REAL ACADEMIA DE MEDICINA DE LA COMUNIDAD VALENCIANA

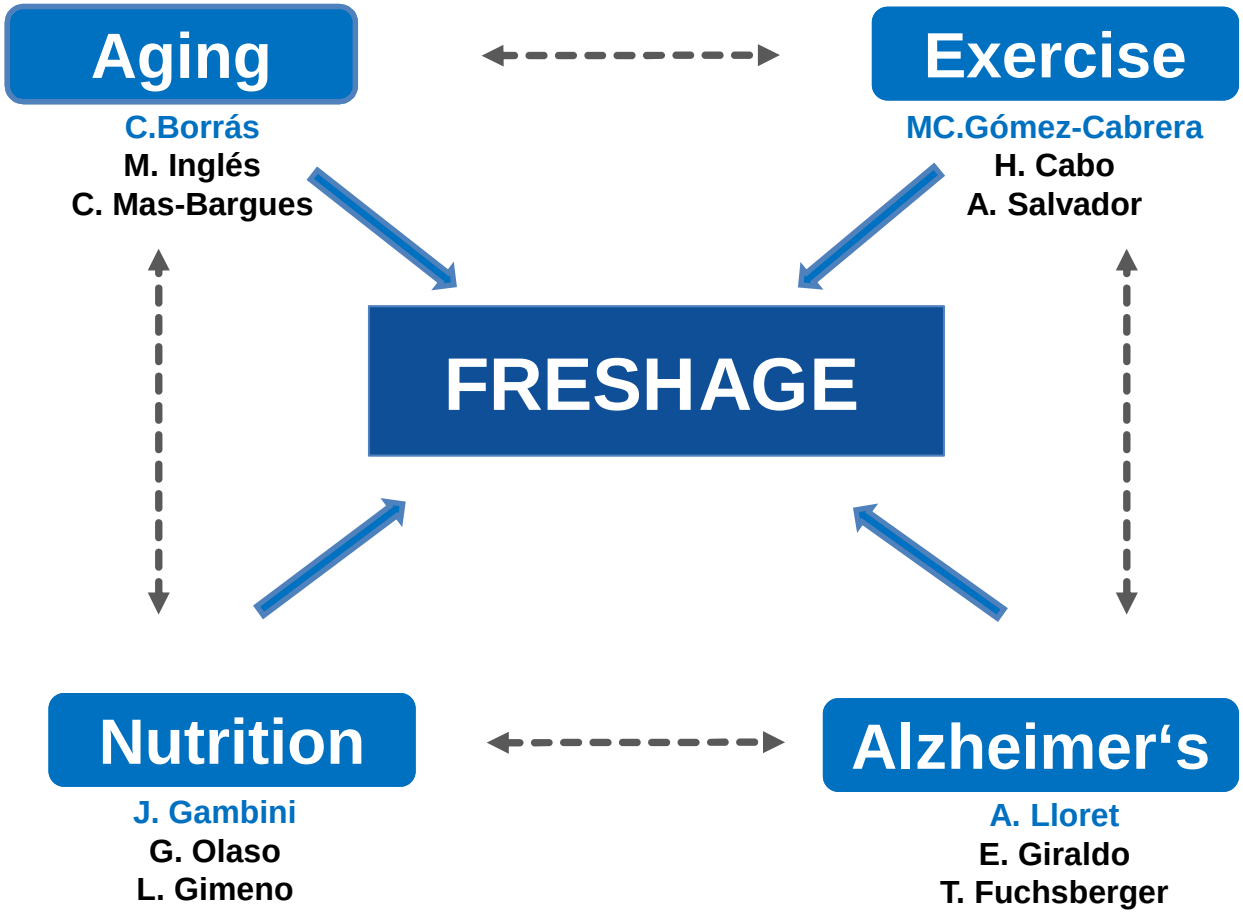
ENVEJECER ES NORMAL: REFLEXIONES DE UN GERONTÓLOGO

JOSE VIÑA

Facultad de Medicina.

UNIVERSIDAD DE VALENCIA

A TEAM IS A GROUP OF PERSONS OF DIFFERENT BACKGROUNDS AND ABILITIES THAT ATTACK A COMMON PROBLEM.



M. Dormant, J. Cuesta, C. Escrivá, MR. Noyes

ENVEJECIMIENTO FISIOLOGICO

- ¿ENVEJECIMIENTO COMO PROBLEMA?
- CARACTERISTICAS DEL ENVEJECIMIENTO: G
- CENTENARIANOS: ENVEJECIMIENTO EXCEPCI
- MODULACION DEL ENVEJECIMIENTO ¿PODEM
- COROLLARIO : ENVEJECIMIENTO SATISFACT
- MENSAJE: CUIDESE HOY

1988- 2013

INSTITUTO GERONTOLÓGICO de la COMUNIDAD VALENCIANA

Fundado en 1988

Entidad sin ánimo de lucro para fomentar la investigación en el envejecimiento

Instituto Gerontológico de la Comunidad Valenciana
Departamento de Fisiología, Facultad de Medicina,
Avda. Blasco Ibáñez 15
46010 VALENCIA
Tno. 96 386 4646 Fax 96 386 4642

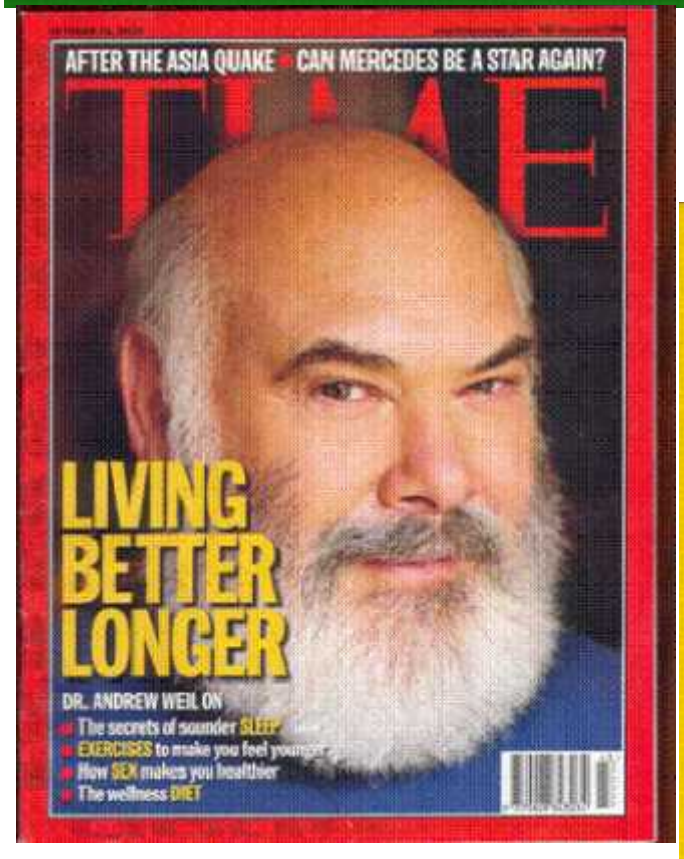
Presidente
José Viña

Secretario
Federico V.

Aging as a problem:THAÏS

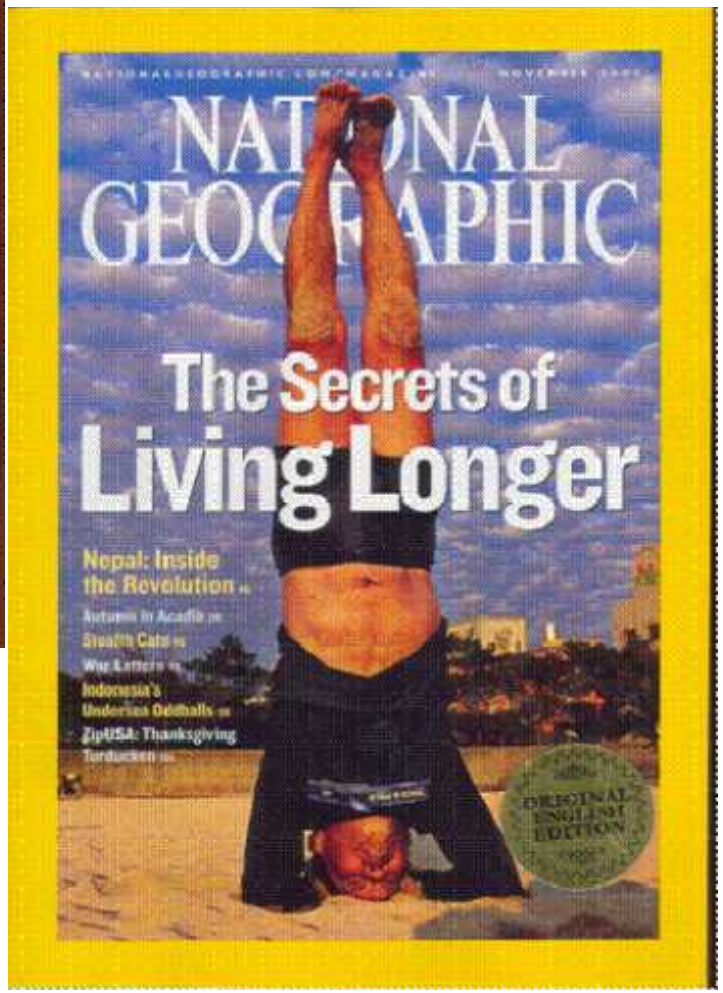
Ah ! tais-toi, voix impitoyable, Voix que me dis: **Thaïs**, **tu vieilliras**! Un jour, ainsi,
Thaïs ne serait plus **Thaïs**! Non! Non! je n’y puis croire

Social impact of aging studies

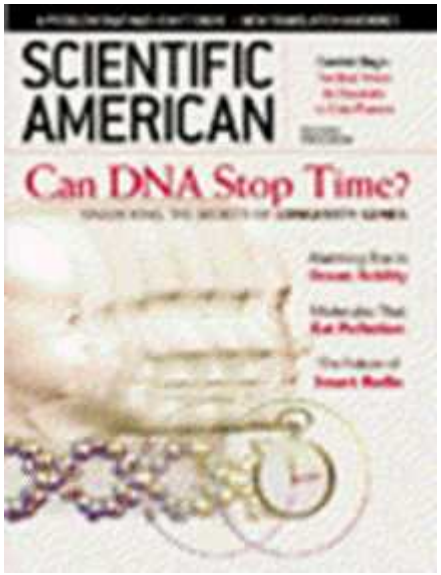


Time
October 2005

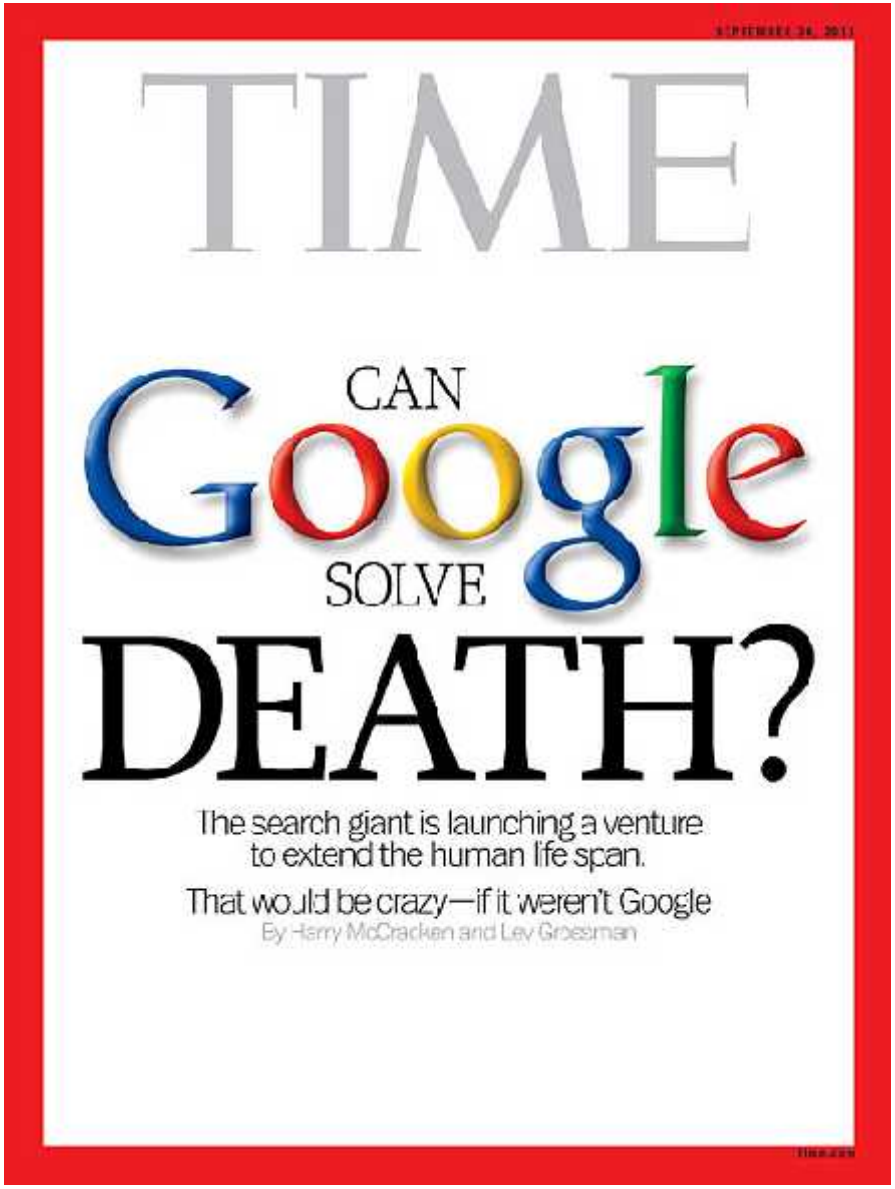
National Geographic
November 2005



Scientific American
March 2006



TIME: sept 10, 2013



TIME: feb 23, 2015

ENVEJECIMIENTO FISIOLOGICO

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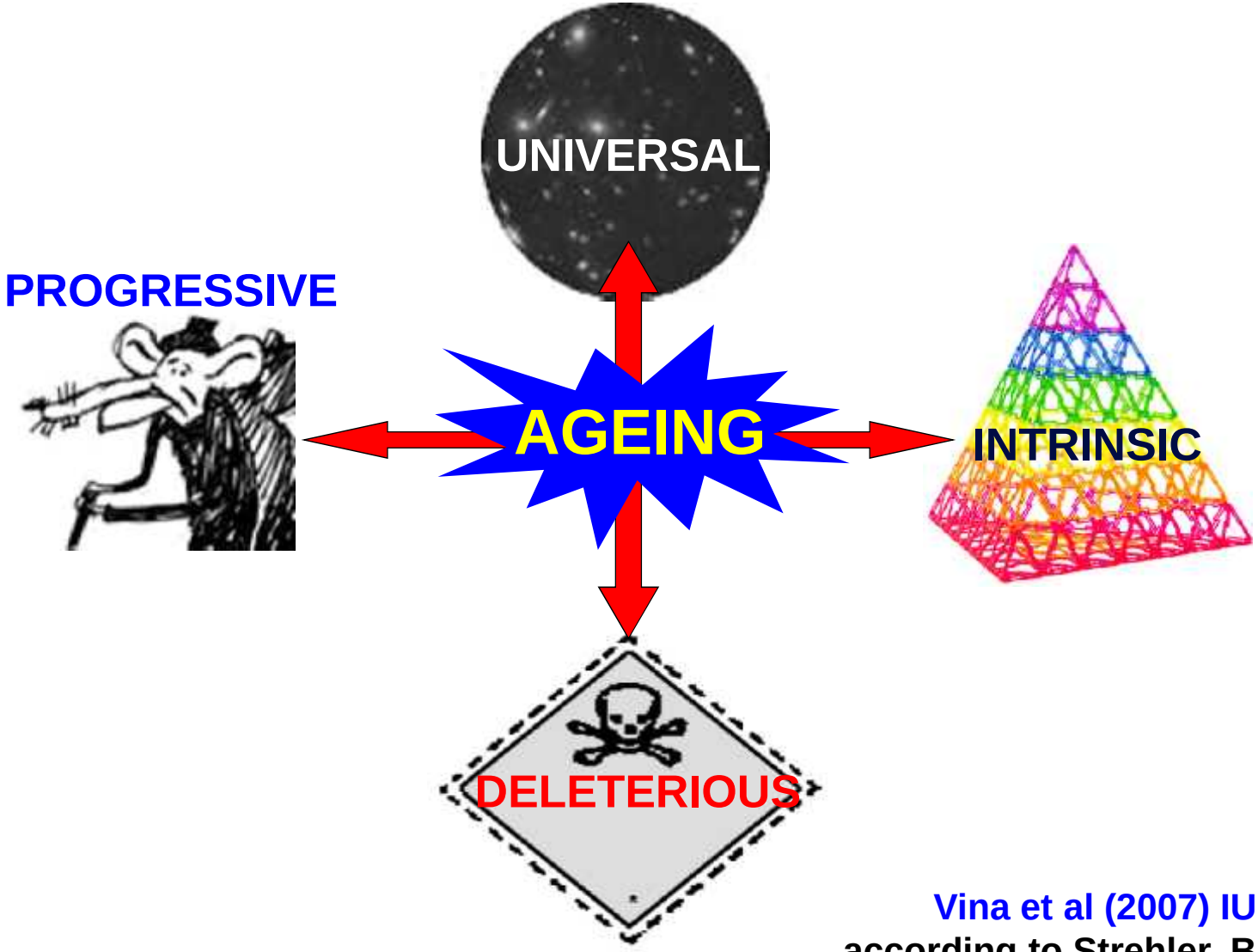
Characteristics of aging



Vina et al (2007) IUBMB Life,
according to Strehler, B. L. (1977)

Aging is not a disease: AGE ASSOCIATED CHANGES

Biological Aging Is No Longer an Unsolved Problem

LEONARD HAYFLICK

Ann. N.Y. Acad. Sci. 1100: 1–13 (2007). © 2007 New York Academy of Sciences.
doi: 10.1196/annals.1395.001

Aging is not a disease: AGE ASSOCIATED CHANGES

(1) occur in every multicellular animal that reaches a fixed size at reproductive maturity
(2) cross virtually all species barriers
(3) occur in all members of a species only after the age of reproductive maturation

Aging is not a disease: AGE ASSOCIATED CHANGES

(4) occur in all animals removed from the wild and protected by humans even when that species probably has not experienced aging for thousands or even millions of years
(5) occur in virtually all animate and inanimate matter
(6) have the same universal molecular etiology, that is, thermodynamic instability.

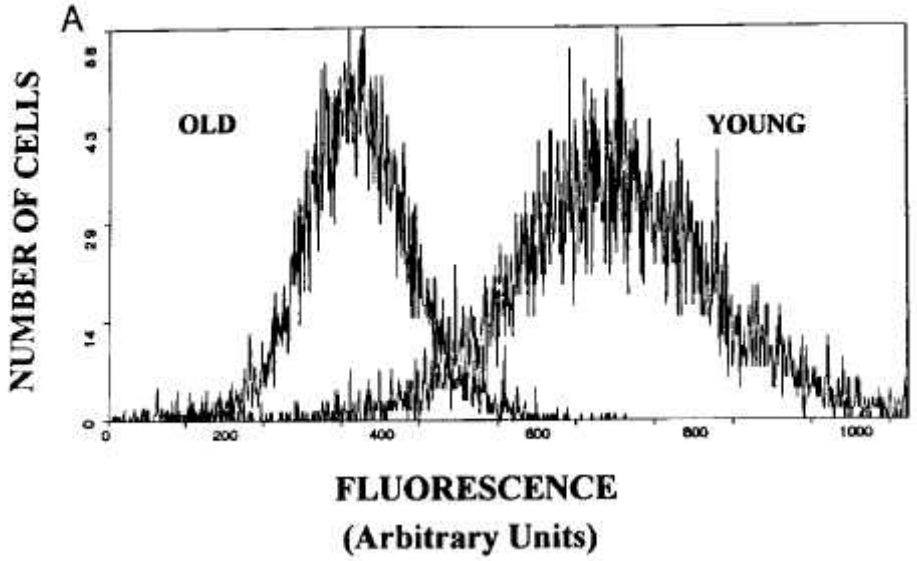
Unlike aging, there is no disease or pathology that shares these six qualities.

The role of mitochondria in aging

Aging of the Liver: Age-Associated Mitochondrial Damage in Intact Hepatocytes

JUAN SASTRE,[1] FEDERICO V. PALLARDÓ,[1] ROSA PLÁ,[1] ANTONIO PELLÍN,[2] GLORIA JUAN,[3] JOSÉ E. O'CONNOR,[3] JOSÉ M. ESTRELA,[1] JAIME MIQUEL,[4] AND JOSÉ VIÑA[1]

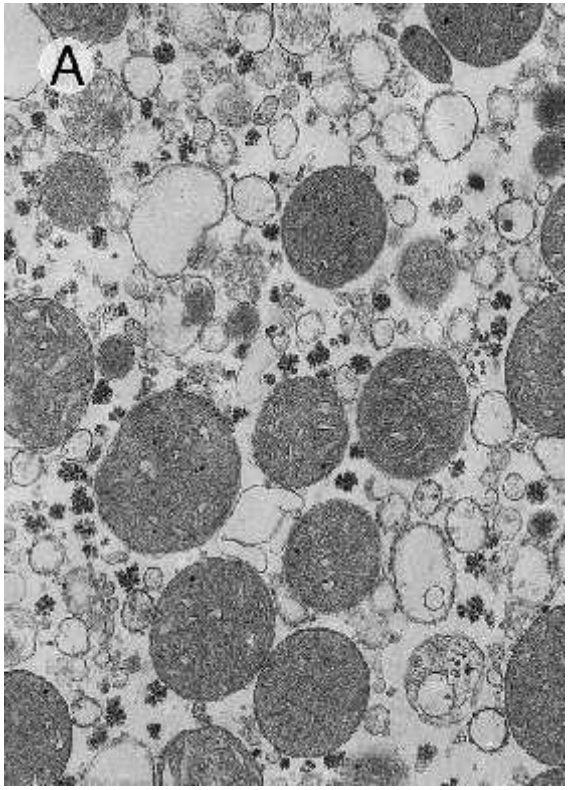
fell in hepatocytes from old rats. Our results show, for the first time in intact cells, a correlation between age-associated impairment of cell metabolism and specific changes in mitochondrial function and morphology, supporting the hypothesis that mitochondrial damage plays a key role in aging. (HEPATOLOGY 1996;24:1199-120

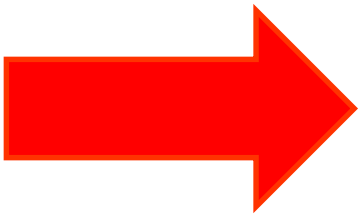


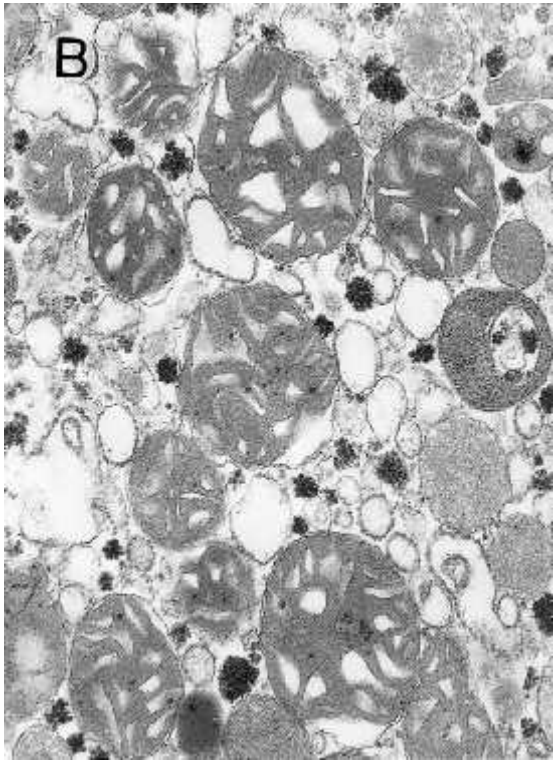
Role of mitochondria in aging

Aging of the Liver: Age-Associated Mitochondrial Damage in Intact Hepatocytes

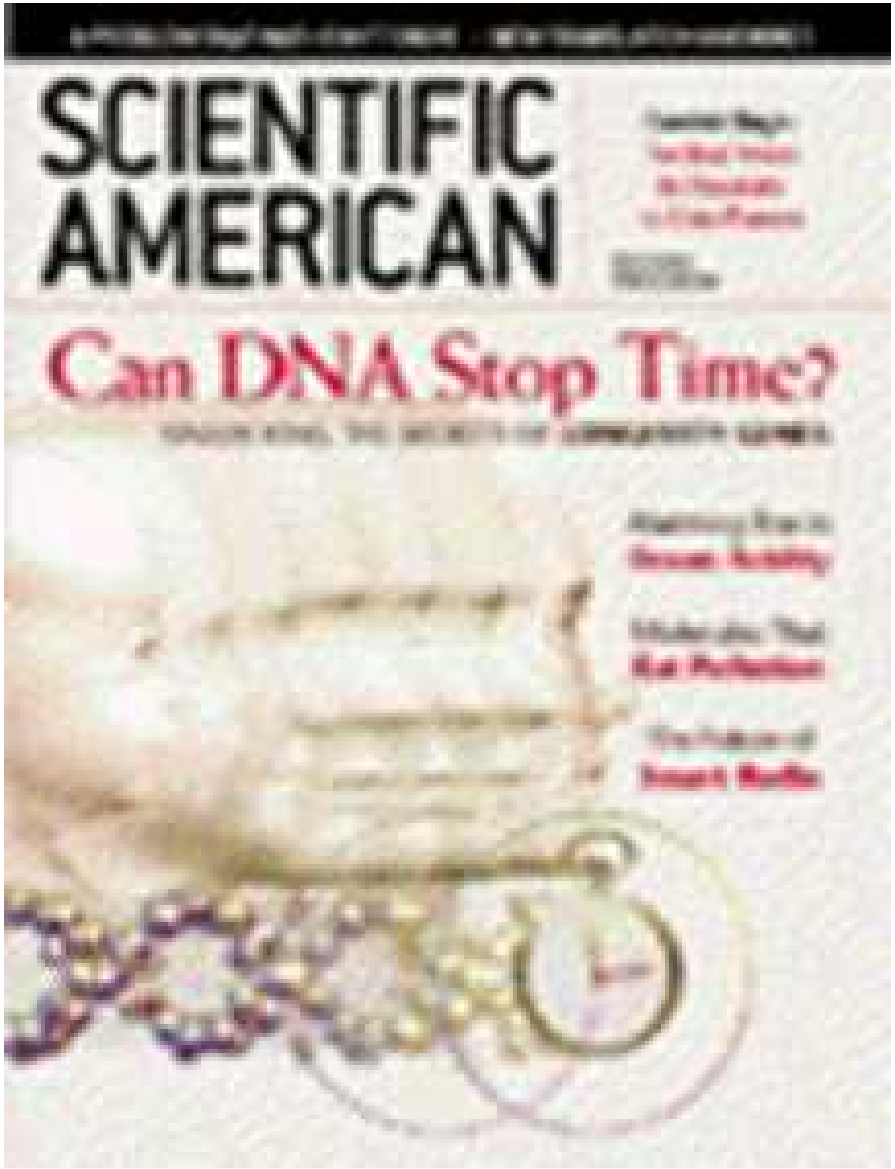
Juan Sastre,[1] Federico V. Pallardó,[1] Rosa Plá,[1] Antonio Pellín,[2] Gloria Juan,[3] José E. O'Connor,[3] José M. Estrela,[1] Jaime Miquel,[4] and José Viña[1]







LA BUSQUEDA DE GENES DE LONGEVIDAD

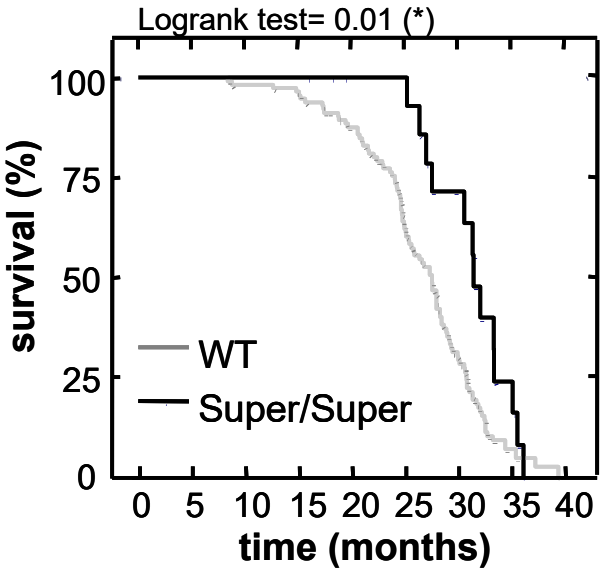


The search for longevity genes: p53

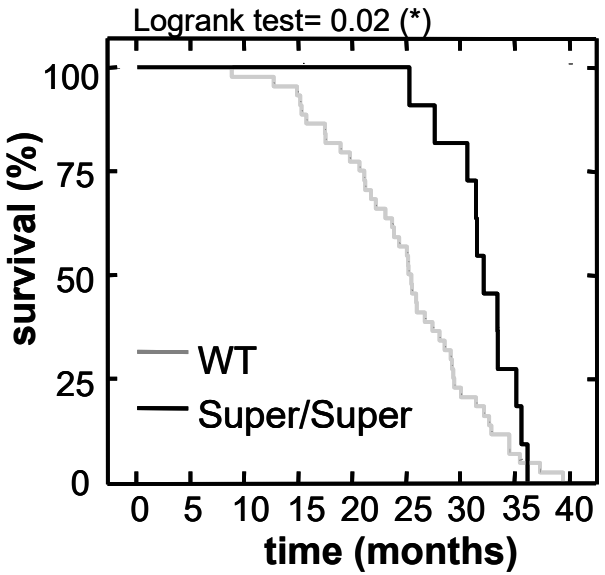
Delayed ageing through damage protection by the Arf/p53 pathway

Ander Matheu[1]*†, Antonio Maraver[1]*, Peter Klatt[1], Ignacio Flores[2], Isabel Garcia-Cao[1], Consuelo Borras[3]†, Juana M. Flores[4], Jose Viña[3], Maria A. Blasco[2] & Manuel Serrano[1]

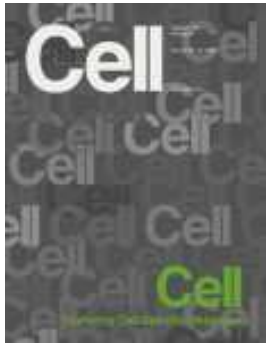
spontaneous survival curve



survival curve without tumors



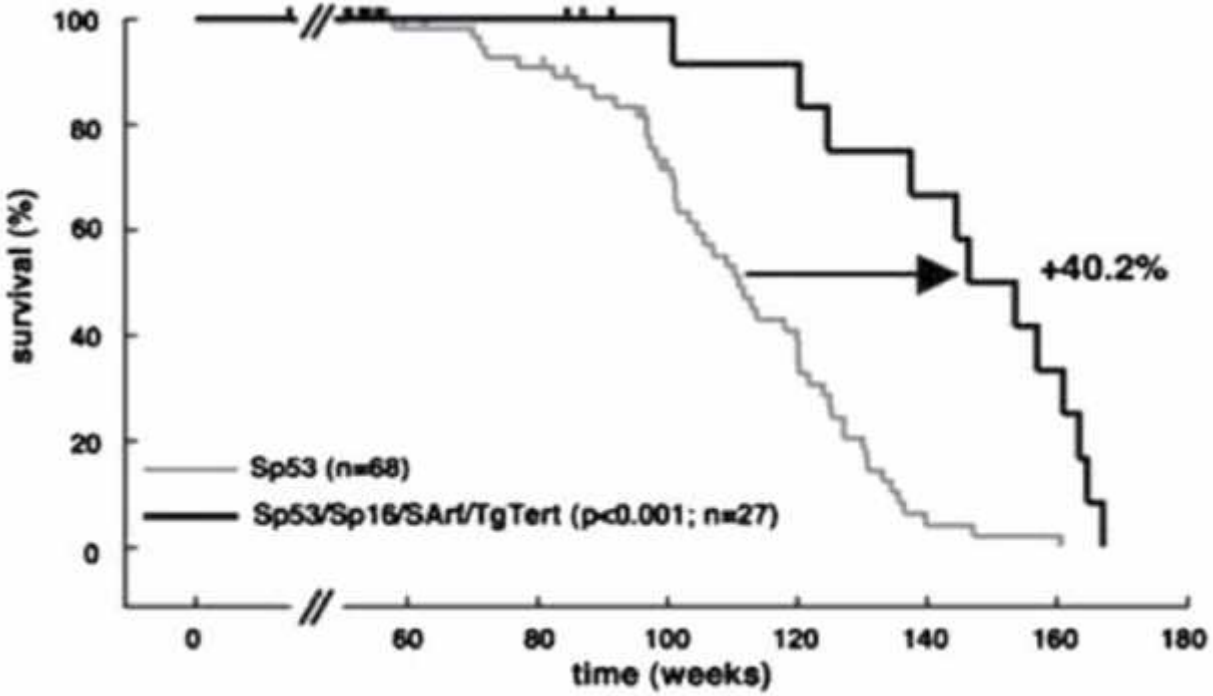
The search for longevity genes: telomerase



Telomerase Reverse Transcriptase Delays Aging in Cancer-Resistant Mice

Antonia Tomás-Loba,[1,5] Ignacio Flores,[1,5] Pablo J. Fernández-Marcos,[2] María L. Cayuela,[1,6] Antonio Maraver,[2] Agueda Tejera,[1] Consuelo Borrás,[3] Ander Matheu,[2] Peter Klatt,[1,2] Juana M. Flores,[4] José Viña,[3] Manuel Serrano,[2] and Maria A. Blasco[1,*]

Sp53
vs
Sp53/Sp16/SArf/TgTert



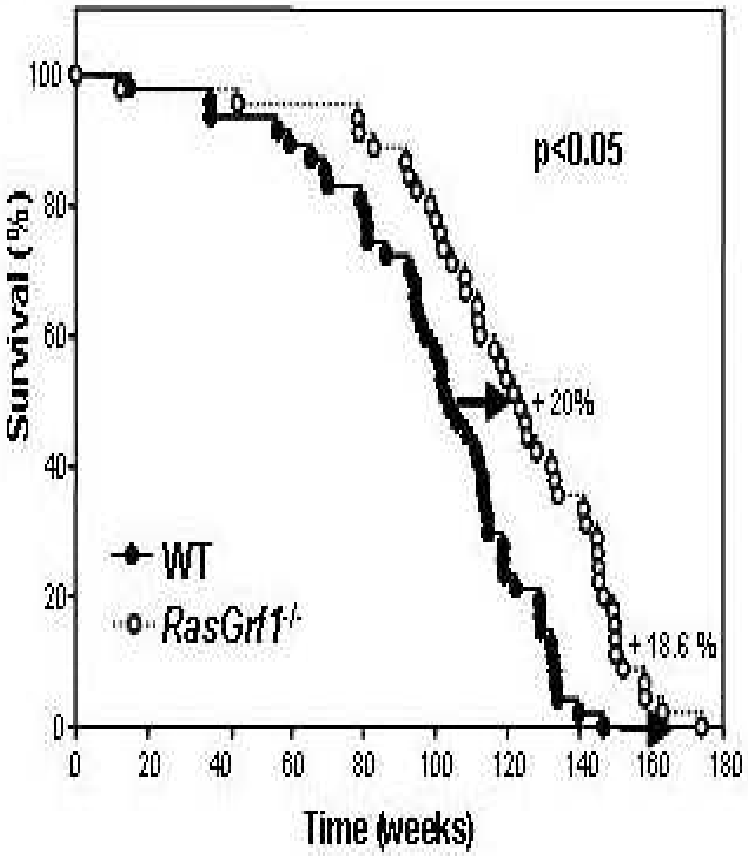
www.impactaging.com AGING, March 2011, Vol. 3 No 3

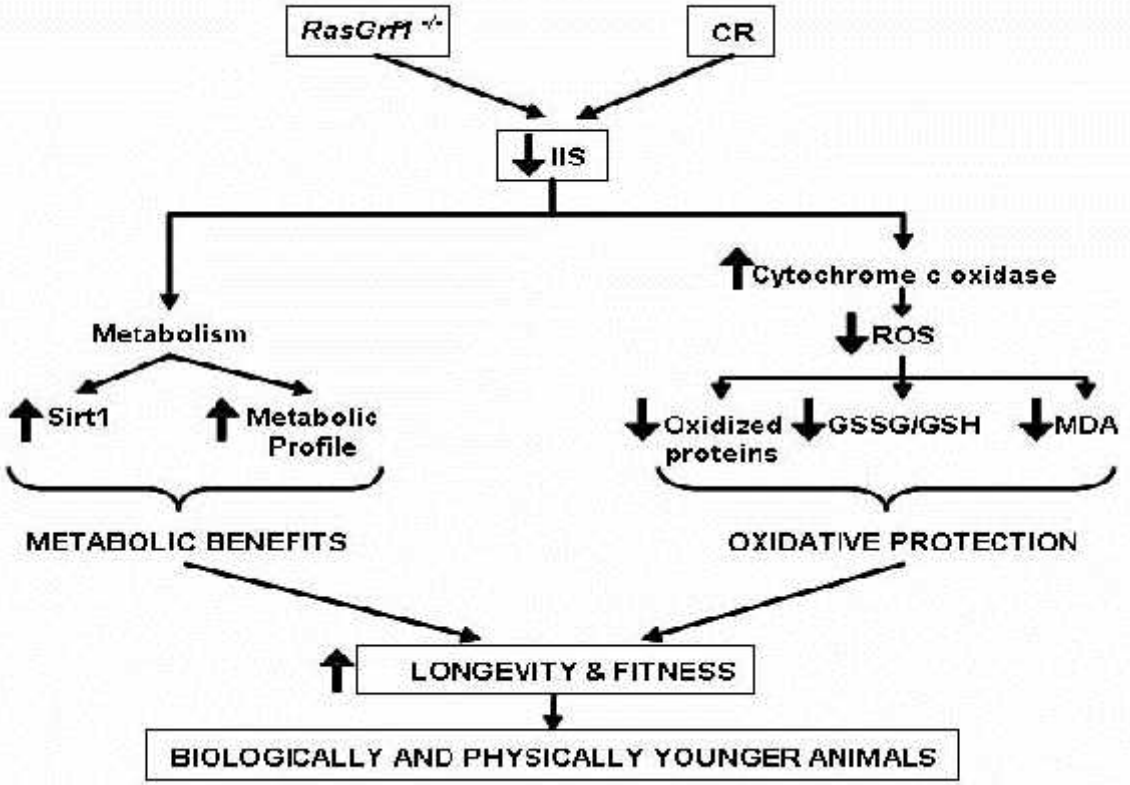
Research Paper

RasGrf1 deficiency delays dging in mice

Consuelo Borrás[1], Daniel Monleón[2], Raul López-Grueso[1], Juan Gambini[1], Leonardo Orlando[3], Federico V. Pallardó[1], Eugenio Santos[4], José Viña[1,*] and Jaime Font de Mora[3,*]

The search for longevity genes: Ras





AGING : THE PROBLEM WITH MODELS

CALORIC RESTRICTION

- MICE (NEJM)

AGING : THE PROBLEM WITH MODELS

CALORIC RESTRICTION

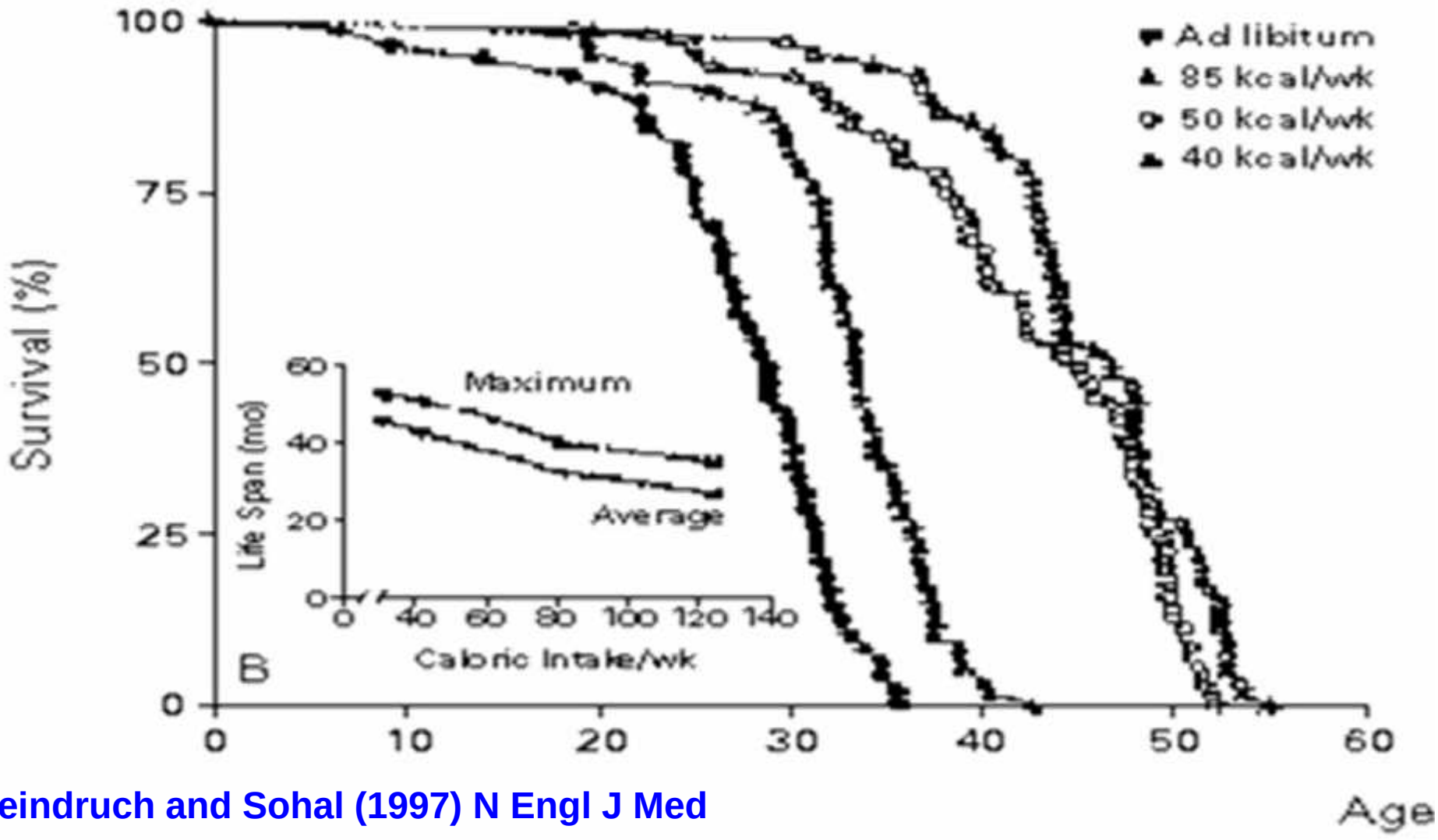
- MICE (NEJM)
- MONKEYS (Science vs Nature)

AGING : THE PROBLEM WITH MODELS

CALORIC RESTRICTION

- MICE (NEJM)
- MONKEYS (Science vs Nature)
- HUMANS (JAMA)

Caloric restriction increases life span in mice



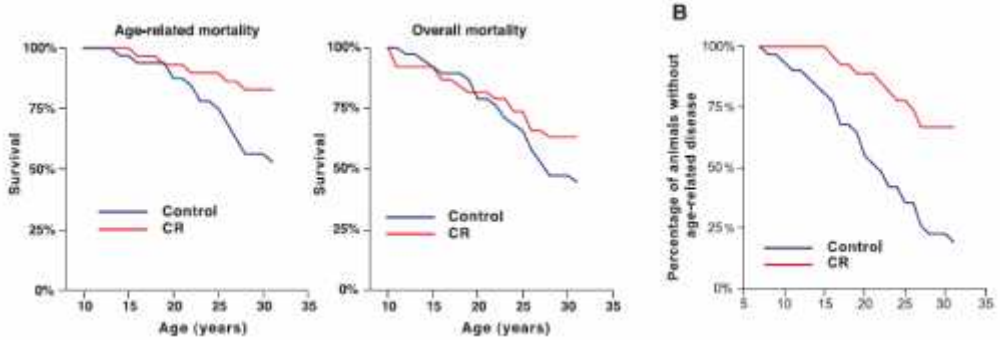
Weindruch and Sohal (1997) N Engl J Med

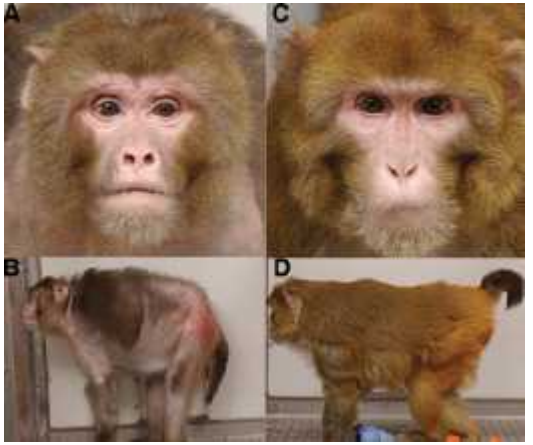
Science **325**, 201 (2009);

Science
AAAS

Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys

Ricki J. Colman,[1]* Rozalyn M. Anderson,[1] Sterling C. Johnson,[1,2,3] Erik K. Kastman,[2,3] Kristopher J. Kosmatka,[2,3] T. Mark Beasley,[4] David B. Allison,[4] Christina Cruzen,[1] Heather A. Simmons,[1] Joseph W. Kemnitz,[1,2,5] Richard Weindruch[1,2,3]*



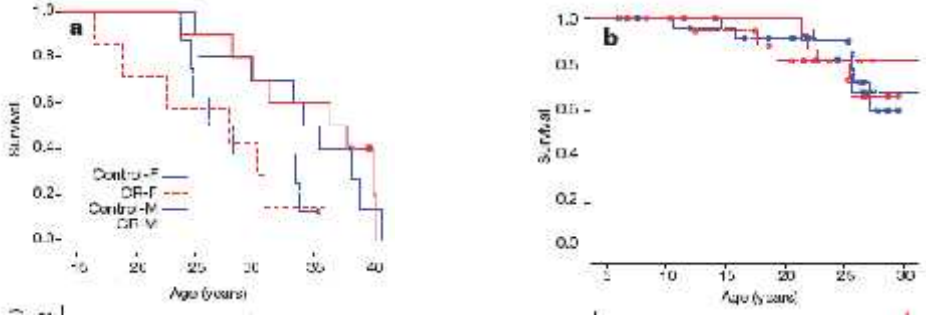


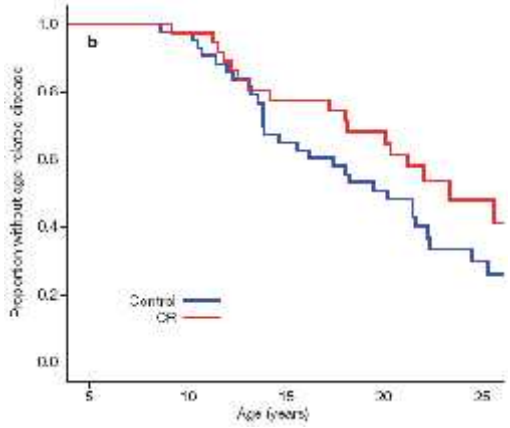
LETTER

doi:10.1038/nature11432

Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study

Julie A. Mattison[1], George S. Roth[2], T. Mark Beasley[3], Edward M. Tilmont[3], April M. Handy[1,2], Richard L. Herbert[4], Dan L. Longo[4], David B. Allison[3], Jennifer E. Young[1], Mark Bryant[5], Dennis Barnard[5], Walter F. Ward[1,6], Wenbo Qi[1], Donald K. Ingram[1,2] & Rafael de Cabo[1,2]





BMI and mortality

Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories

A Systematic Review and Meta-analysis

Katherine M. Flegal, PhD
Brian K. Kit, MD
Heather Orpana, PhD
Barry I. Graubard, PhD

Importance Estimates of the relative mortality risks associated with normal weight, overweight, and obesity may help to inform decision making in the clinical setting.

Objective To perform a systematic review of reported hazard ratios (HRs) of all-cause mortality for overweight and obesity relative to normal weight in the general population.

Data Sources PubMed and EMBASE electronic databases were searched through September 30, 2012, without language restrictions.

Study Selection Articles that reported HRs for all-cause mortality using standard body mass index (BMI) categories from prospective studies of general populations of adults were selected by consensus among multiple reviewers. Studies were excluded that used nonstandard categories or that were limited to adolescents or to those with specific medical conditions or to those undergoing specific procedures. PubMed searches yielded 7034 articles, of which 141 (2.0%) were eligible. An EMBASE search yielded 2 additional articles. After eliminating overlap, 97 studies were retained for analysis, providing a combined sample size of more than 2.88 million individuals and more than 270 000 deaths.

Data Extraction Data were extracted by 1 reviewer and then reviewed by 3 independent reviewers. We selected the most complex model available for the full sample and used a variety of sensitivity analyses to address issues of possible overadjustment (adjusted for factors in causal pathway) or underadjustment (not adjusted for at least age, sex, and smoking).

Results Random-effects summary all-cause mortality HRs for overweight (BMI of 25–<30), obesity (BMI of ≥30), grade 1 obesity (BMI of 30–<35), and grades 2 and 3 obesity (BMI of ≥35) were calculated relative to normal weight (BMI of 18.5–<25). The summary HRs were 0.94 (95% CI, 0.91–0.96) for overweight, 1.18 (95% CI, 1.12–1.25) for obesity (all grades combined), 0.96 (95% CI, 0.88–1.04) for grade 1 obesity, and 1.29 (95% CI, 1.18–1.41) for grades 2 and 3 obesity. These findings persisted when limited to studies with measured weight and height that were considered to be adequately adjusted. The HRs tended to be higher when weight and height were self-reported rather than measured.

Conclusions and Relevance Relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality. The use of prespecified standard BMI groupings can facilitate between-study comparisons.

JAMA. 2013;309(1):71-82 www.jama.com

THE TOPIC OF THE MORTALITY differences between weight categories has sometimes been described as controversial.[1] The appearance of controversy may arise in part because studies of body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) and mortality have used a wide variety of BMI categories and varying reference categories, which can make findings appear more variable than when standard categories are used and also can make it difficult to compare and synthesize studies. A report[2] in 1997 from the World Health Organization Consultation on Obesity defined BMI-based categories of underweight, normal weight, preobesity, and obesity. The same cutoff BMI values were adopted by the National Heart, Lung, and Blood Institute in 1998.[3]

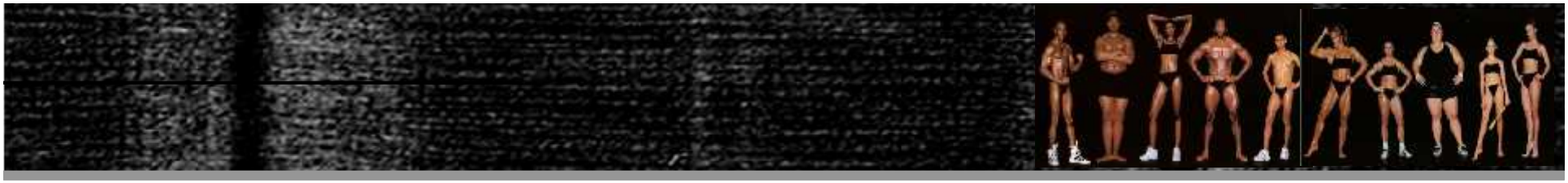
In this study, we used the National Heart, Lung, and Blood Institute's

For editorial comment see p 87.

CME available online at www.jamaarchivescme.com and questions on p 91.

Author Video Interview available at www.jama.com.

Author Affiliations: National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland (Drs Flegal and Kit); School of Psychology, University of Ottawa, Ottawa, Ontario, Canada (Dr Orpana); and Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Dr Graubard).
Corresponding Author: Katherine M. Flegal, PhD, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Rd, Room 4336, Hyattsville, MD 20782 (kmf2@cdc.gov).



Letter to the Editor JAMA

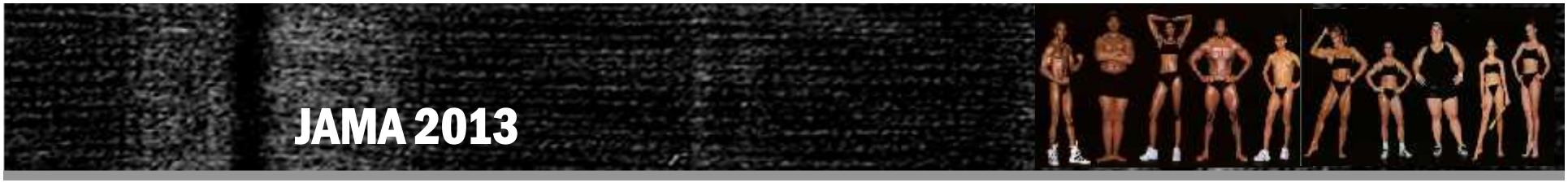
Title: Overweight is not overweight : comment on “Association of all-cause mortality with overweight and obesity” .

Authors: Jose Viña, Consuelo Borras, and Mari Carmen Gomez-Cabrera

JAMA13-0598 Decision Letter

Dear Prof. Vina:

We have completed our review of your Letter to the Editor and are pleased to accept it for publication in JAMA. Your manuscript is accepted with the understanding that its contents, all or in part, have not been published elsewhere and will not be published elsewhere in print or electronic format except in abstract form or by the consent of the editor.



. Thus, direct estimates of total fat mass will provide a more accurate body assessment. It has been shown that, for the general population, in addition to BMI, waist circumference and waist to hip ratio are of importance for assessing mortality risk [7].

Consequently, even though it is widely accepted, classifications of obesity based on BMI are inadequate. **Indeed, if overweight decreases all-cause mortality, then it is not overweight.**

Viña et al JAMA, 2013

Overweight and life span

The *big fat* truth

More and more studies show that being overweight does not always shorten life — but some public-health researchers would rather not talk about them.

BY VIRGINIA HUGHES

Late in the morning on 20 February, more than 200 people packed an auditorium at the Harvard School of Public Health in Boston, Massachusetts. The purpose of the event, according to its organizers, was to explain why a new study about weight and death was absolutely wrong.

The report, a meta-analysis of 97 studies including 2.88 million people, had been released on 2 January in the *Journal of the American Medical Association* (*JAMA*)[1]. A team led by Katherine Flegal, an epidemiologist at the National Center for Health Statistics in Hyattsville, Maryland, reported that people deemed 'overweight' by international standards were 6% less likely to die than were those of 'normal' weight over the same time period.

The result seemed to counter decades of advice to avoid even modest weight gain, provoking coverage in most major news outlets — and a hostile backlash from some public-health experts. "This study is really a pile of rubbish, and no one should waste their time reading it," said Walter Willett, a leading nutrition and epidemiology researcher at the Harvard school, in a radio interview. Willett later organized the Harvard symposium — where speakers lined up to critique Flegal's study — to counteract that coverage and highlight what he and his colleagues saw as problems with the paper. "The Flegal paper was so flawed, so misleading and so confusing to so many people, we thought it really would be important to dig down more deeply," Willett says.

But many researchers accept Flegal's results and see them as just the latest report illustrating what is known as the obesity paradox. Being overweight increases a person's risk of diabetes, heart disease, cancer and many

ILLUSTRATION BY GARY NEIL

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- COROLLARIO : ENVEJECIMIENTO SATISFACT
- MENSAJE: CUIDESE HOY

The Spanish centenarian study

Which genes are modulated in extreme longevity?

Unión Europea
Fondo Europeo de Desarrollo Regional

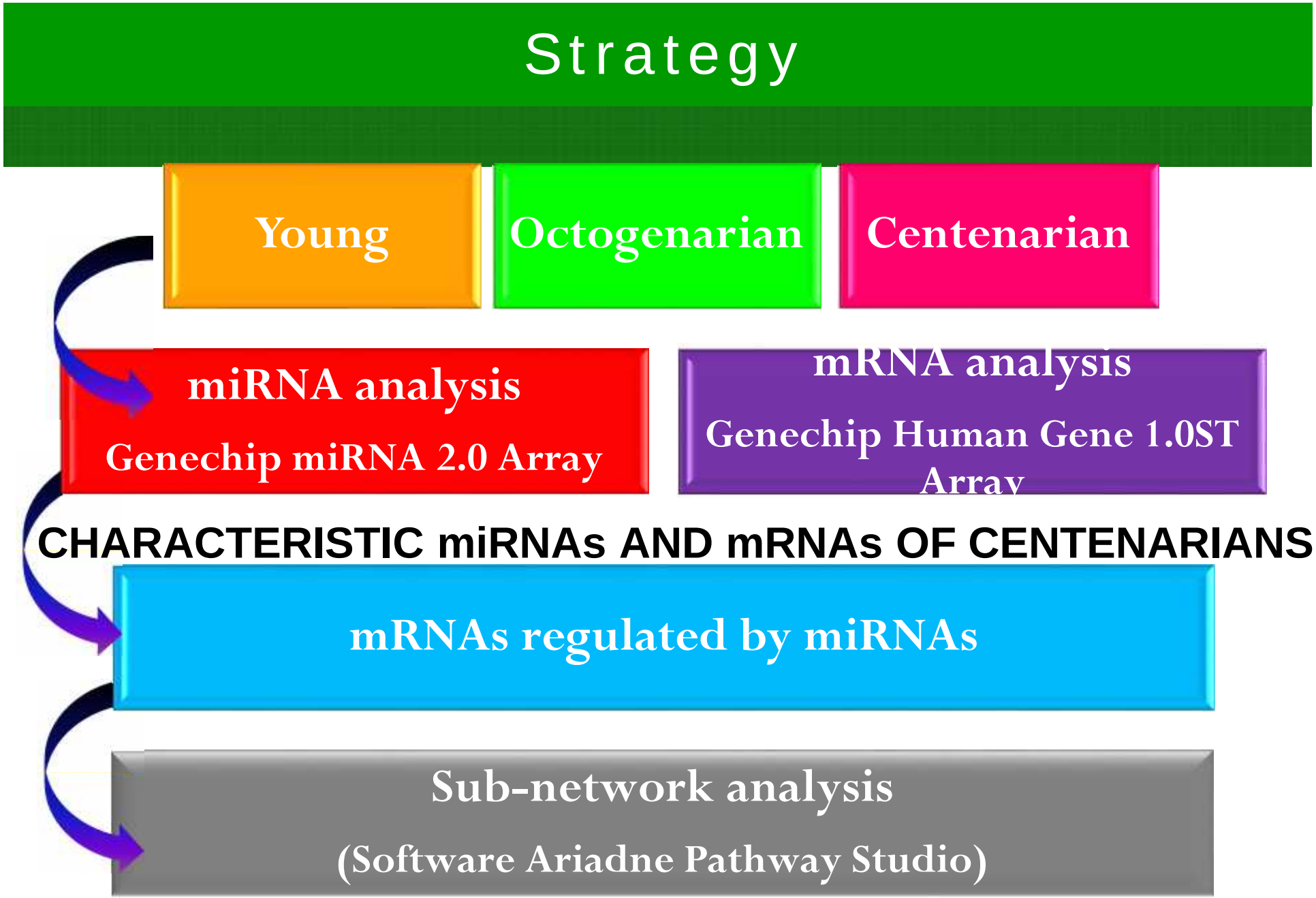
red envejecimiento y fragilidad

VNIVERSITAT DE VALÈNCIA

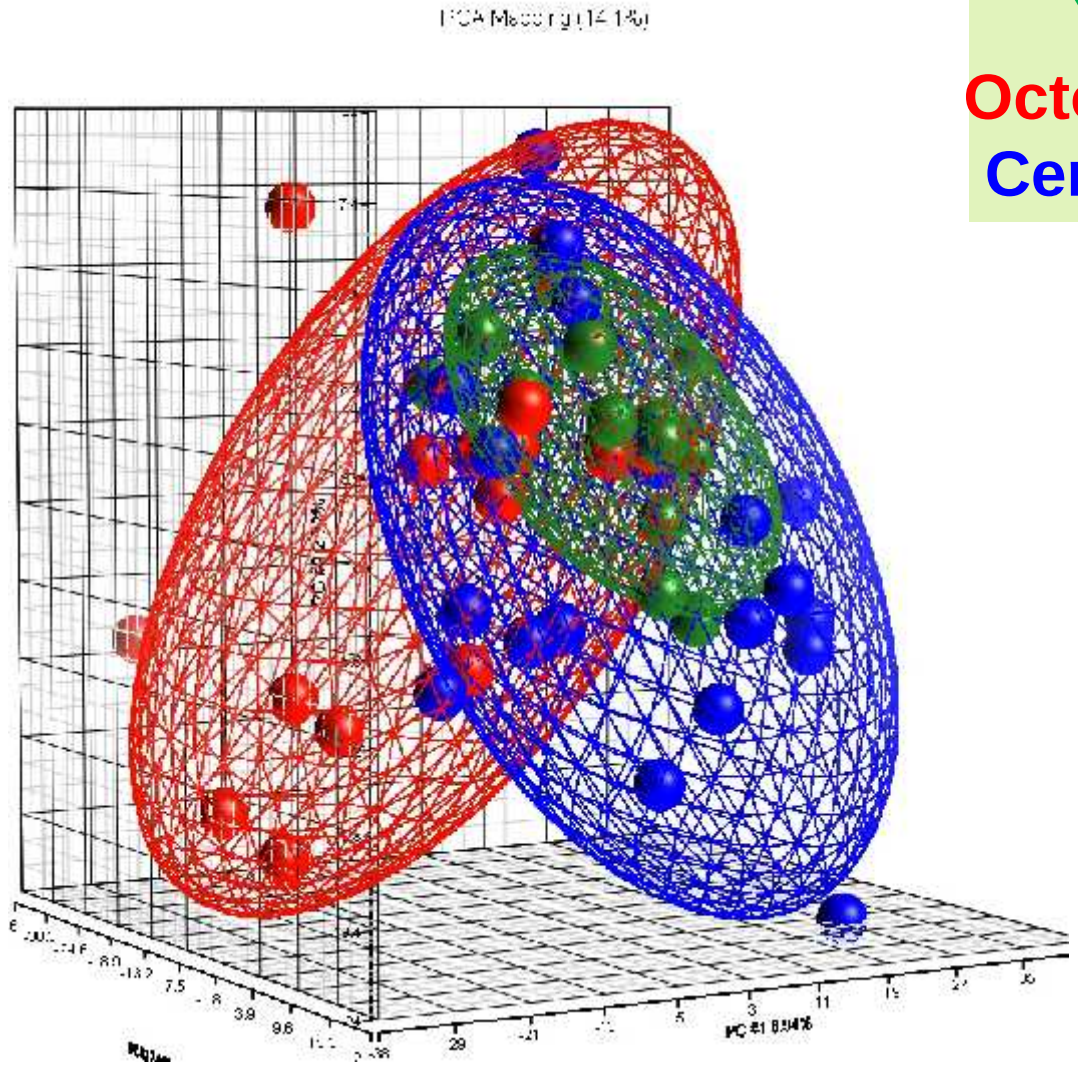
HOSPITAL DE LA RIBERA
ÁREA DE SALUD 10

Unpublished results

Strategy


Young
Octogenarian
Centenarian
miRNA analysis
Genechip miRNA 2.0 Array
mRNA analysis
Genechip Human Gene 1.0ST Array
CHARACTERISTIC miRNAs AND mRNAs OF CENTENARIANS
mRNAs regulated by miRNAs
Sub-network analysis
(Software Ariadne Pathway Studio)

miRNAs in centenarians



Young
Octogenarian
Centenarian

miRNAs are similar in young and centenarians!!!!!

Centenarians up-regulate miRNAs

Pvalue≤0.05 Fold-change|1.8|	Up-regulated	Down-regulated	All
C vs Y	7	0	7
O vs Y	1	50	51
C vs O	102	1	103

Functional transcriptomic analysis

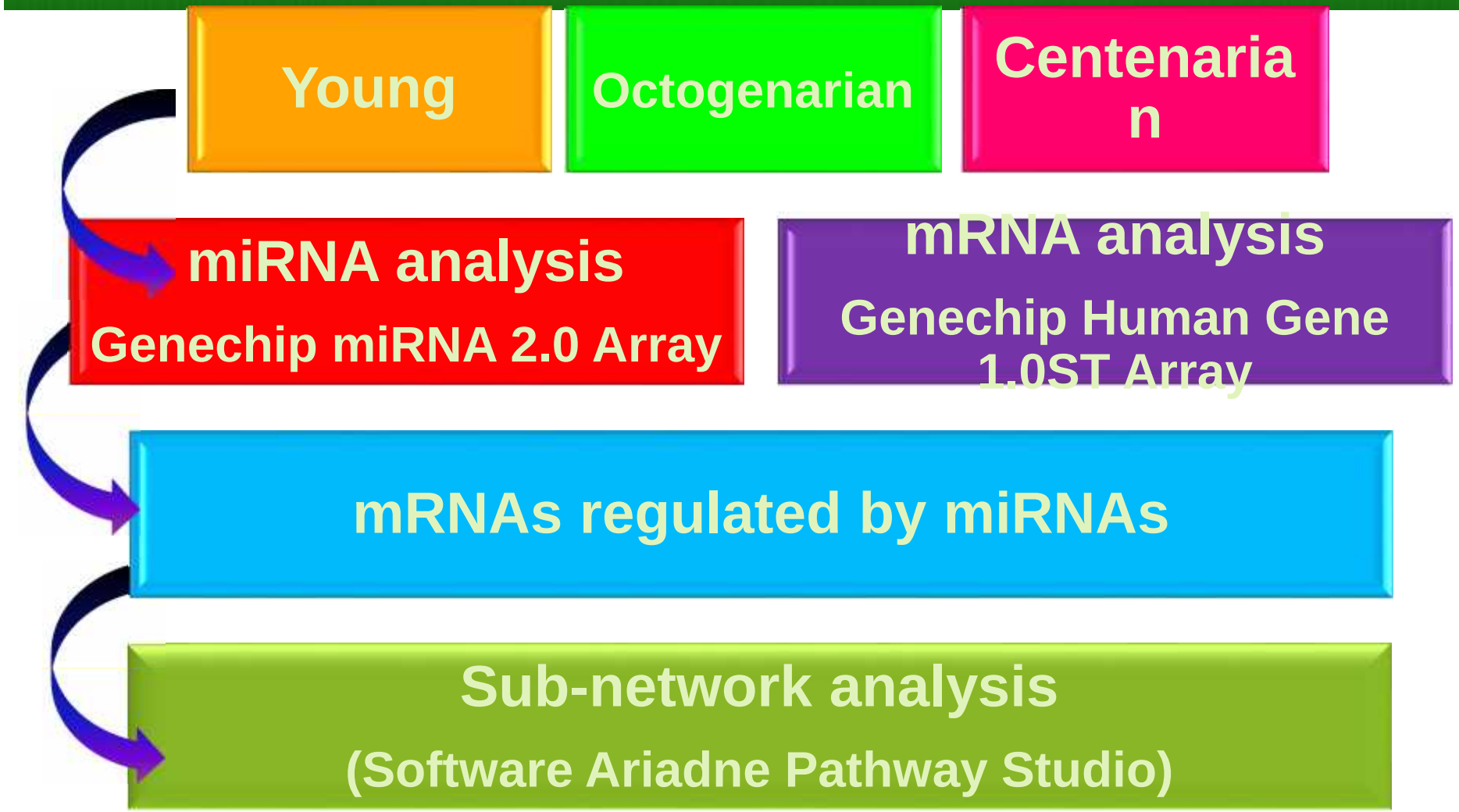
Centenarians, but not octogenarians, up-regulate the expression of microRNAs

Eva Serna[1], Juan Gambini[2], Consuelo Borras[2], Kheira Mohammed[2], Angel Belenguer[3], Paula Sanchis[3], Juan A. Avellana[3], Leocadio Rodriguez- Mañas[4] & Jose Viña[2]

SCIENTIFIC REPORTS SREP-12-02982-T.3d 3/12/12 13:37:19

www.nature.com/scientific reports

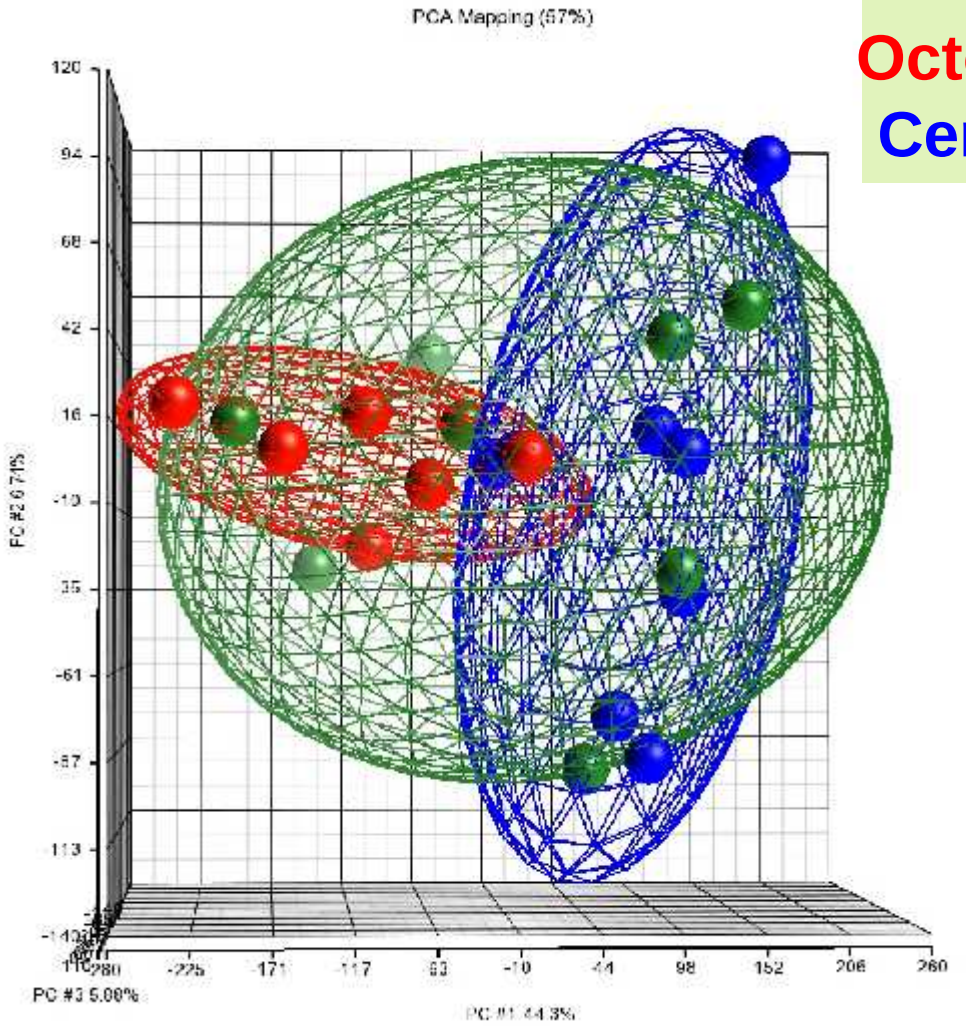
Strategy


Young
Octogenarian
Centenarian
miRNA analysis
Genechip miRNA 2.0 Array
mRNA analysis
Genechip Human Gene 1.0ST Array
mRNAs regulated by miRNAs
Sub-network analysis
(Software Ariadne Pathway Studio)

Functional transcriptomic analysis

- **Genechip Human Gene 1.0ST Array**
  - Estimated number of genes: 28.869
  - 200ng de RNAtotal
  - Hibridación a 45ºC 60rpm durante 18h

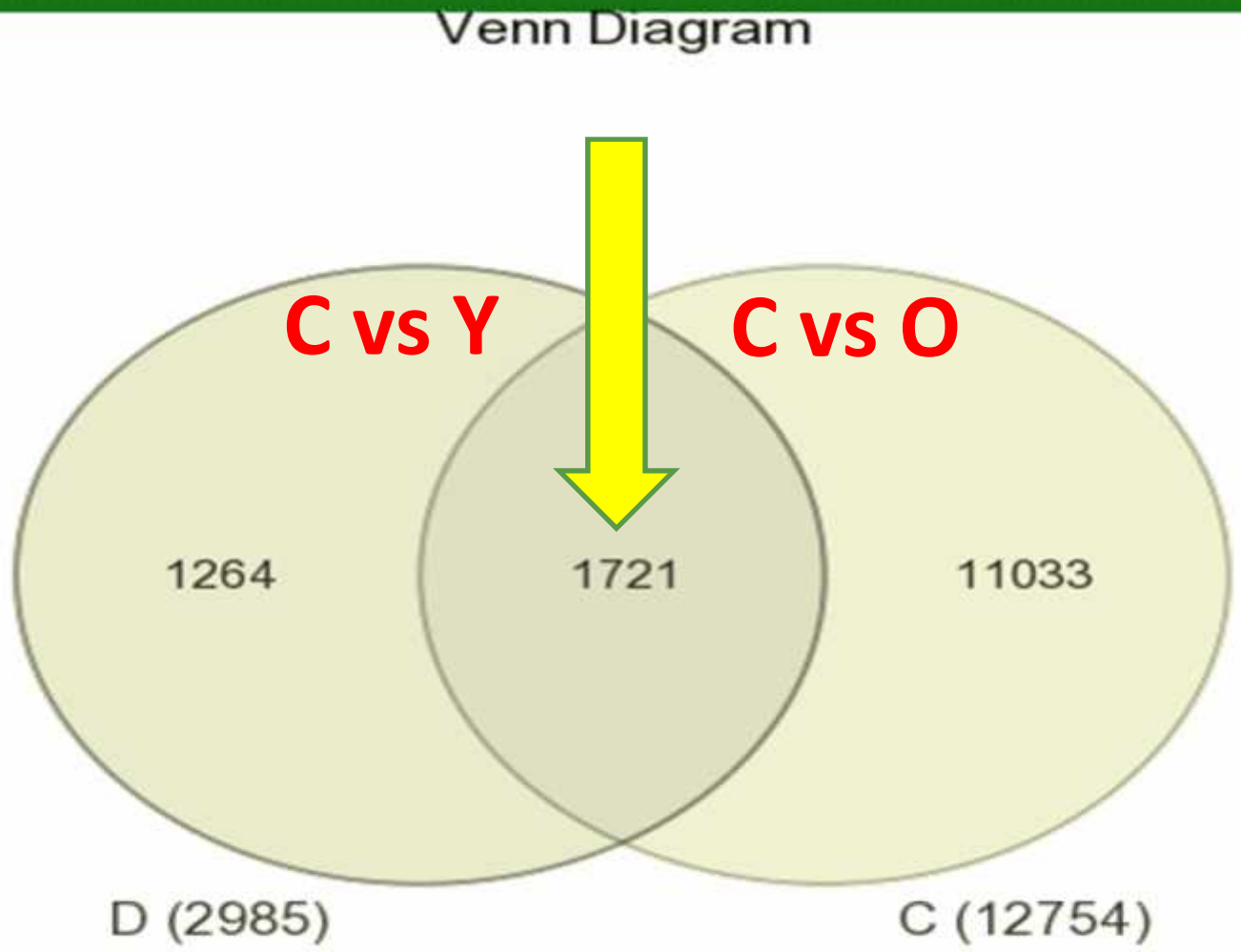
mRNAs in centenarians



Young
Octogenarian
Centenarian

mRNAs are different between octogenarians and centenarians!!!!

Comparison of mRNAs



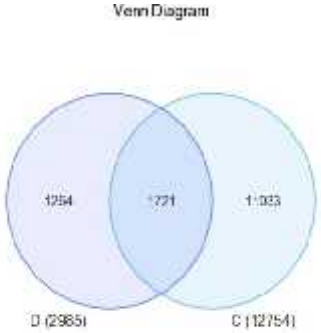
The subnetworks...

A "*sub- network*" is a group of genes connected structurally or functionally to one common gene

A "*sub- network*" is identified when there are known realtionships between the genes involved in the Ariadne data base,

Subnetwork analysis

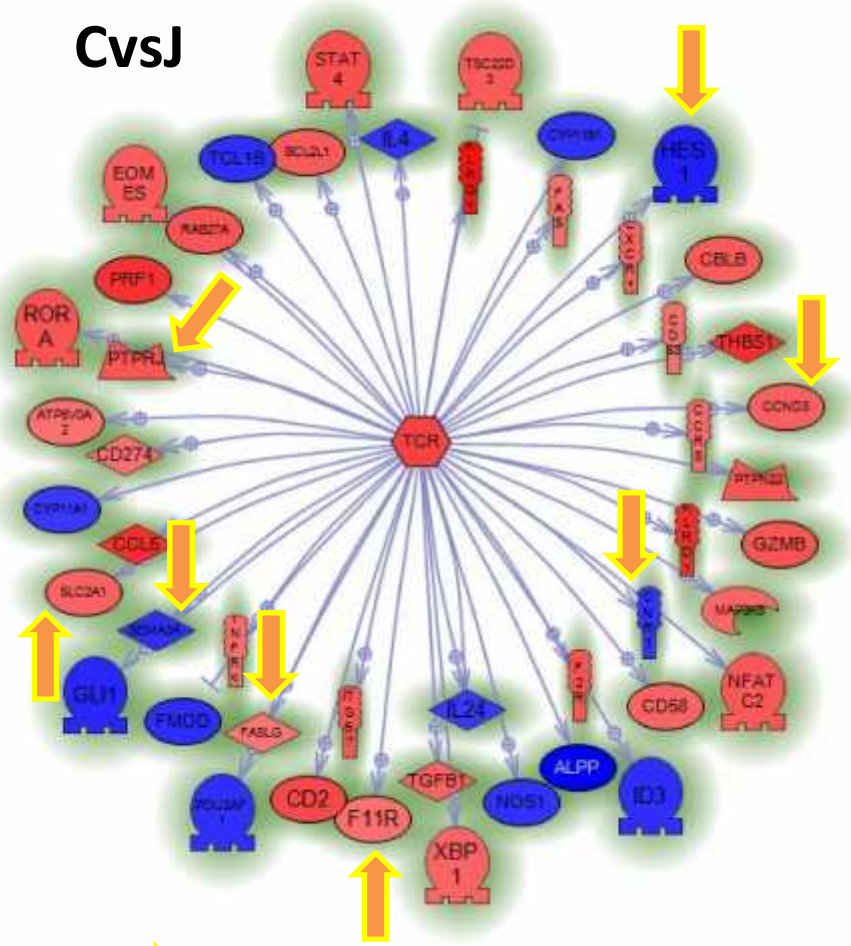
- **All**- 1721 genes that change in centenarians



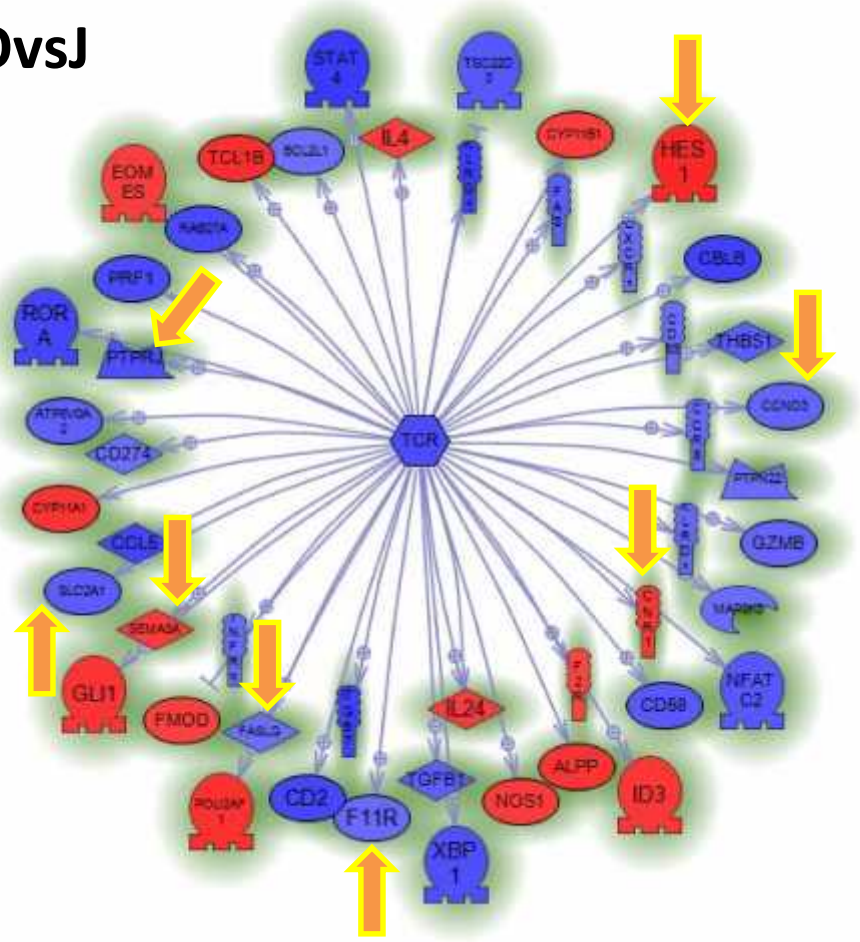
- **Combine**- 51 genes regulated by the 3 miRNAs specific for centenarians (from 1721 genes that change in centenarians)

T Cell Receptor

CvsJ

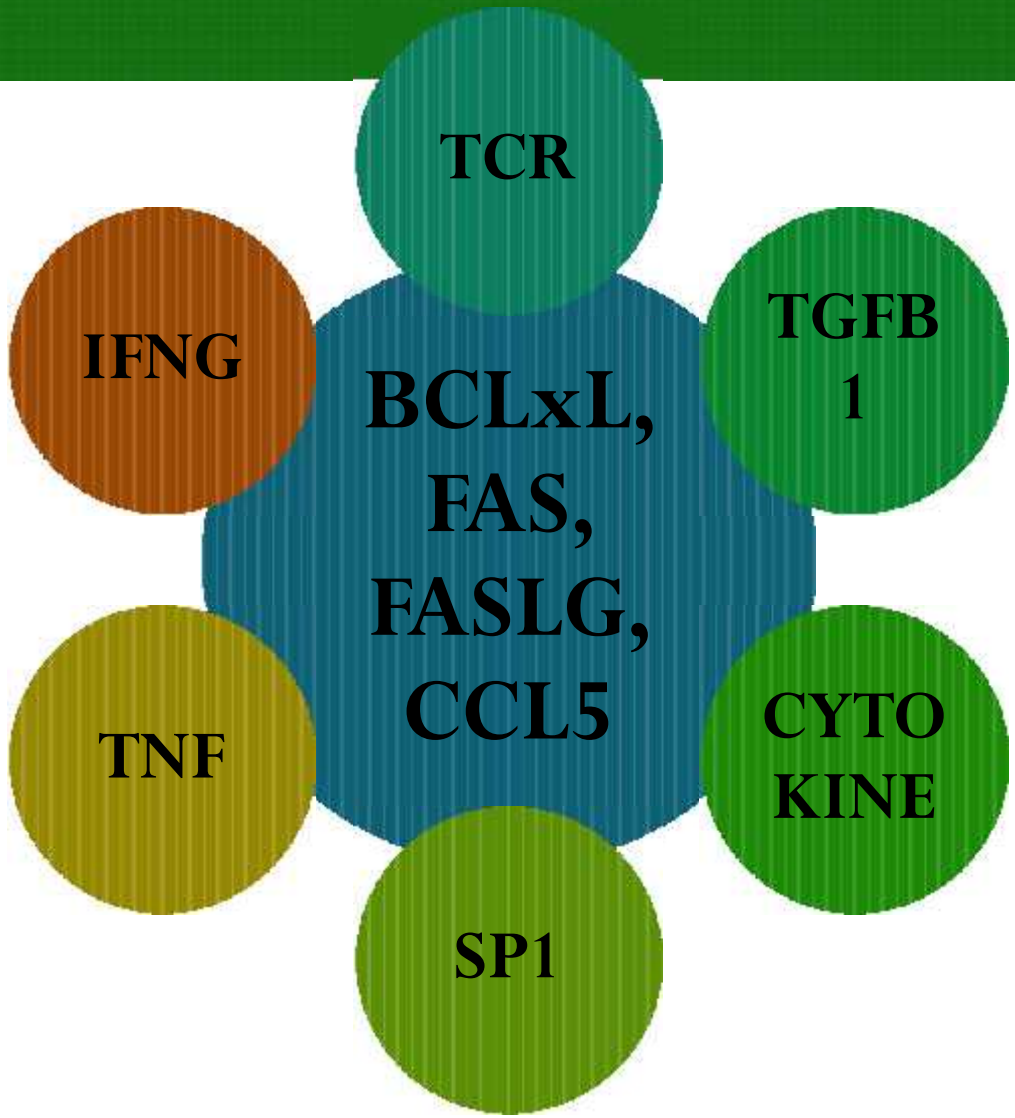


OvsJ

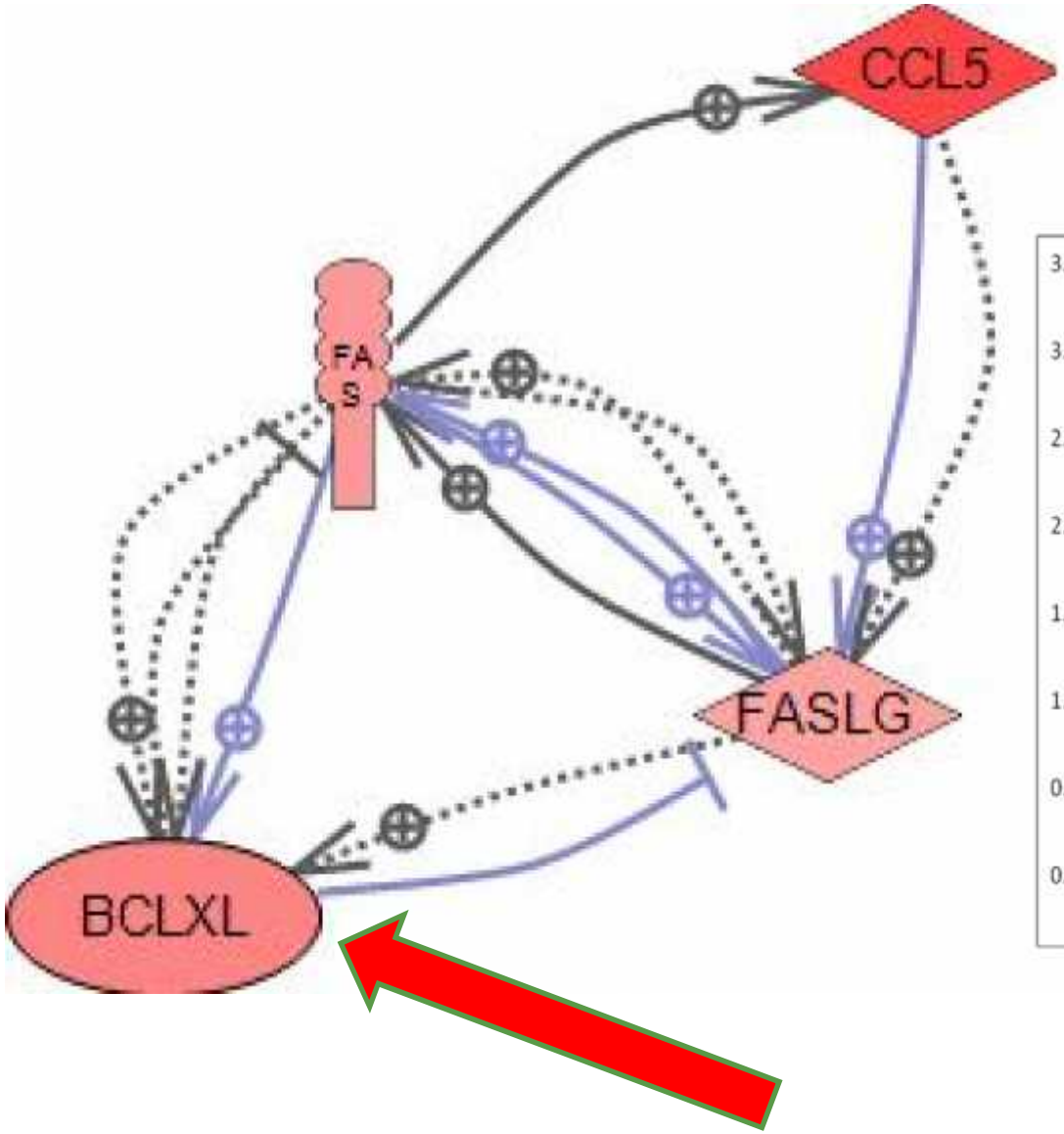


Arrows indicate genes that are in the “combine” list

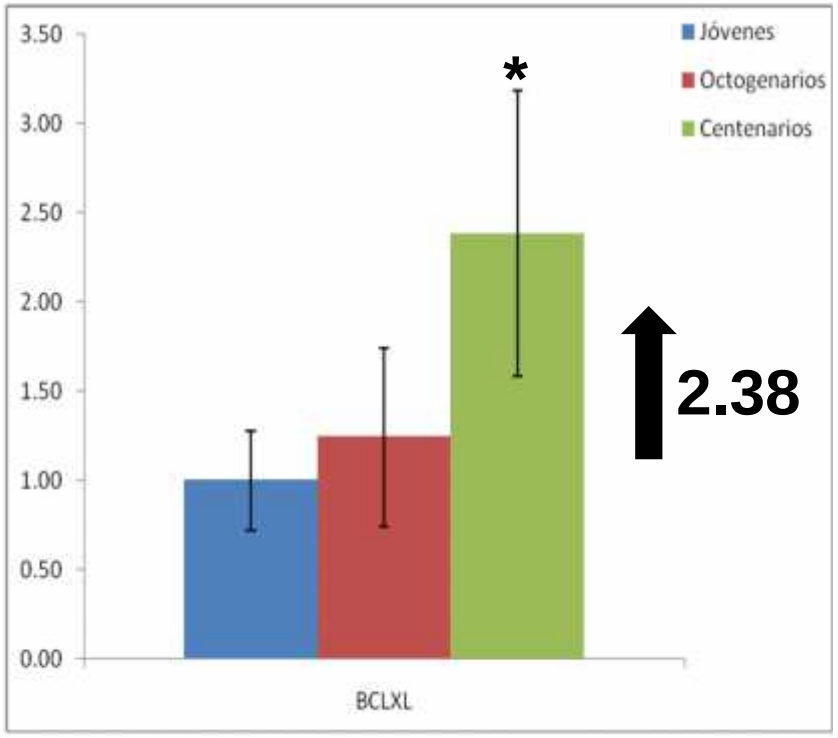
Subnetworks : summary



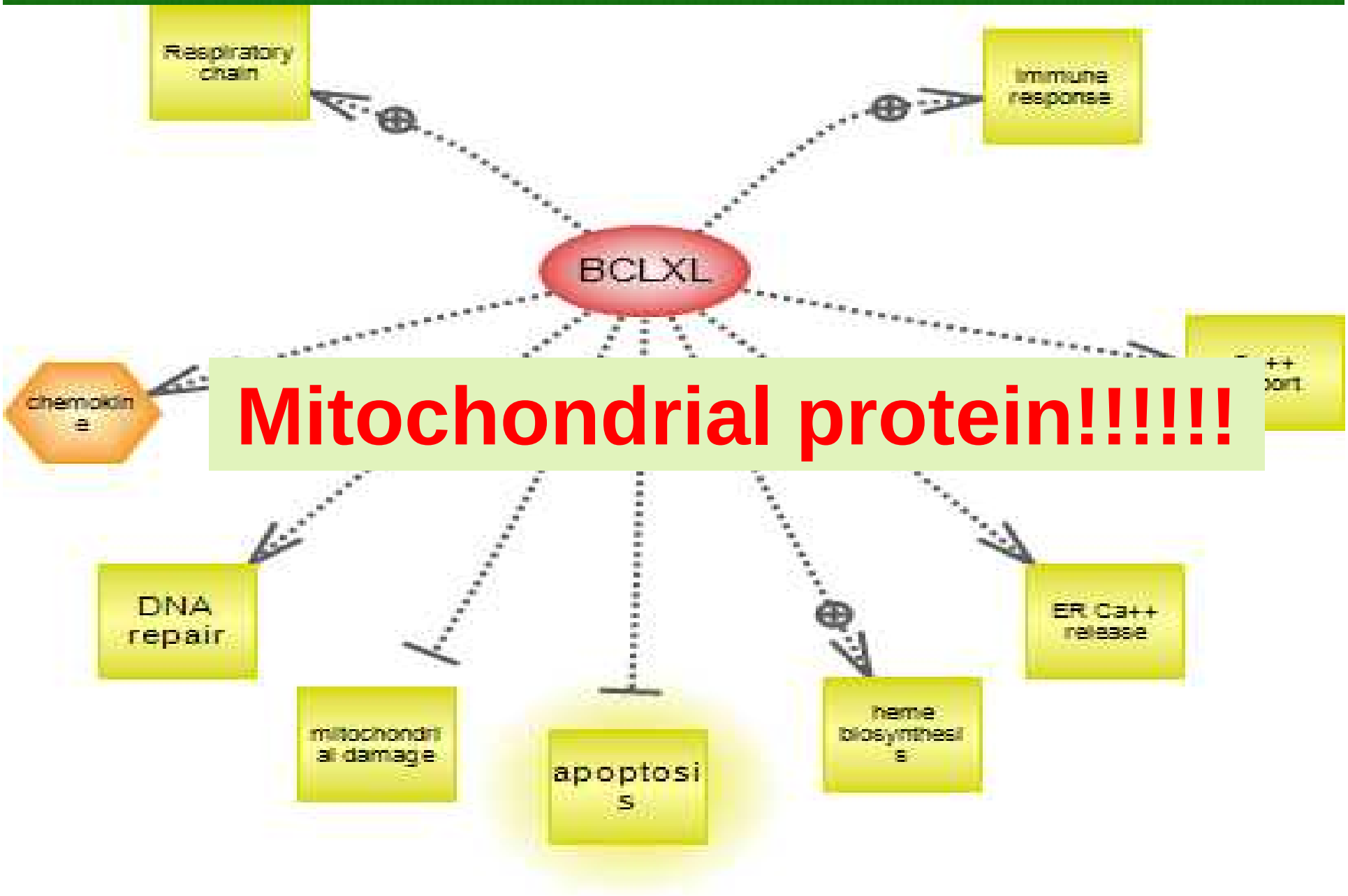
The four critical genes converge in...



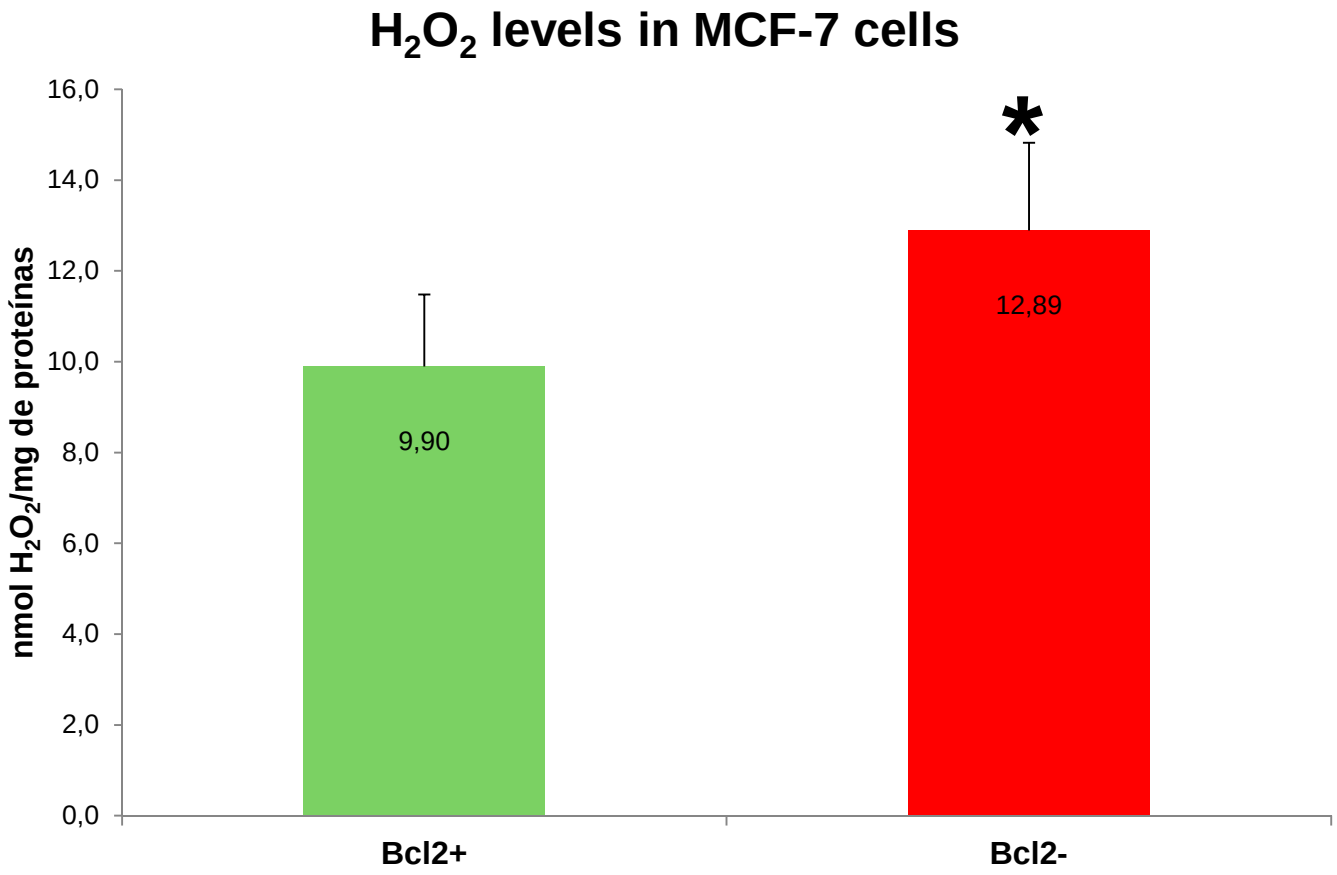
Young
Octogenarian
Centenarian



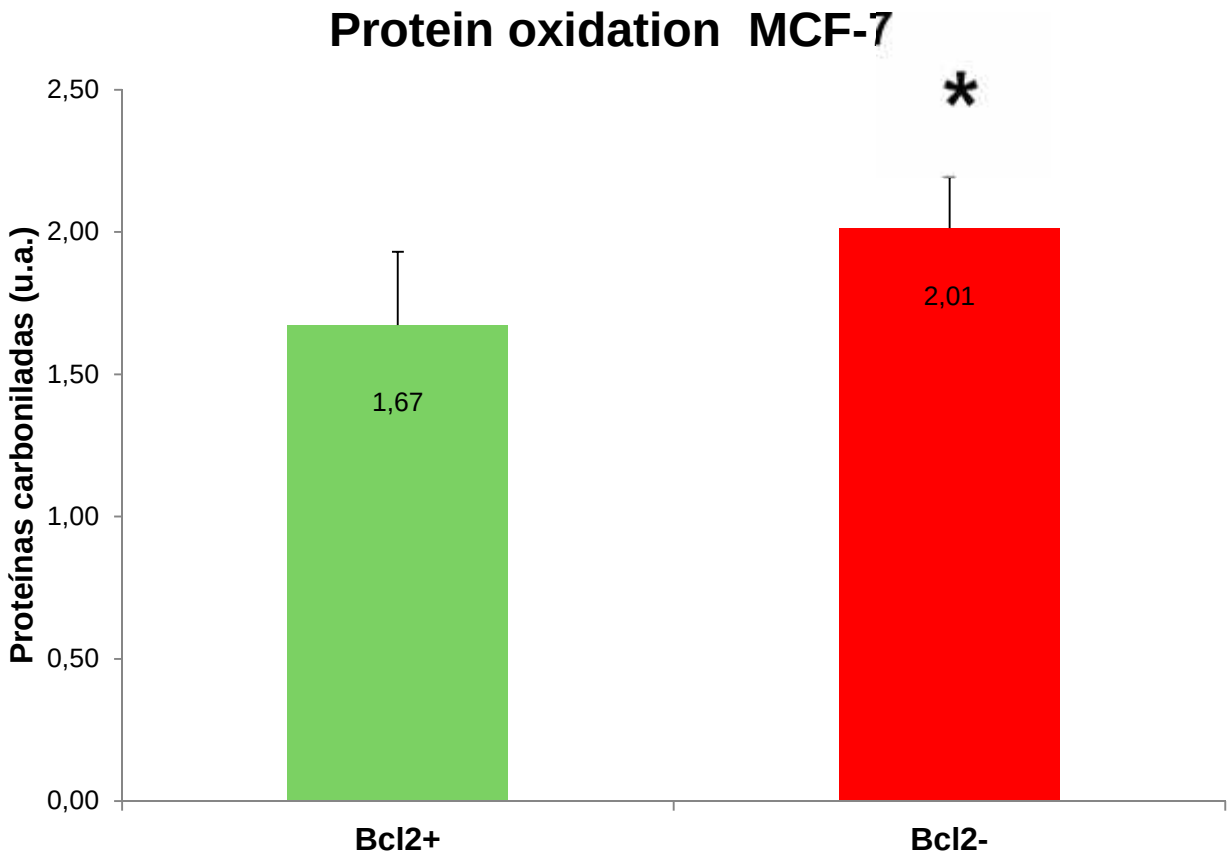
Bcl-xL


Respiratory chain
Immune response
BCLXL
chemokine
DNA repair
mitochondrial damage
apoptosis
heme biosynthesis
ER Ca++ release
Mitochondrial protein!!!!!!

Bcl2 lowers H2O2 levels in cells



Bcl2 lowers protein oxidation in cells



ENVEJECIMIENTO FISIOLOGICO

- ¿ENVEJECIMIENTO COMO PROBLEMA?
- CARACTERISTICAS DEL ENVEJECIMIENTO: G
- CENTENARIANOS: ENVEJECIMIENTO EXCEPCI
- MODULACION DEL ENVEJECIMIENTO ¿PODEM
- COROLLARIO : ENVEJECIMIENTO SATISFACT
- MENSAJE: CUIDESE HOY

HEALTH SPAN AND LIFESPAN

LIFESPAN IS INCREASING SIGNIFICANTLY

HEALTH SPAN IS NOT IMPROVING

Increases in life span have led to more age associated disaseaes

Osteoporosis
Alzheimer
Degeneración macular
Problemas de audición
Accidentes cerebrovasculares

AGING CAN BE MODULATED

- **Moderate exercise**
- **Four helpings of fruit**
- **Two wine glasses**
- **Do not smoke**

Increases life 14 years

Khaw et al Plos Med (2008)

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Increases life 14 years

Khaw et al Plos Med (2008)

BJP British Journal of Pharmacology

REVIEW

Exercise acts as a drug; the pharmacological benefits of exercise

J Vina, F Sanchis-Gomar, V Martinez-Bello and MC Gomez-Cabrera

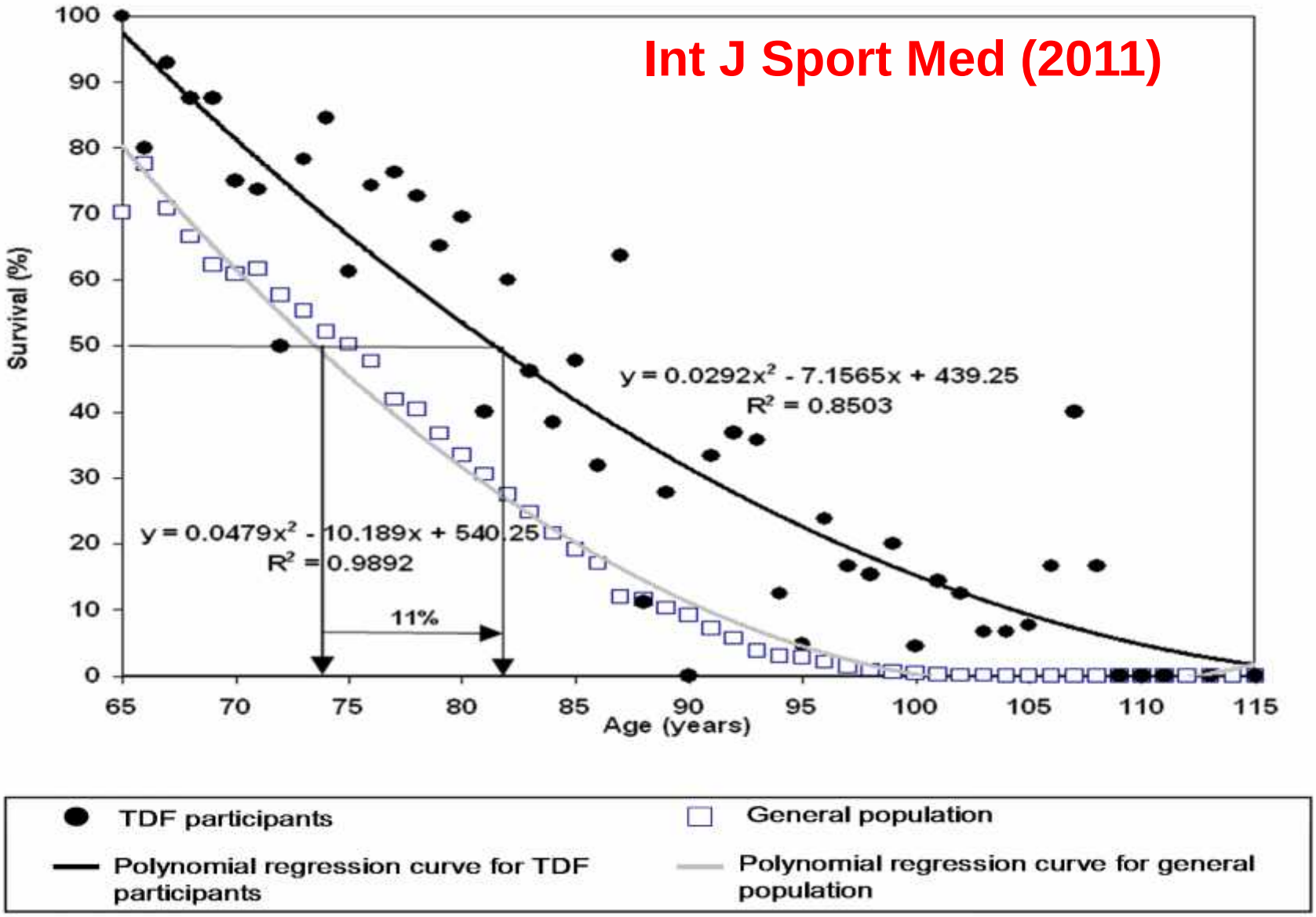
Department of Physiology, University of Valencia, Fundacion Investigacion Hospital Clinico Universitario/INCLIVA, Valencia, Spain

Accepted
16 March 2012

EXERCISE ACTS AS A DRUG (BJP, 2012)

- ***Exercise is beneficial for your health***
- ***The dosing of exercise***
- ***Exhaustive exercise and longevity***
- ***Systemic adaptations to exercise***
- ***Exercise, a psychoactive drug***
- ***Contraindications of exercise***

Participation in the Tour de France significantly enhances longevity.



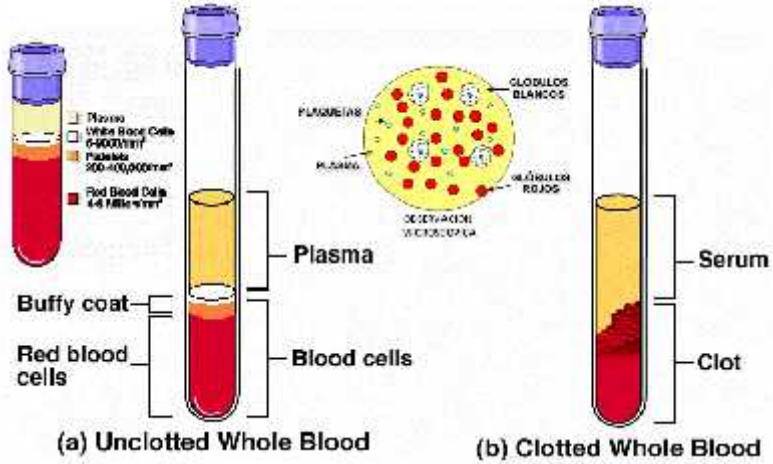
THE VALENCIA NUN STUDY

Effect of moderate wine consumption on longevity gene expression in humans

Favorable effects of wine…

Effect of wine (moderate) on gene expression in catholic nuns

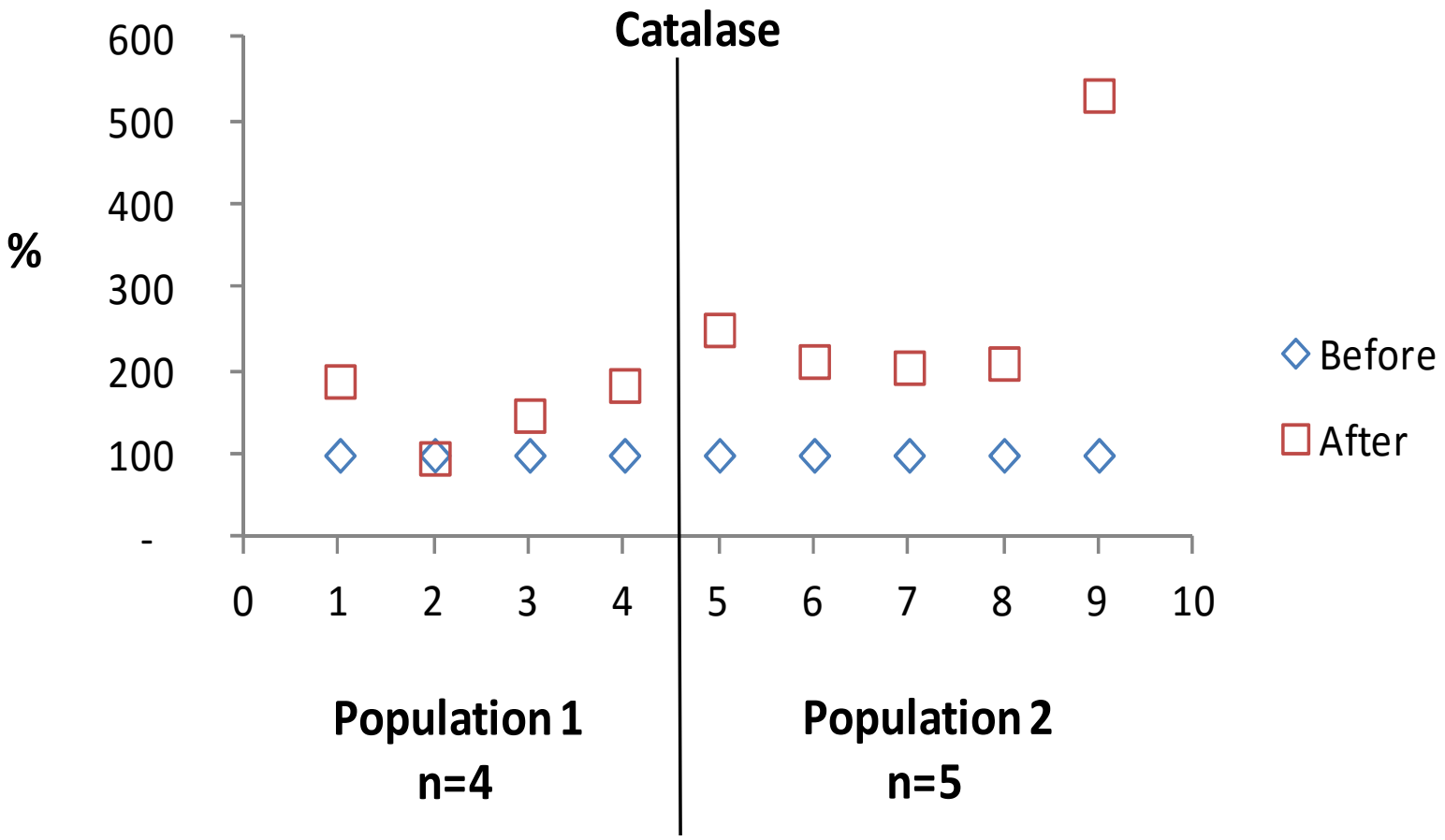
Blood sampling: Before the study



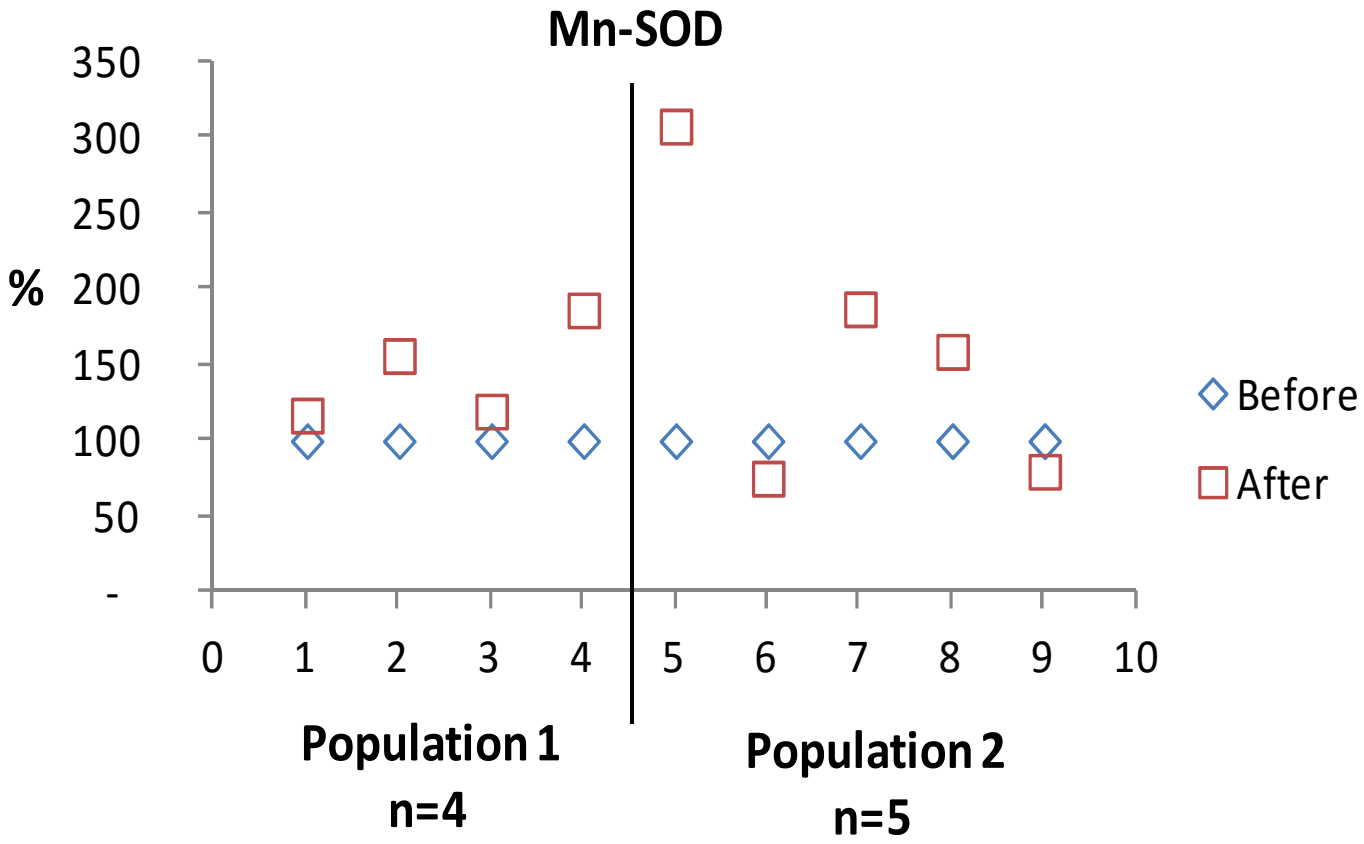
Blood sampling : after 14 days of wine

Gene	Pathway
AKT1, CDKN2A, FOXO3, IRS1, FRAP1	Insulin
TERF1, TERF2, TERT	Telomerase
SESN2,CAT, SOD2, P53	Oxidative stress
SIRT1	Caloric restriction
IL1A	Inflamation

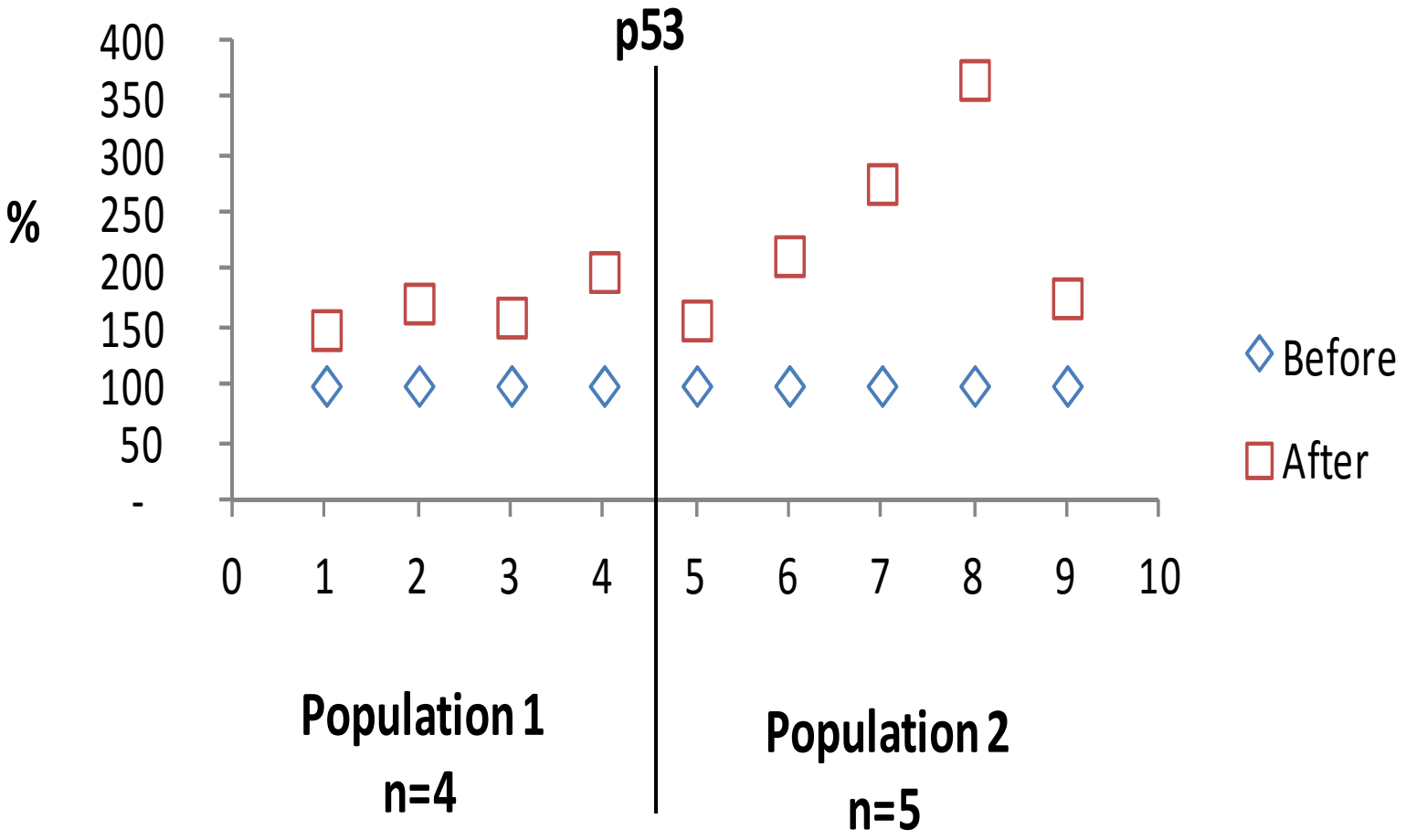
Red wine increases catalase expression



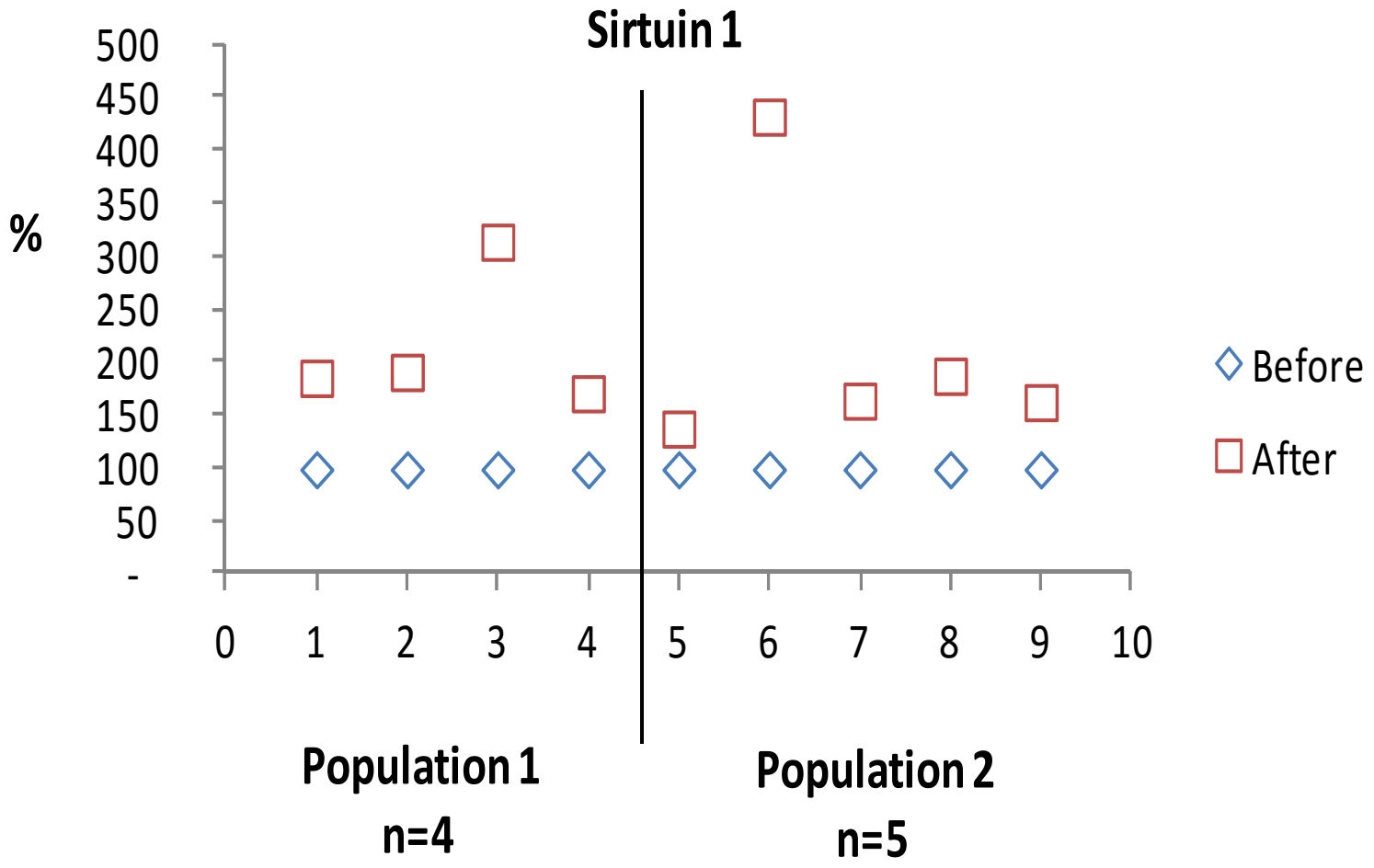
Red wine increases Mn-SOD expression



Red wine increases p53 expression



Red wine increases sirtuin expression



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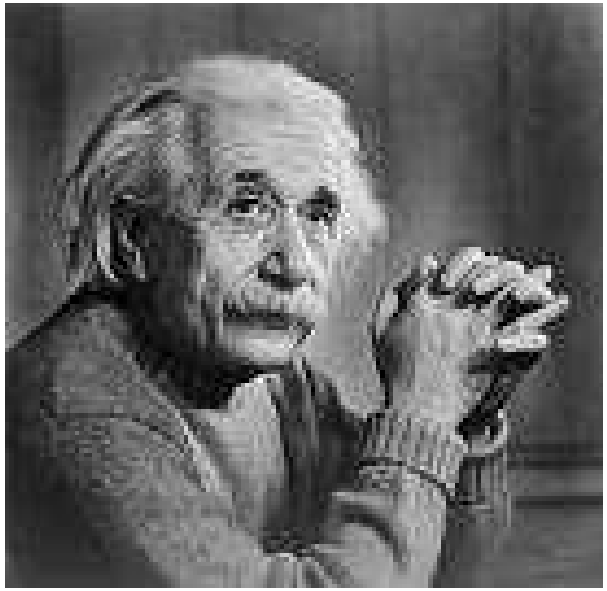
SUCCESSFUL AGING

Aims:

- Adapt to changes that are going to occur
- Compress morbidity
- Prevent frailty and dependency
- Feel that you are useful

Successful aging

- People like you and I, though mortal, of course, do not grow old no matter how long we live. What I mean is that we never cease to stand like curious children before the great Mistery into which we were born



AE. to Otto Juliusberger, close friend and doctor

Successful aging

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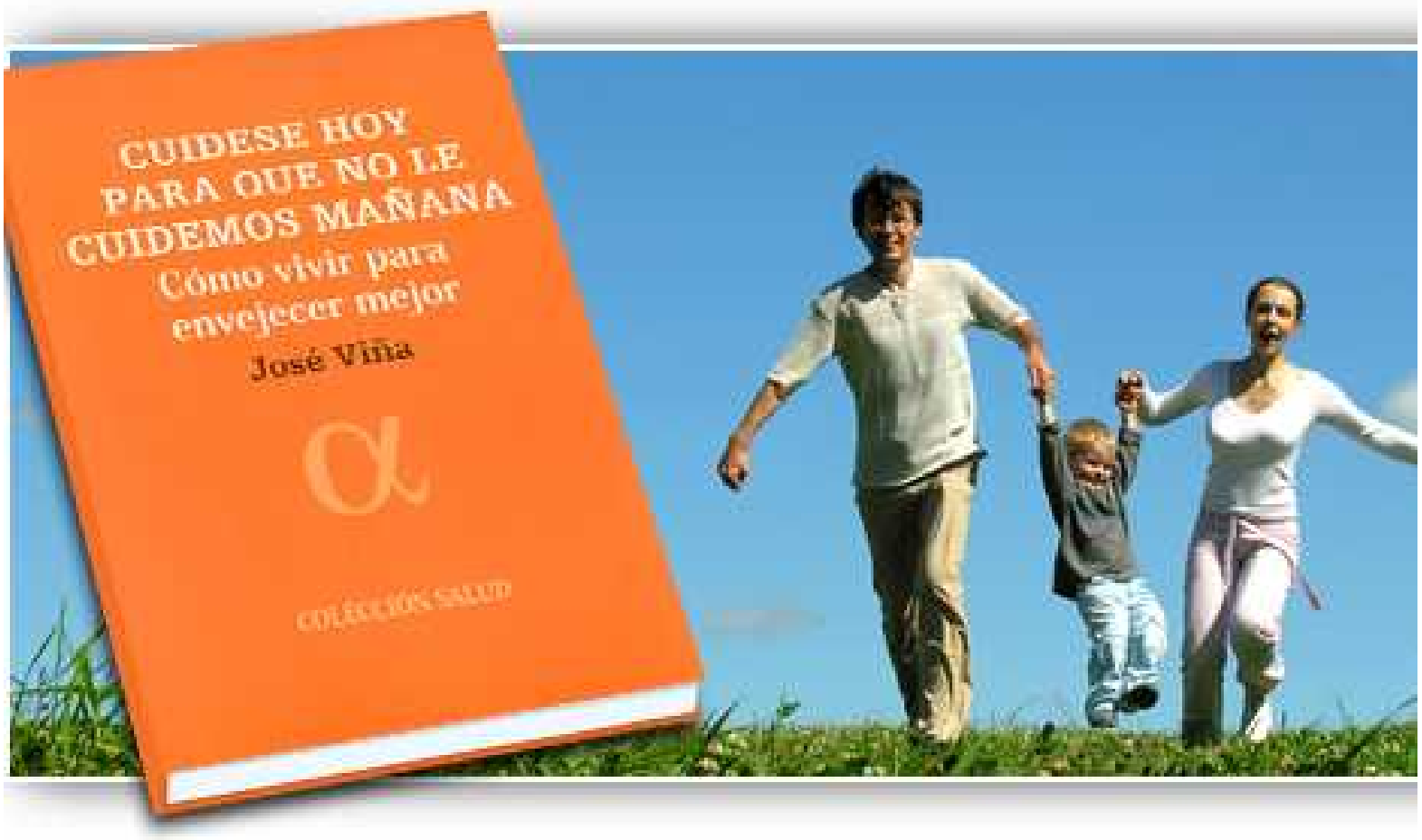
CUÍDESE AHORA

CUIDARSE NO ES SER EGOISTA SINO ALTRUISTA

[www.cuidesehoy.es]

CUIDESE HOY PARA QUE NO LE CUIDEMOS MAÑANA



Conclusiones (1)

- Prepararnos para la vejez es una responsabilidad nuestra
- La medicina antienvejecimiento es una especialidad nueva que pretende aplicar conocimientos actuales al objetivo de llegar a la vejez de la mejor manera posible

Conclusiones (2)

Las maniobras antiaging se basan en

- Moderación dietética (restr. Calórica)
- Aumentar el aporte de productos vegetales
- Ejercicio fisico moderado
- Control del estrés
- Dejar de fumar
- PREVENCION de enfermedades degenerativas (cuanto antes mejor!)

EPILOGO

- **La madurez puede ser un periodo de gran felicidad porque las personas mayores saben su sitio en el mundo(L. Pauling).**
- **Para disfrutar de ese periodo hace falta cuidarse para llegar bien al mismo**

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VNIVERSITAT DE VALÈNCIA Facultat de Medicina i Odontologia

VIÑA'S LAB

¡GRACIAS!