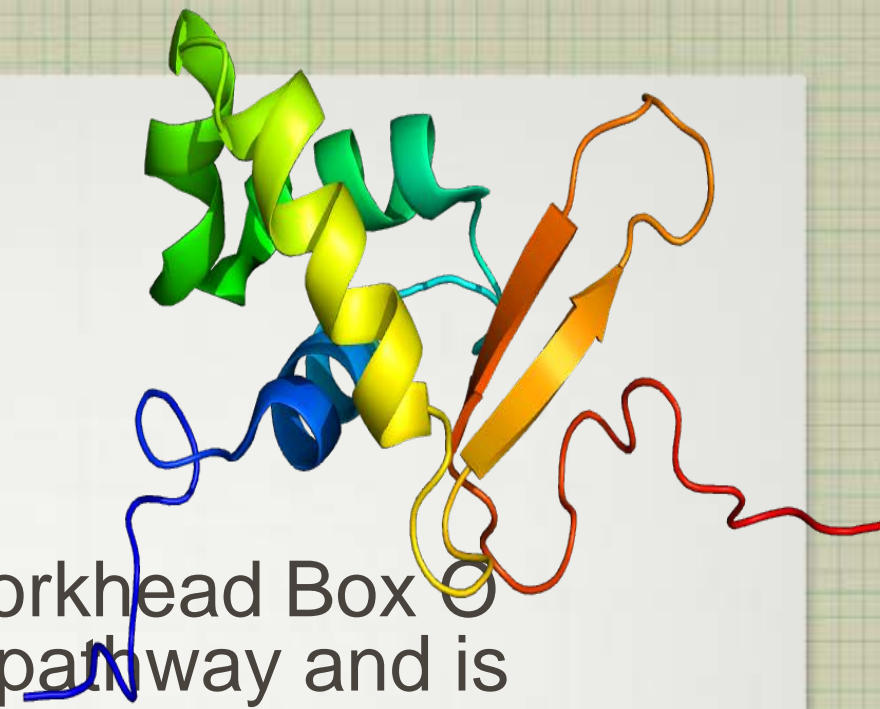
**THE D TEAM (NEVER REPLICATED)**  
**... HUNDREDS**

<http://genomics.senescence.info/longevity/>

Tacutu et al. (2013) "Human Ageing Genomic Resources: Integrated databases and tools for the biology and genetics of ageing." *Nucleic Acids Research* 41(D1):D1027-D1033.



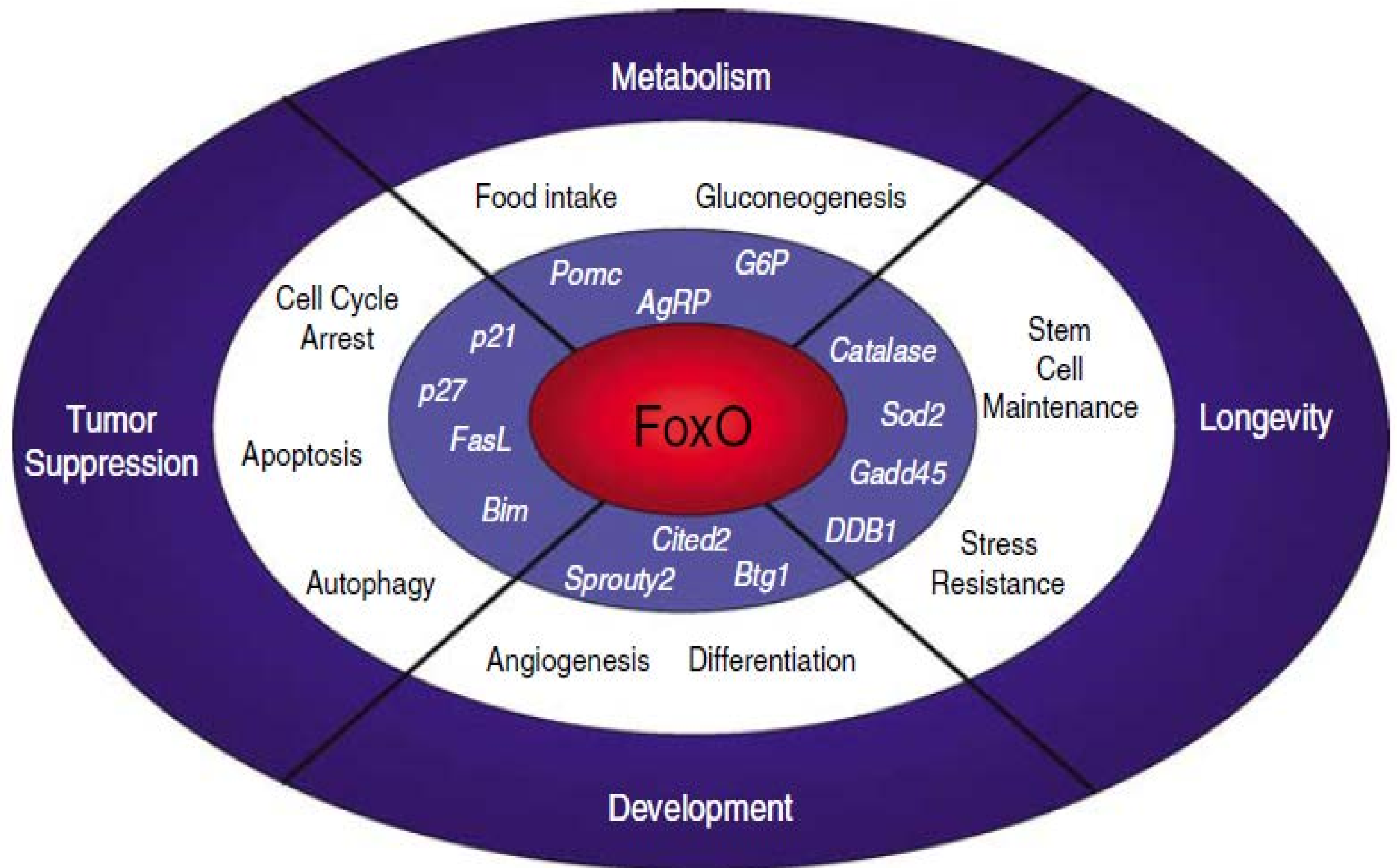
# FOXO3 is a “master” gene in human aging



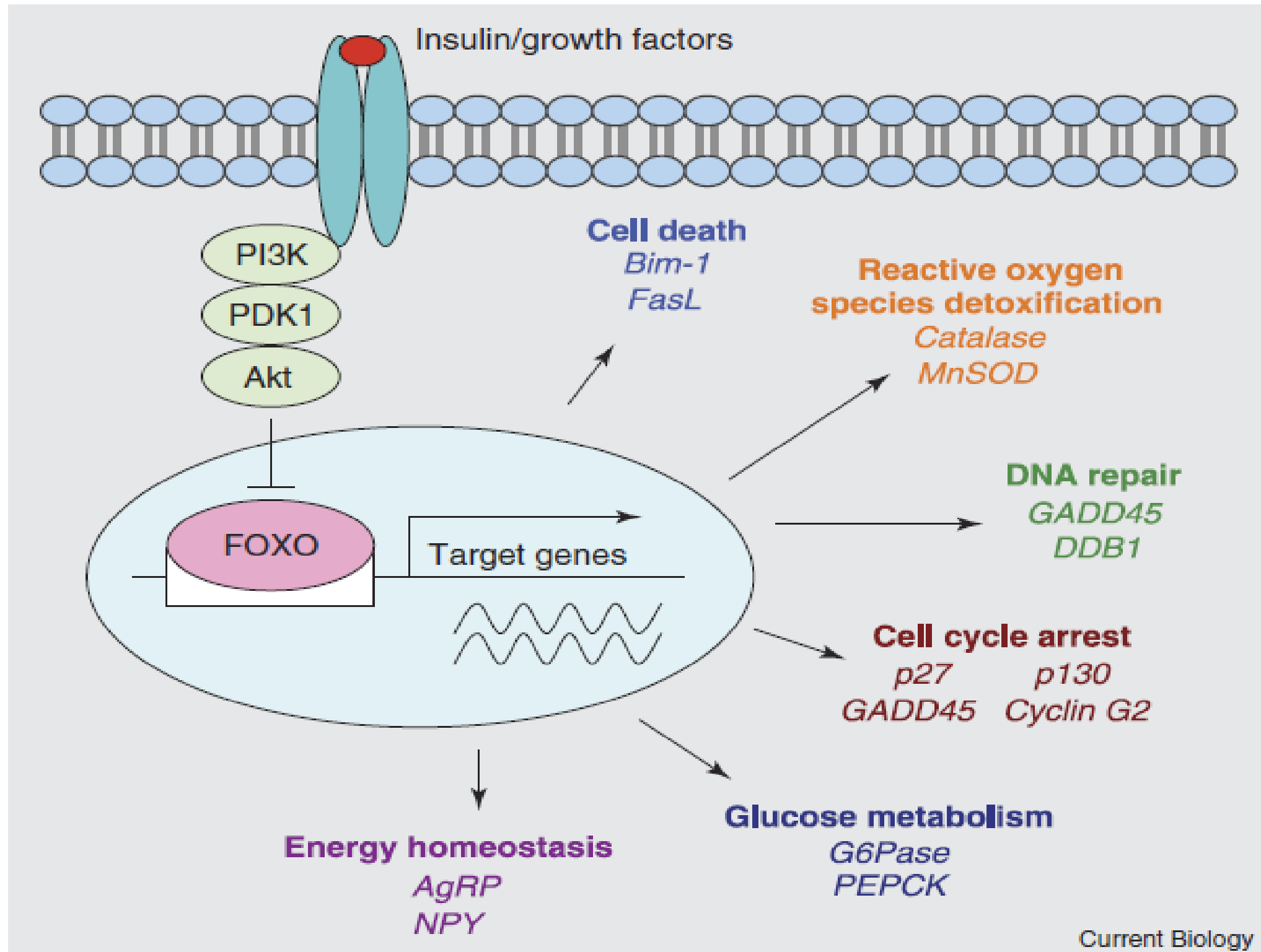
- FOXO3 is a key regulatory gene (codes for a forkhead Box O transcription factor), in the insulin/IGF1 signaling pathway and is evolutionarily conserved across multiple species
- FOXO3 is a “master” gene in human aging since its association with longevity is strong and has been replicated in multiple human populations
- Protective allele(s) initially found to double (heterozygotes) or triple (homozygotes) the odds of near-centenarianism in men of Japanese ancestry in Hawaii (Hawaii Lifespan Study I) and findings were replicated within 2 years in over a dozen human populations of European and Asian ancestry
- A group of single nucleotide polymorphisms (SNPs) in linkage disequilibrium with the coding region has been associated with human longevity but the functional variant is unidentified.
- We are interested in identifying the mechanism by which the “functional variant” protects against aging.



# FOXOs are Master Regulators



# FOXO3 GENE AND HEALTHY AGING



When the *FOXO* gene is stimulated, it targets downstream genes that activate *stress resistance and anti-inflammatory* mechanisms among other important regulatory processes and programs.



# FoxO is a critical regulator of stem cell maintenance in immortal Hydra

[Boehm AM](#), [Khalturin K](#), [Anton-Erxleben F](#), [Hemmrich G](#), [Klostermeier UC](#), [Lopez-Quintero JA](#), [Oberg HH](#), [Puchert M](#), [Rosenstiel P](#), [Wittlieb J](#), [Bosch TC](#).

Zoological Institute, Christian-Albrechts-University, 24098 Kiel, Germany.

## Abstract

Hydra's unlimited life span has long attracted attention from natural scientists. The reason for that phenomenon is the *indefinite self-renewal capacity of its stem cells*. The underlying molecular mechanisms have yet to be explored. Here, comparing the transcriptomes of Hydra's stem cells followed by functional analysis using transgenic polyps, we identified the transcription factor forkhead box O (FoxO) as one of the critical drivers of this continuous self-renewal. foxO overexpression increased interstitial stem cell and progenitor cell proliferation and activated stem cell genes in terminally differentiated somatic cells. ***foxO down-regulation led to increase in the number of terminally differentiated cells, resulting in a drastically reduced population growth rate.*** In addition, caused down-regulation of stem cell genes and antimicrobial peptide (AMP) expression. These findings contribute to a molecular understanding of Hydra's immortality, indicate an evolutionarily conserved role of FoxO in controlling longevity from Hydra to humans, and have implications for understanding cellular aging.

# *Longevity and FOXO3 ???*

## *So how does it work ?*

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# Prevalence of Major Age-related Diseases by *FOXO3* Genotype

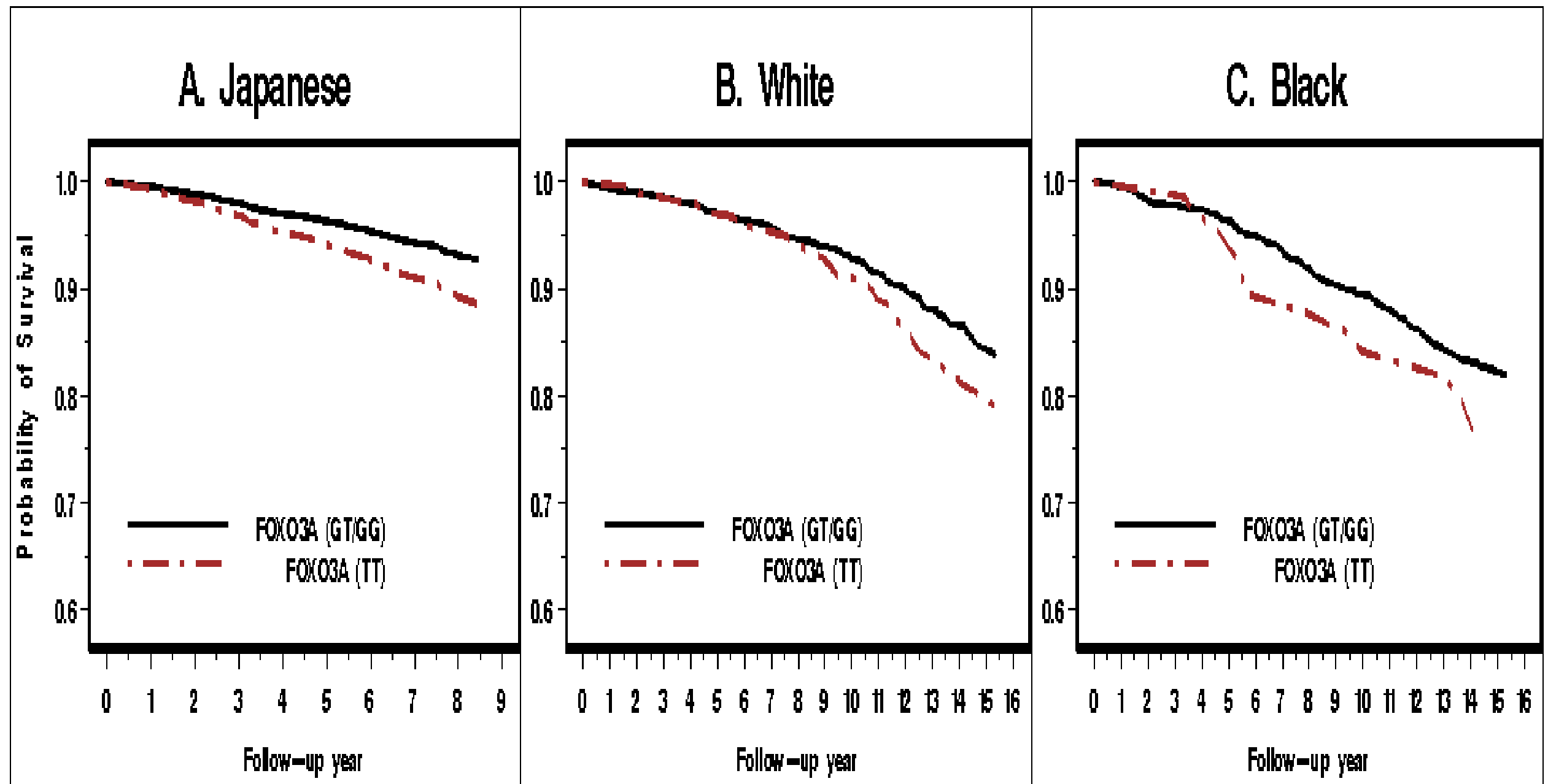
Adapted from Willcox et al. *Aging Cell* 2016;15(4):617-24

Disease <sup>#</sup>	- allele	+ allele*	p-value
CHD	21.7%	15.0%	0.01
Cancer	17.2%	12.5%	0.06
Stroke	5.2%	4.7%	0.78
Diabetes	23.5%	23.2%	0.16

# Disease prevalence (%)

\* Hetero- and homozygous for rs2802292 minor (protective) allele

# CHD Mortality by *FOXO3* Genotype in Japanese, Whites and Blacks over 15 years



Willcox et al. *J Gerontol A Biol Sci Med Sci*. 2016

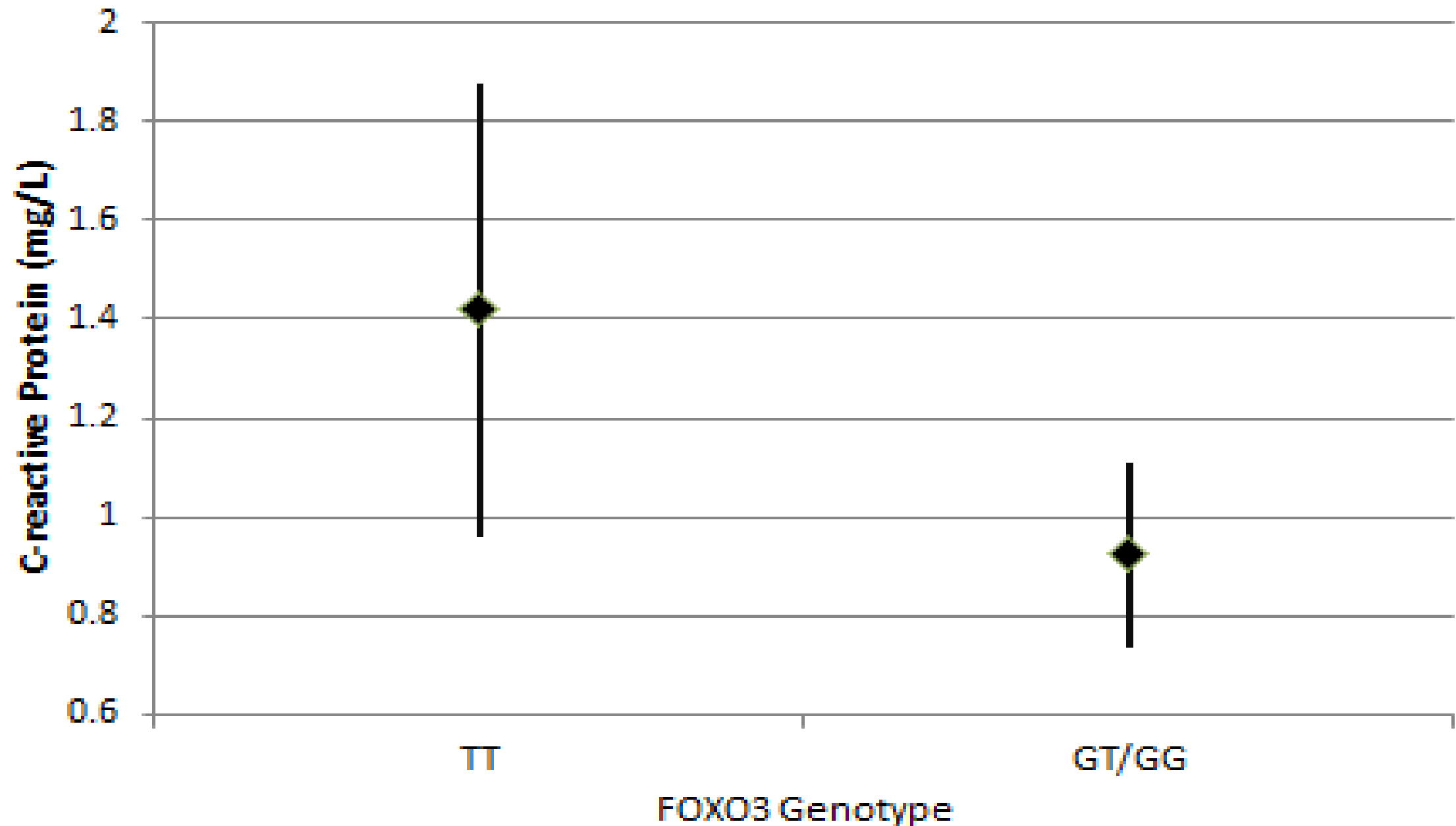


# So What? Context and Implications

---

- Protective allele (G) carriers had a combined (Japanese, Whites, Blacks) risk reduction of **10%** for total (all-cause) mortality which was mostly contributed by **26% fewer deaths** from CHD
- Population attributable risk (PAR) models found that the non-protective (TT) genotype was one of the **top 3** contributing factors to CHD mortality (others being hypertension and smoking)
- The magnitude of the impact of an absence of the FOXO3 G allele was comparable to the increase in risk of death from smoking a pack of cigarettes a day for 25 years in Japanese men and was the **top risk factor** in Japanese men *equivalent to hypertension*
- In black males and females it was equivalent to having a 20 mmHg higher systolic blood pressure and in white men and women it was equivalent to a 20 mg/dl elevation in fasting blood glucose.

# *Is Inflammation the Smoking Gun ?*



*Note: FOXO3 G allele carriers have lower plasma CRP level than non-carriers indicative of lower blood inflammation ( $p=0.05$ ) and therefore less risk for plaque formation & atherosclerosis.*



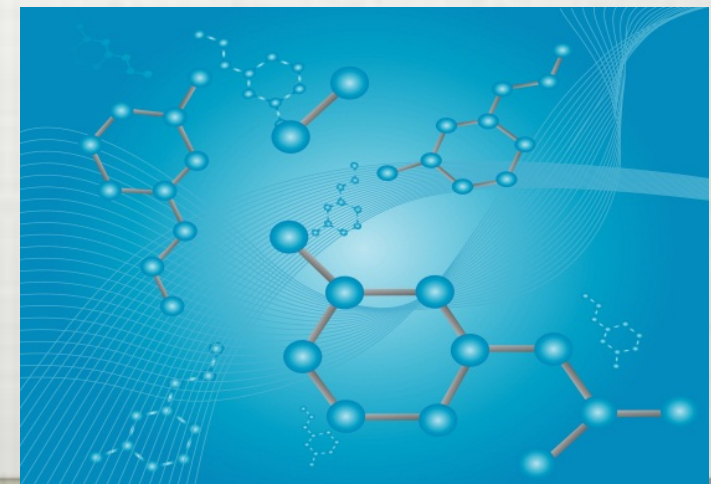
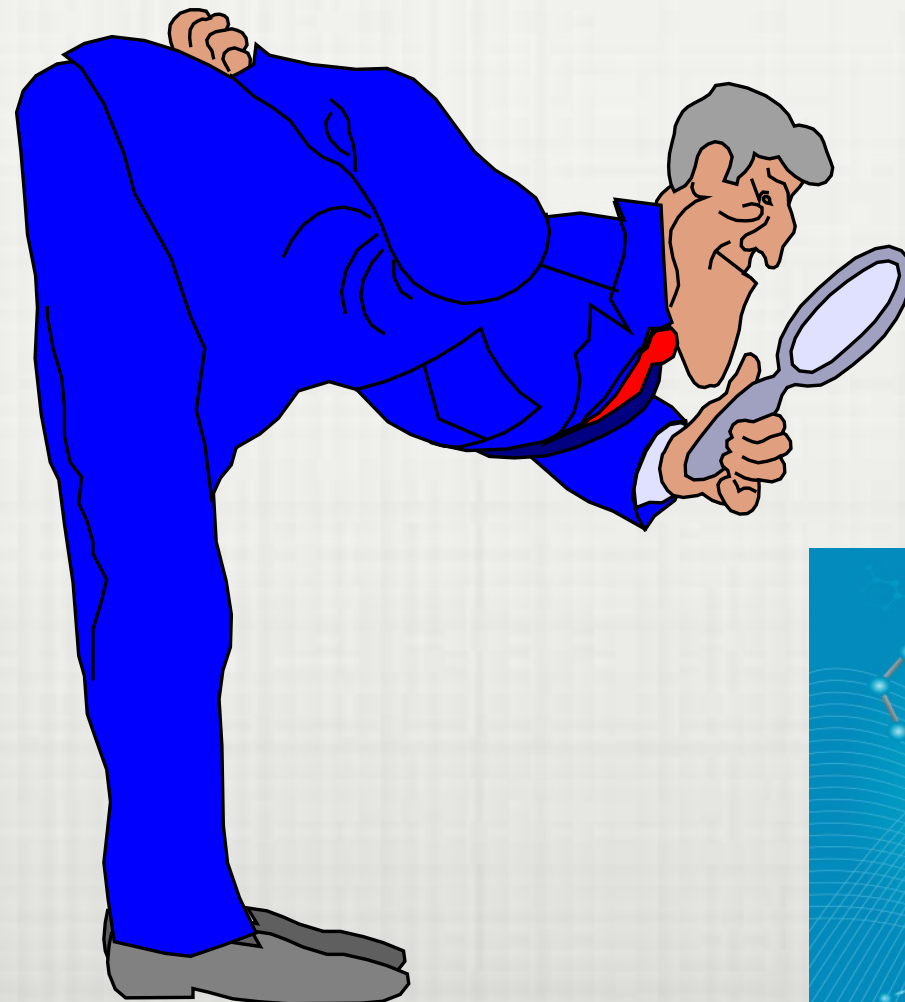


What if you don't have  
the *Protective Version*  
of the Gene?

*Answer: Turn on the  
Gene by your Health  
Habits !!*

→ Diet, Physical  
Activity,  
Pharmacology

*Can the Okinawa diet decrease inflammation and other risk factors for CVD and other age associated diseases? Are there natural CR mimetics in the traditional diet?*





# What do the Okinawan Elders Eat?



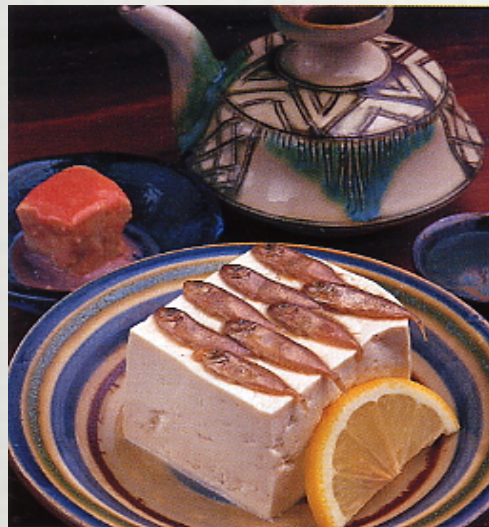
Bitter Melon with Tofu



Nigana Greens



Mozuku Seaweed



Tofu with Fish



Rice with Vegetables



Lean Meat Dishes



 NATIONAL  
GEOGRAPHIC

Eat Like the World's Longest-Lived People  
Discover Ways to Add Life to Your Years  
Make the Healthy Choice the Easy Choice

# Blue Zones

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Recipes and  
Advice  
From the  
*New York Times*  
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Author  
**DAN  
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TIME INC. SPECIALS





## »TOP LONGEVITY FOODS *From Okinawa*

» **BITTER MELON** Known as goya, this long, knobby gourd looks something like a warty cucumber. It is often served in stir-fried dishes. Recent studies found it an “effective antidiabetic” as powerful as pharmaceuticals in helping to regulate blood sugar.

» **TOFU** Okinawans eat tofu like the French eat bread: It’s a daily habit. Studies show that people who eat soy products in place of meat have lower cholesterol and triglyceride levels, which reduces their risk of heart disease.

» **SWEET POTATOES** Okinawan imo is a supercharged purple sweet potato, a cousin of the yellow-orange sweet varieties. Despite its sweet, satisfying taste, the supercharged purple imo does not cause blood sugar to spike as much as a regular white potato does.

» **GARLIC** Sometimes eaten pickled, garlic is one of nature’s most powerful natural medicines. A recent scientific review

found that “intake of garlic by humans may either prevent or decrease the incidence of major chronic diseases associated with old age.”

» **TURMERIC** Ginger’s golden cousin, turmeric figures in the Okinawan diet as both a spice and a tea. A powerful anti-cancer, antioxidant, and anti-inflammatory agent, turmeric contains several compounds now under study for anti-aging properties.

» **BROWN RICE** Okinawan brown rice, tastier than the brown rice Americans know, is soaked in water to germinate until it just begins to sprout, unlocking enzymes that break down sugar and protein and giving the rice a sweet flavor and softer texture.

» **GREEN TEA** Okinawans drink a special kind of green tea they call *shan-pien*, or “tea with a bit of a scent,” made by adding jasmine flowers and

often a little turmeric. Green tea contains substances that may protect against a host of age-related problems.

» **SHIITAKE MUSHROOMS** These smoky-flavored fungi help flavor Okinawans’ customary miso soup and stir-fries. They contain more than 100 compounds with immune-protecting properties.

» **SEAWEEDS (KOMBU AND WAKAME)** Seaweeds in general provide a filling, low-calorie, nutrient-rich boost to the diet. These two are used in many soups and stews on Okinawa. They are rich in carotenoids, folate, magnesium, iron, calcium, and iodine.





# CR-Mimetic Foods

**Sweet Potatoes**



**Green Tea**

Permission: Yamasa Seicha, Shizuoka Japan



**Turmeric**



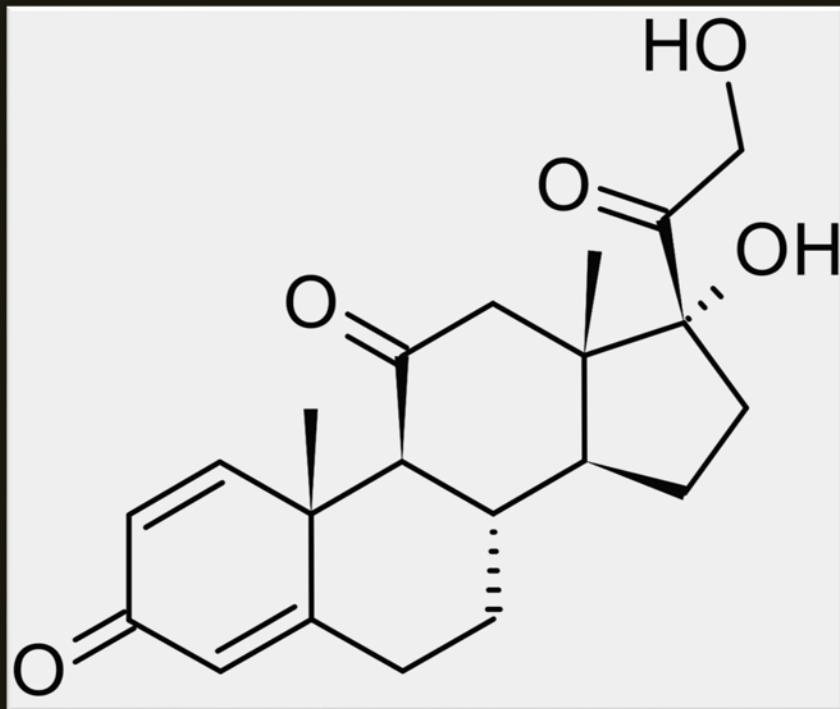
**Chlorophyta**

Permission: Frank Fox for Creative Commons

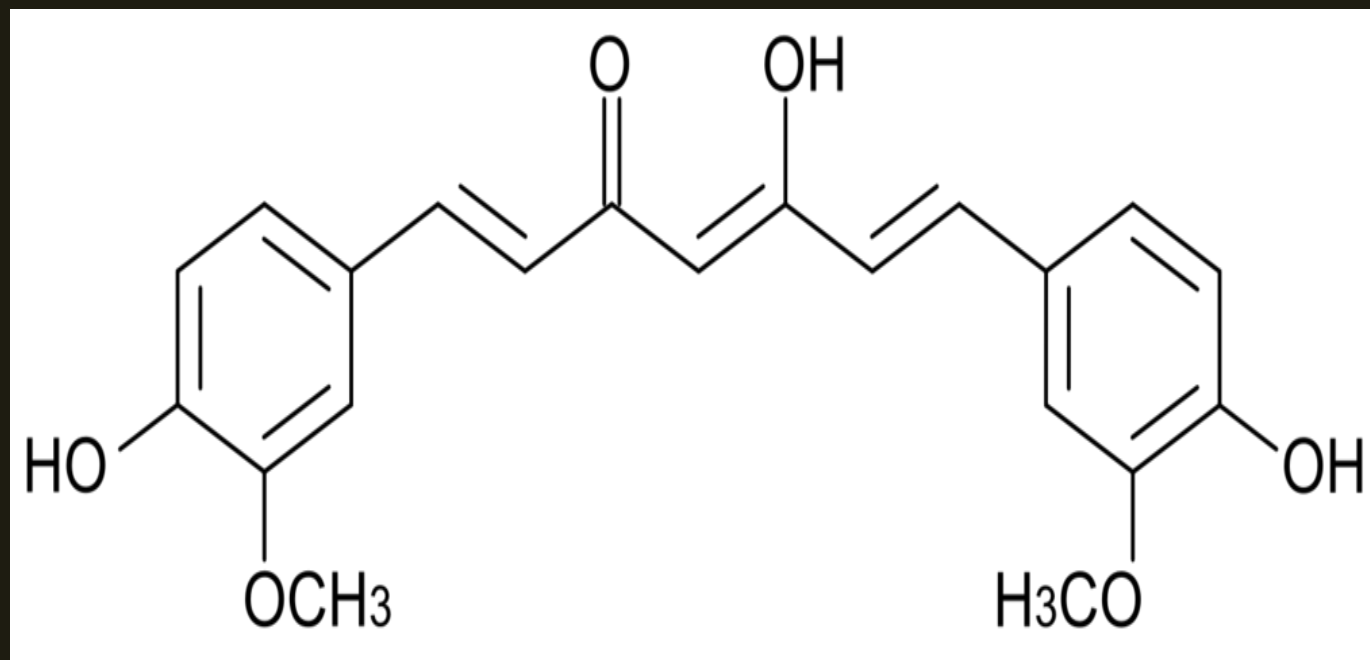
Permission: Badagnani for Creative Commons



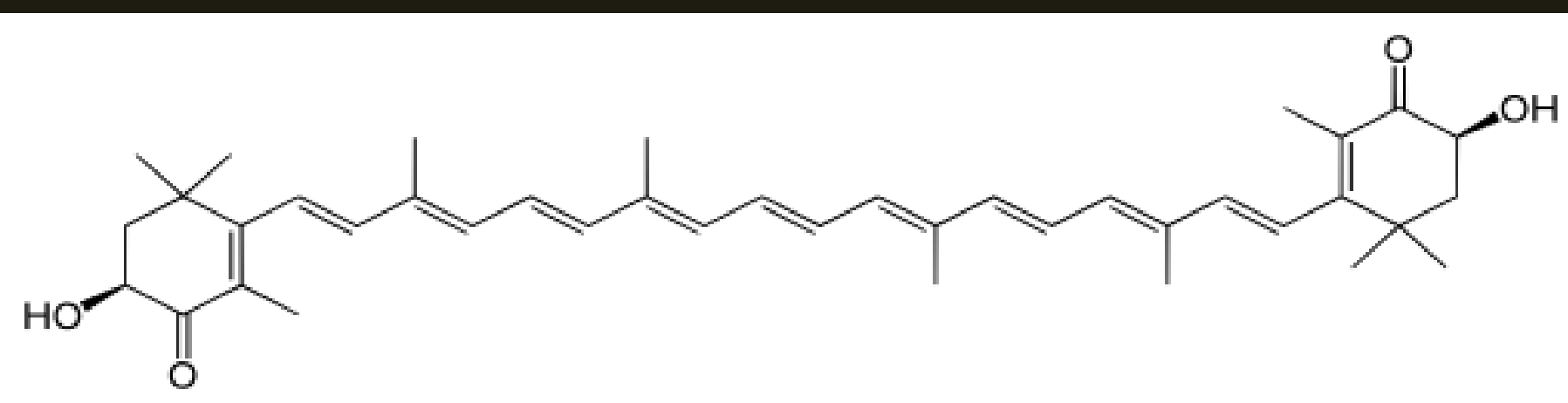
# Pharmacologics and Nutraceuticals that Stimulate the FOXO3 Gene and Reduce Inflammation



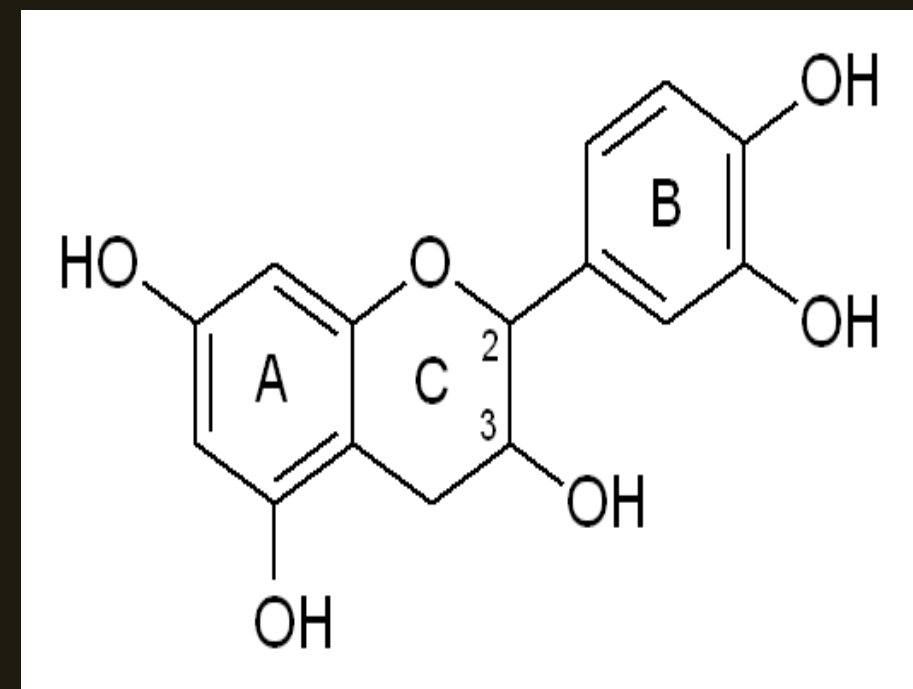
# Prednisone



# Curcumin



# Astaxanthin



# Catechins

# Key Features of Traditional Okinawa Diet

---

- 1) Low Caloric Density (plant-based, low fat, moderate protein from soy, fish, lean meats)
- 2) High Nutrient Density (Vitamins A, C, E, potassium, magnesium, folate, and healthy oils)
- 3) Phyto-nutrient Rich (anti-oxidants, polyphenols, flavonoids, carotenoids mostly from green leafy and yellow root vegetables)
- 4) Low in Glycemic Load (high quality carbohydrates from staple sweet potato)
- 5) Anti-inflammatory (CR, antioxidants, polyphenols, flavonoids, omega 3 fatty acids, curcumins)



# Okinawan Sweet Potatoes



Kano et al. 2005. Antioxidative activity of anthocyanins from purple sweet potato, *Ipomoea batatas* cultivar Ayamurasaki. *Biosci Biotechnol Biochem* 69:979–988.

# Okinawan Sweet Potato is highly anti-inflammatory !

## FOOD SUMMARY

### Nutrition Facts

Serving Size 200 g

#### Amount Per Serving

Calories 180      Calories from Fat 3

% Daily Value\*

Total Fat 0g      0%

Saturated Fat 0g      0%

Trans Fat

Cholesterol 0mg      0%

Sodium 72mg      3%

Total Carbohydrate 41g      14%

Dietary Fiber 7g      26%

Sugars 13g

Protein 4g

Vitamin A 769% • Vitamin C 65%

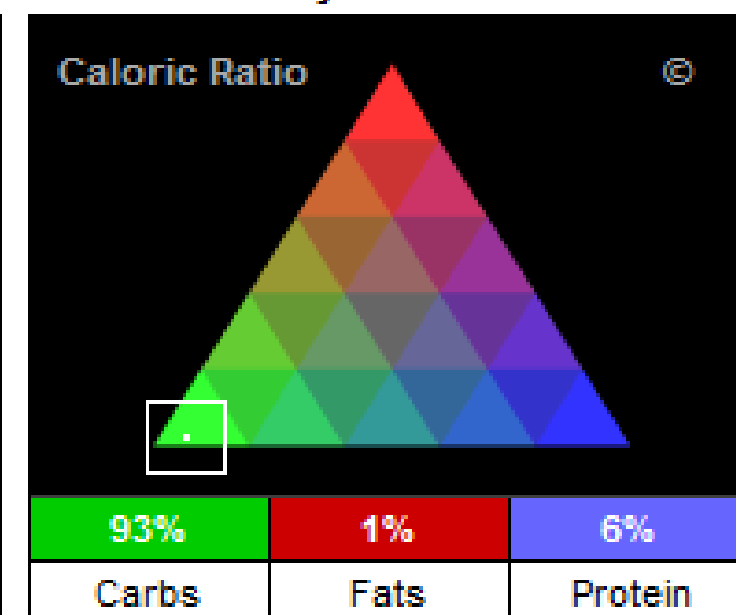
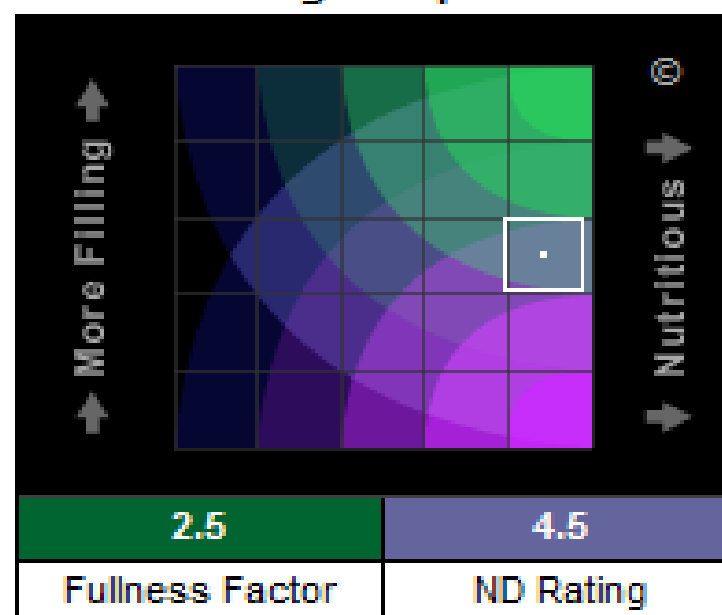
Calcium 8% • Iron 8%

\*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

NutritionData.com

[Download Printable Label Image](#)

#### Nutritional Target Map [? What is this?](#)      Caloric Ratio Pyramid [? What is this?](#)



#### NutritionData's Opinion [? What is this?](#)

Weight loss: ★★★★★

Optimum health: ★★★★★

Weight gain: ★★★★★

**The good:** This food is low in Sodium, and very low in Saturated Fat and Cholesterol. It is also a good source of Dietary Fiber, Vitamin B6 and Potassium, and a very good source of Vitamin A, Vitamin C and Manganese.

#### Estimated Glycemic Load

17

0      250

Typical target total is 100/day or less

[? What is this?](#)

#### Inflammation Factor

378

strongly anti-inflammatory

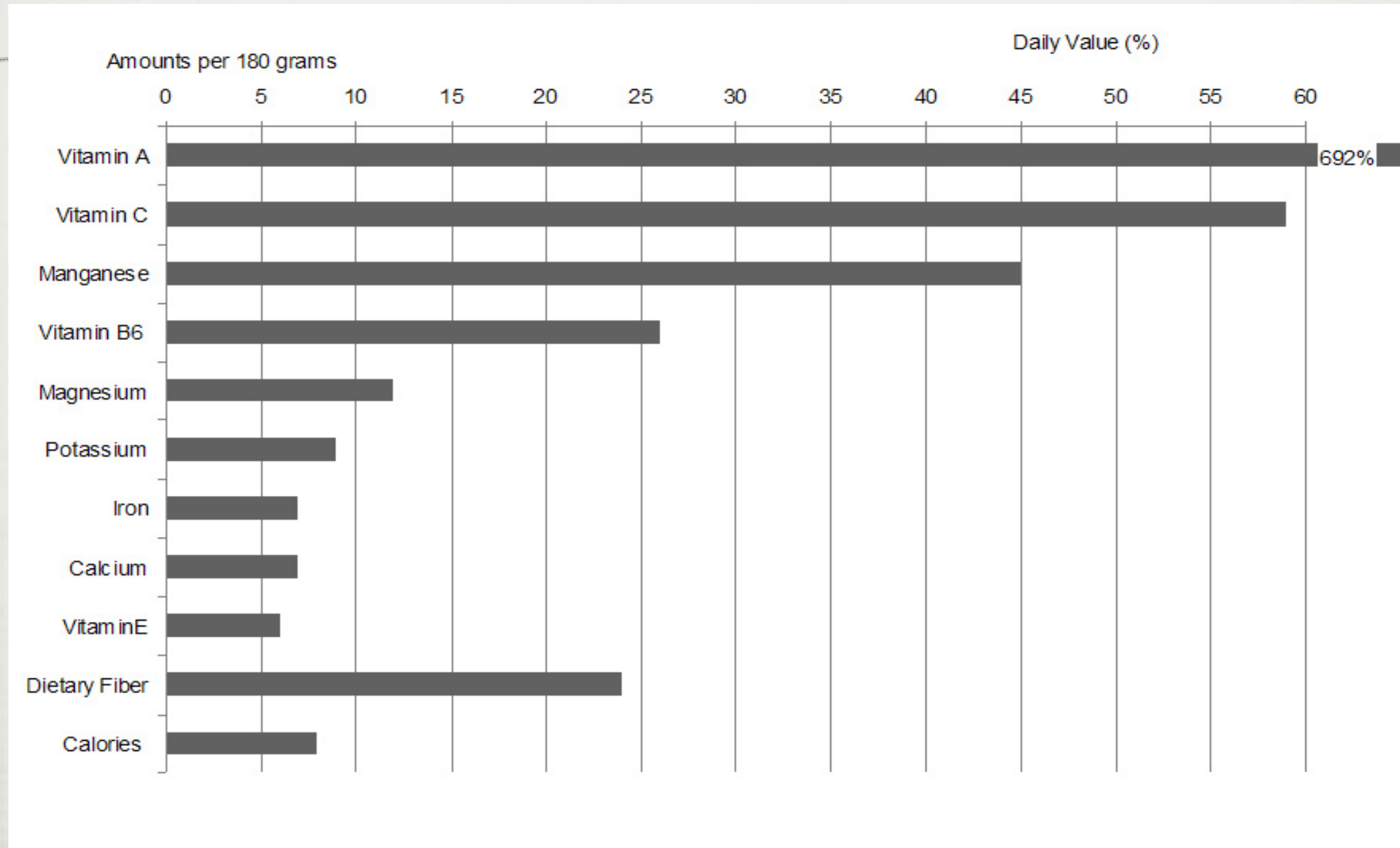
-      0      +

Typical target net is 50/day or higher

[? What is this?](#)

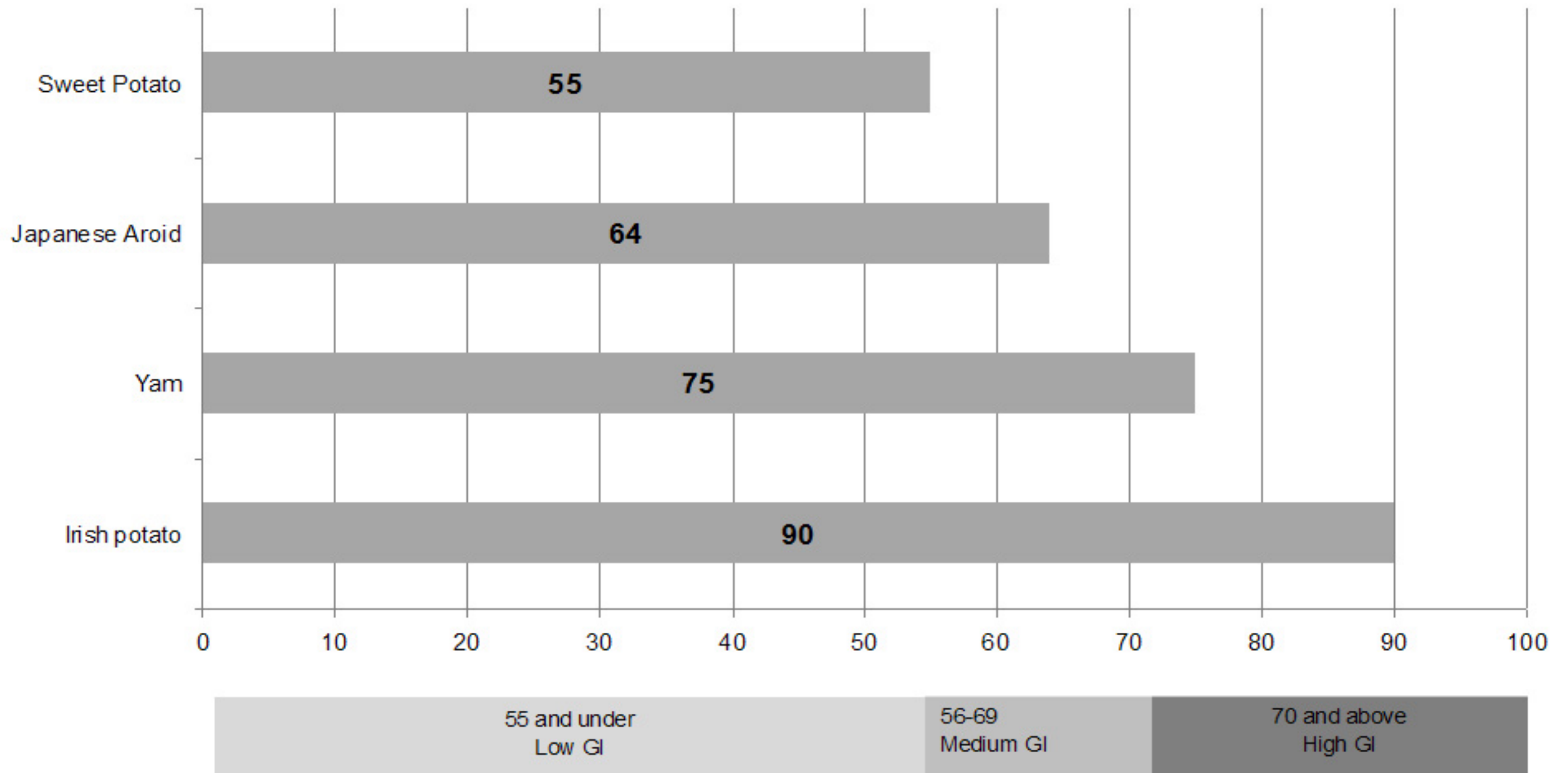


# Sweet Potato: Staple of the Traditional Okinawa Diet



USDA: Americans lack sufficient amounts of dietary fiber, calcium, magnesium, potassium, and the antioxidant vitamins A (as carotenoids), C and E.

# GI of *Satsuma Imo* (Sweet Potato) and Other Potatoes





The Sweet Potato truck comes a`calling.....



# CURCUMIN : A STRONG ANTI-OXIDANT AND ANTI-INFLAMMATORY



[Molecules](#). 2011 Jun 3;16(6):4567-98. doi: 10.3390/molecules16064567.

## **Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment.**

[Basnet P](#), [Skalko-Basnet N](#).

Drug Transport and Delivery Research Group, Department of Pharmacy, University of Tromsø, Tromsø N-9037, Norway. [purusotam.basnet@uit.no](mailto:purusotam.basnet@uit.no)

### **Abstract**

Oxidative damage and inflammation have been pointed out in preclinical studies as the root cause of cancer and other chronic diseases such as diabetes, hypertension, Alzheimer's disease, etc. Epidemiological and clinical studies have suggested that cancer could be prevented or significantly reduced by treatment with anti-oxidant and anti-inflammatory drugs, therefore, curcumin, a principal component of turmeric (a curry spice) showing strong anti-oxidant and anti-inflammatory activities, might be a potential candidate for the prevention and/or treatment of cancer and other chronic diseases. However, curcumin, a highly pleiotropic molecule with an excellent safety profile targeting multiple diseases with strong evidence on the molecular level, could not achieve its optimum therapeutic outcome in past clinical trials, largely due to its low solubility and poor bioavailability. Curcumin can be developed as a therapeutic drug through improvement in formulation properties or delivery systems, enabling its enhanced absorption and cellular uptake. This review mainly focuses on the anti-inflammatory potential of curcumin and recent developments in dosage form and nanoparticulate delivery systems with the possibilities of therapeutic application of curcumin for the prevention and/or treatment of cancer.



# Mice Fed Curcumin and Polyphenols Live Longer

Kitani et al (2004) Ann NY Acad Sci 1019:424-426

---

Average life span in **TC fed mice**\* was 11.7% longer than in control mice. The 10% longest survival also significantly greater and increase in average life expectancy after 24 months of age was 126%. In mice fed polyphenols average life span increased 6.4% and increase in average life expectancy after 24 months was 72.6%.

\* **TC: tetrahydrocurcumin**

\* **Green tea polyphenols**



ジです。翻訳しますか？

翻訳

いいえ

英語を翻訳しない

eCENTRAL™

## Tetrahydrocurcumin extends life span and inhibits the oxidative stress response by regulating the FOXO forkhead transcription factor.

### Authors

Xiang L, Nakamura Y, Lim YM, et al.

### Institution

Department of Cognitive Brain Sciences, National Center for Geriatrics and Gerontology, Obu, Aichi, 474-8511, Japan.

### Source

Aging (Albany NY) 2011 Nov; 3(11) :1098-109.

### Abstract

The O-type forkhead domain transcription factor (FOXO) is involved in many biological processes such as aging, the oxidative stress response, and growth regulation. FOXO activity is tightly controlled within cells. In particular, growth factor signaling pathways and the oxidative stress response can both stimulate nuclear translocation of this transcription factor. Here, we show that tetrahydrocurcumin (THC), a curcumin metabolite, regulates the oxidative stress response and aging via FOXO. In NIH3T3 cells, THC induced nuclear accumulation of FOXO4, a member of the FOXO family of transcription factors, by inhibiting phosphorylation of protein kinase B (PKB)/Akt. In *Drosophila melanogaster*, THC attenuated the oxidative stress response, an effect that was blocked in a foxo mutant background. THC also extended the life span of *Drosophila* under normal conditions, and loss of either foxo or Sir2 activity eliminated this effect. Based on these results, THC may regulate the aging process via an evolutionarily conserved signaling pathway that includes both foxo and Sir2.

### Mesh

[Animals](#)

[Blotting, Western](#)

[Curcumin](#)

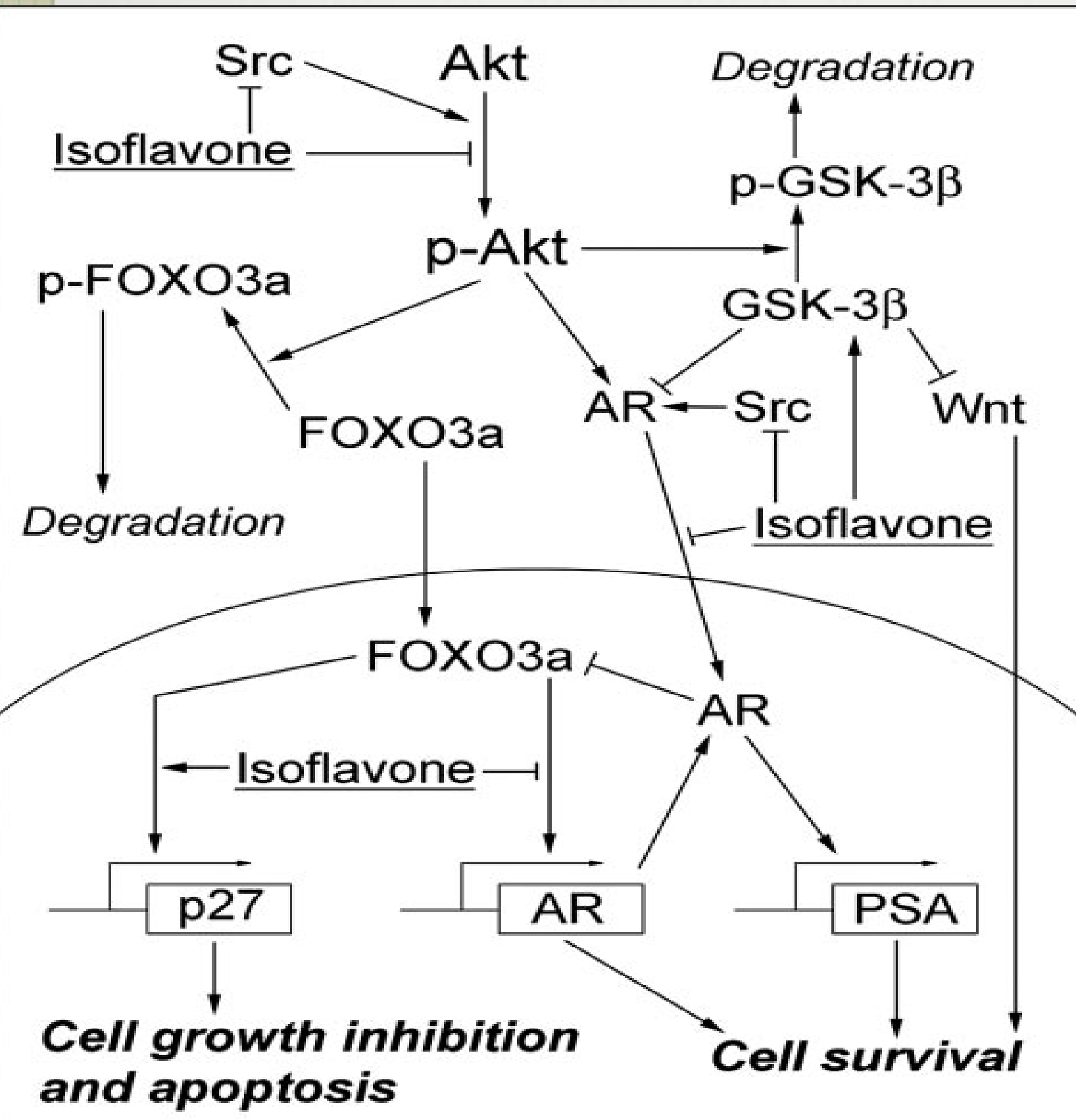
[Drosophila melanogaster](#)

[Forkhead Transcription Factors](#)

[Immunohistochemistry](#)



# Effects of Isoflavones on Akt/FOXO3a/GSK-3/AR Signaling Network



Soy flavonoids have antioxidant-like effects and hormetic properties and are potent activators of gene expression in FOXO3. Isoflavones, the type of flavonoids most common in soy, also regulate the Akt/FOXO3a/GSK-3beta/AR signaling network in prostate cancer cells. Specifically, they inhibit cell proliferation and foster apoptosis suggesting that isoflavones might prove useful for the prevention and/or treatment of prostate cancer (Li et al. 2008. Biol Chem. 283, 27707-16.)

**Astaxanthin is a xanthophyll carotenoid present in microalgae, fungi, complex plants, seafood (salmon, shrimp, krill). A strong antioxidant with anti-inflammatory properties with potential as a therapeutic agent in atherosclerotic cardiovascular disease.**





Oxidative Medicine and Cellular Longevity  
Volume 2011 (2011), Article ID 596240, 9 pages  
<http://dx.doi.org/10.1155/2011/596240>

## Research Article

# Supplemental Cellular Protection by a Carotenoid Extends Lifespan via Ins/IGF-1 Signaling in *Caenorhabditis elegans*

Koumei Yazaki, Chinatsu Yoshikoshi, Satoru Oshiro, and Sumino Yanase

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## Abstract

Astaxanthin (AX), which is produced by some marine animals, is a type of carotenoid that has antioxidative properties. In this study, we initially examined the effects of AX on the aging of a model organism *C. elegans* that has the conserved intracellular pathways related to mammalian longevity. The continuous treatments with AX (0.1 to 1 mM) from both the prereproductive and young adult stages extended the mean lifespans by about 16–30% in the wild-type and long-lived mutant *age-1* of *C. elegans*. In contrast, the AX-dependent lifespan extension was not observed even in a *daf-16* null mutant.

Recent evidence suggests that astaxanthin has promise for modulating aging through activation of the insulin signaling pathway and FOXO gene in particular. Especially, the expression of genes encoding superoxide dismutases and catalases.



# *Getting a Daily Dose of Astaxanthin from Seaweed*

BY DAN BUETTNER   PHOTOGRAPHS BY DAVID McLAIN

## The Secrets of Long Life

### OKINAWA, JAPAN

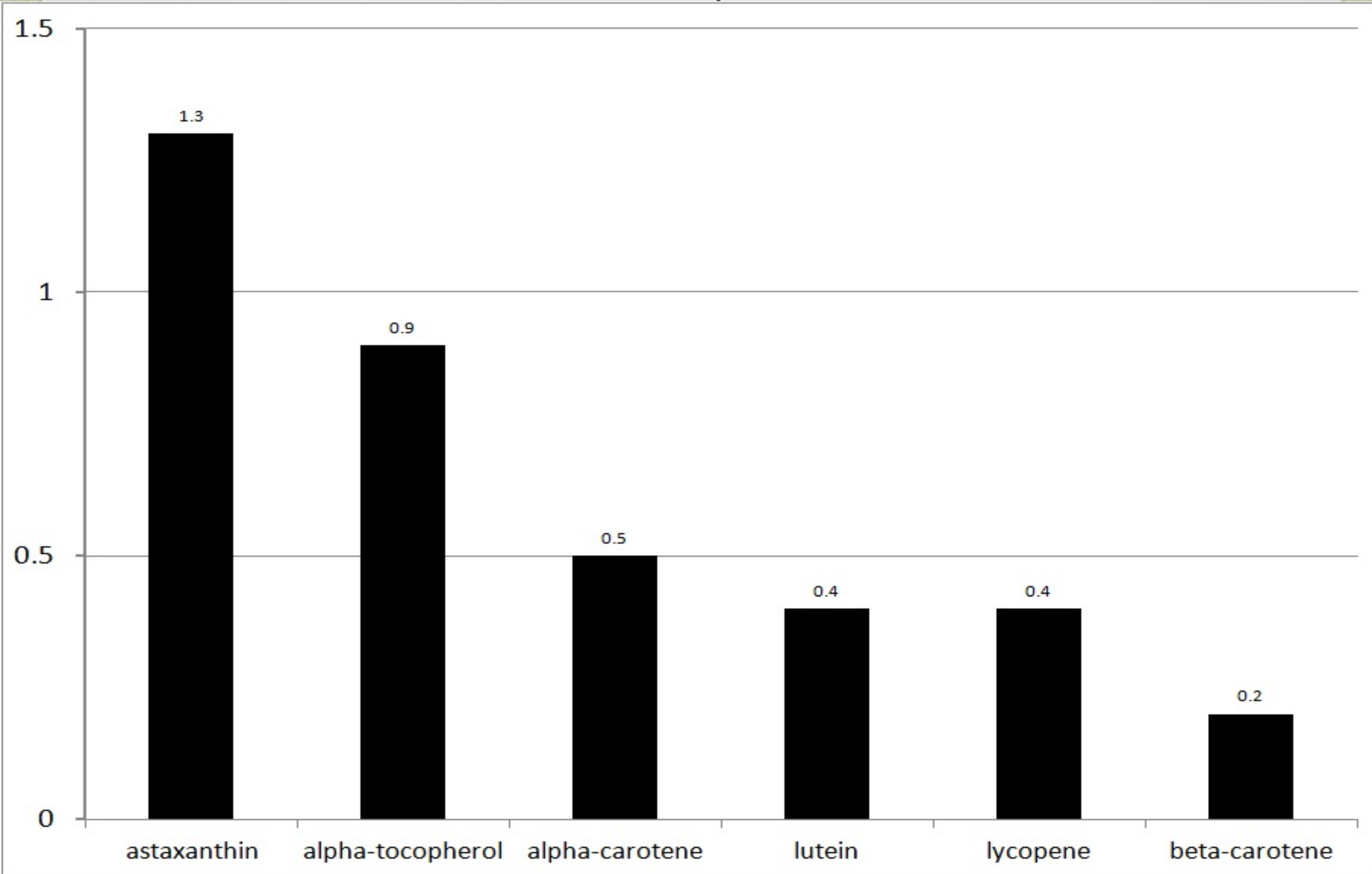
Squinting effortlessly on a slippery embankment, 89-year-old Kame Ogata inspects a pinch of seaweed, part of a low-calorie, plant-based diet that may help give Okinawans an average life expectancy of 82 years, among the longest in the world. These seniors, and others in Italy and California, show how to live longer, healthier lives.

2. NATIONAL GEOGRAPHIC, FEBRUARY 2009



# Anti-Oxidant Activity of Carotenoids

Willcox BJ, Willcox DC. 2014. Curr Opin Clin Nutr Metab Care 17:51-8





# Okinawa Traditional Dietary Intervention Study in Americans



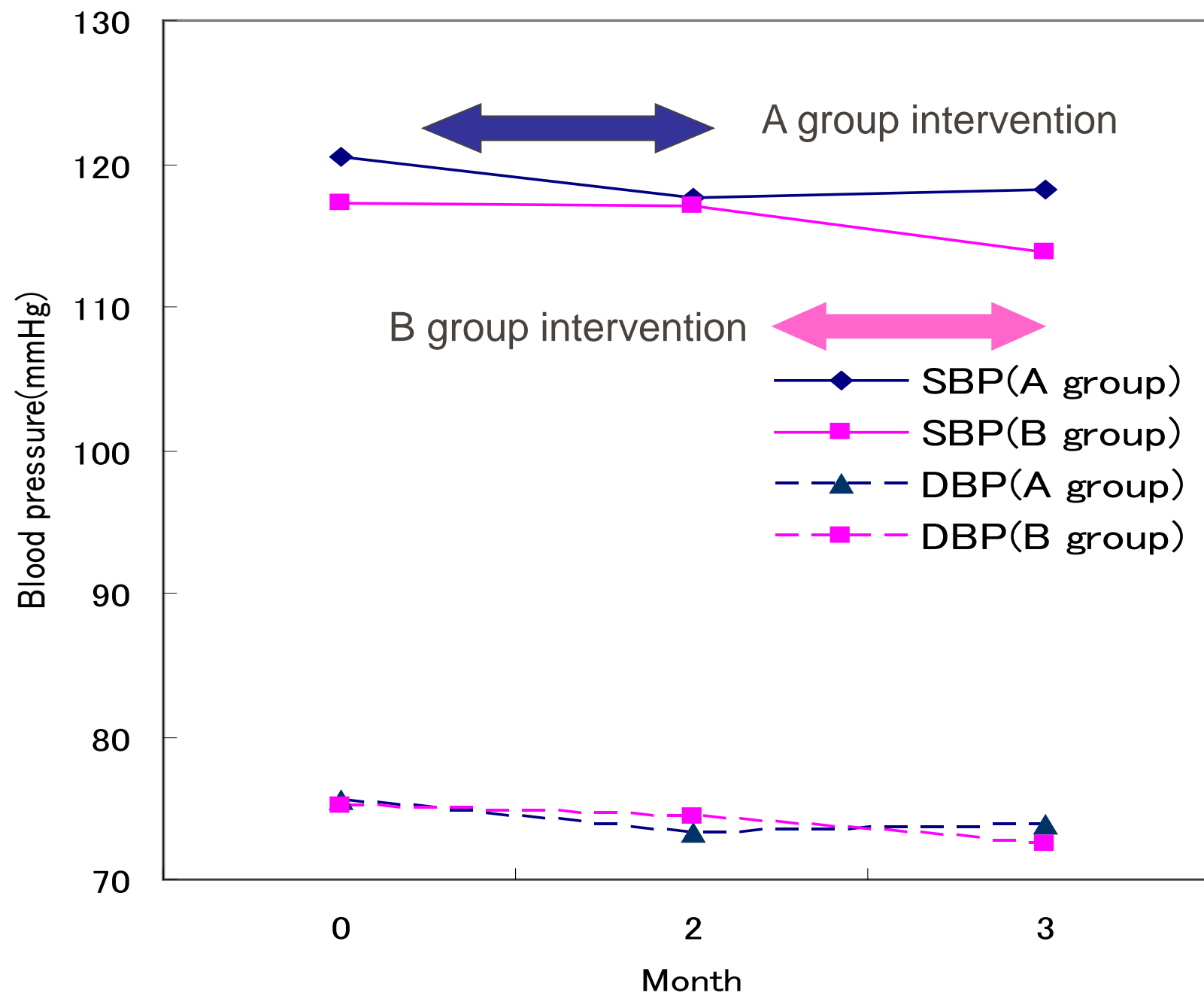


# Vacuum Packed *Bento*





# Okinawa Diet Intervention Achieves “DASH\*-like” Blood Pressure Reductions in Americans

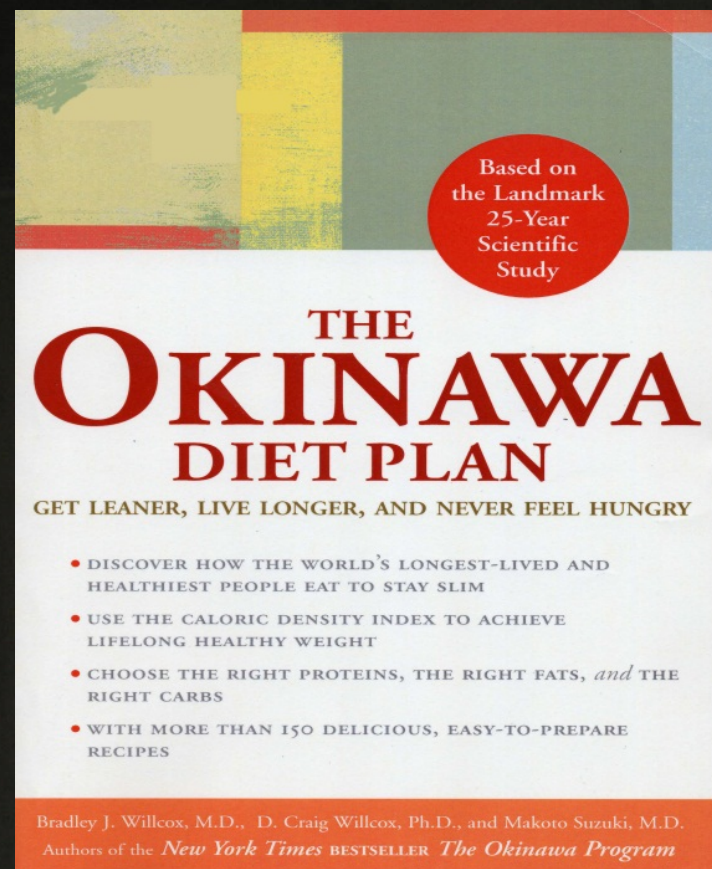


1. **SBP reduced 2.6 mm Hg** (95% CI -4.3, -1.2).
2. **DBP reduced 2.1mm Hg** (95%CI -3.1 -1.0) and 0.3mmHg (95%CI -2.1 0.6).
3. **24h-urinary sodium and body weight reduced** (between-group differences ranged from  $p=0.032$  to  $0.0002$ ).

\***Dietary Approaches to Stop Hypertension (DASH:**

Most common physician prescribed diet to lower high blood pressure in the U.S.





Try  
it !



Dr. Craig Willcox



# An Okinawan-based Nordic diet improves anthropometry, metabolic control, and health-related quality of life in Scandinavian patients with type 2 diabetes: a pilot trial.

Darwiche G<sup>1,2</sup>, Höglund P<sup>3,4</sup>, Roth B<sup>1,5</sup>, Larsson E<sup>4,6</sup>, Sjöberg T<sup>4,6</sup>, Wohlfart B<sup>4,6</sup>, Steen S<sup>4,6</sup>, Ohlsson B<sup>1,5</sup>.

## Author information

### Abstract

**BACKGROUND:** Our hypothesis was that a modified diet would improve blood glucose control with beneficial impact on weight management and overall health in established diabetes.

**OBJECTIVE:** This prospective interventional study investigated the clinical effect of an Okinawan-based Nordic diet on anthropometry, metabolic control, and health-related quality of life (HRQoL) in Scandinavian type 2 diabetes patients.

**DESIGN:** Food was prepared and delivered to 30 type 2 diabetes patients. Clinical information along with data on HRQoL, blood samples, and urine samples were collected during 12 weeks of diet interventions, with follow-up 16 weeks after diet completion.

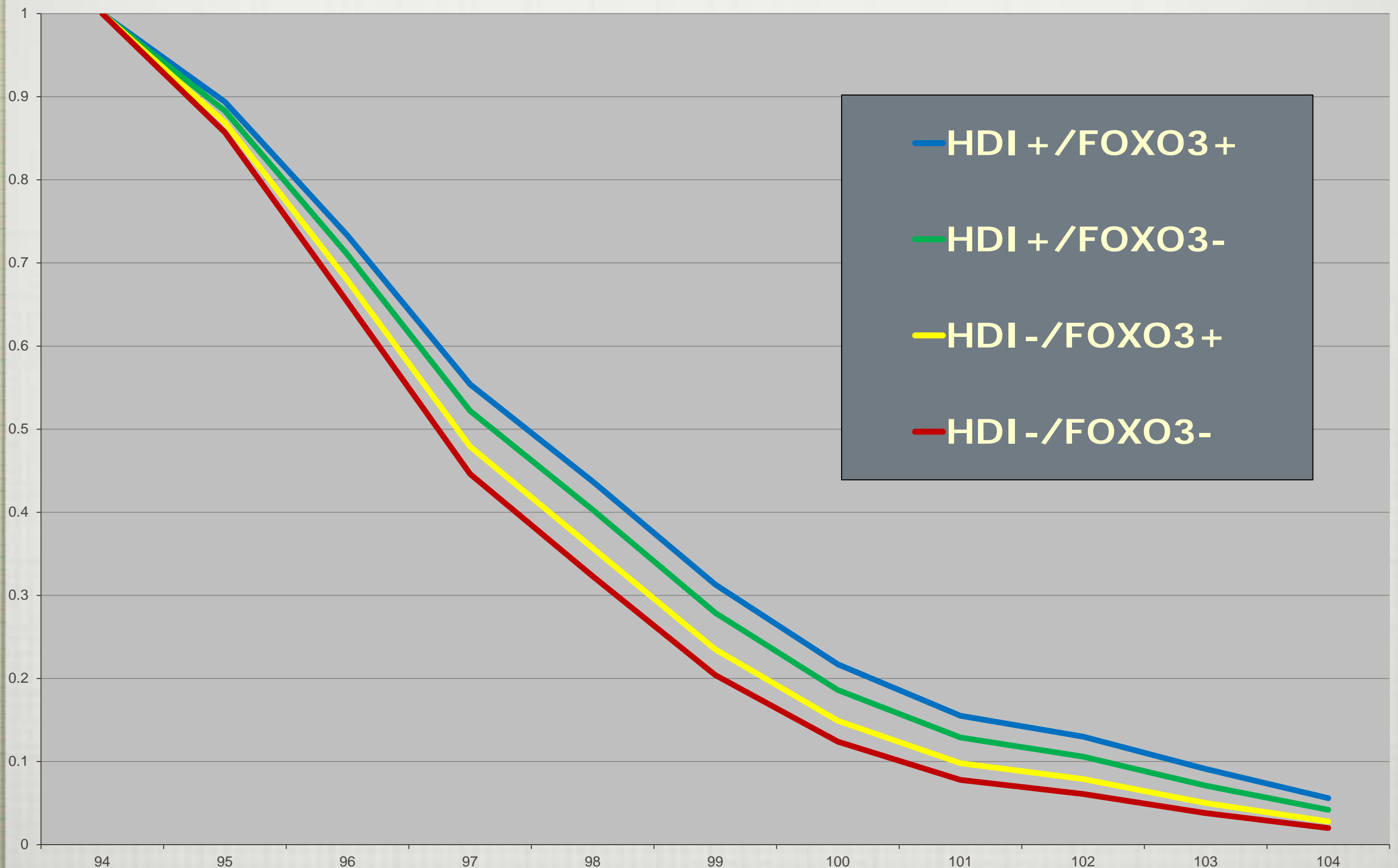
**RESULTS:** After 12 weeks of dietary intervention, a reduction in body weight (7%) ( $p < 0.001$ ), body mass index ( $p < 0.001$ ), and waist circumference (7.0 cm) ( $p < 0.001$ ) was seen. Improved levels of proinsulin ( $p = 0.005$ ), insulin ( $p = 0.011$ ), and fasting plasma glucose ( $p < 0.001$ ) were found already after 2 weeks; these improved levels remained after 12 weeks when lowered levels of C-peptide ( $p = 0.015$ ), triglycerides ( $p = 0.009$ ), total cholesterol ( $p = 0.001$ ), and low-density lipoprotein-cholesterol ( $p = 0.041$ ) were also observed. Insulin resistance homeostasis model assessment for insulin resistance was lowered throughout the study, with a 20% reduction in hemoglobin A1c levels ( $p < 0.001$ ) at week 12, despite reduced anti-diabetes treatment. Lowered systolic blood pressure (9.6 mmHg) ( $p < 0.001$ ), diastolic blood pressure (2.7 mmHg) ( $p < 0.001$ ), and heart and respiratory rates ( $p < 0.001$ ) were accompanied by decreased cortisol levels ( $p = 0.015$ ) and improvement in HRQoL. At follow-up, increased levels of high-density lipoprotein-cholesterol were found ( $p = 0.003$ ).

**CONCLUSION:** This interventional study demonstrates a considerable improvement of anthropometric and metabolic parameters and HRQoL in Scandinavian type 2 diabetes patients when introducing a modified Okinawan-based Nordic diet, independently of exercise or other interventions. Through these dietary changes, anti-diabetes treatment could be decreased or cancelled.

**KEYWORDS:** Nordic diet; Okinawan diet; anthropometry; interventional study; metabolic control; quality of life; type 2 diabetes



# Healthy Diet Index, FOXO3 Genotype and Survival



Unpublished Data: Hawaii Lifespan Study 2016

# Conclusions

- Chronic low grade inflammation may be a major determinant of ageing rate and longevity
- Recent research has uncovered important “longevity genes” and pathways that regulate the aging process (ie. FOXOs)
- Nutritional approaches such as flavonoids, polyphenols, omega 3 fatty acids, and calorie restriction are promising and further research is needed in dietary, cell-based and pharmacological strategies for healthy aging
- The Okinawa diet contains many such compounds with potentially powerful nutrigenomic effects and research is underway in order to isolate the most promising candidates (eg. Sweet potato extracts, curcumin, soy flavonoids, sanpin and green tea, etc.) that will up-regulate the most promising target genes.



# Ushi-san 102 Years Young and Still *Diggin' Life*

Mahalo !



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- Kuakini Medical Center
- US National Institute on Aging
- US National Heart, Lung, and Blood Institute
- Japan Society for the Promotion of Science

Special thanks to Dr. Makoto Suzuki (Founder of Okinawa Centenarian Study) and Dr. Hidemi Todoriki (PI of Chample Study). For more information on the Okinawa Centenarian Study see the website: [www.okicent.org](http://www.okicent.org)