Dietary Interventions for Healthy Aging

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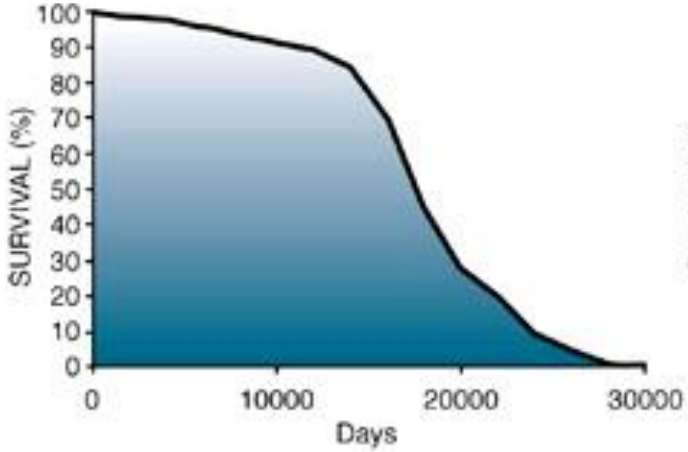
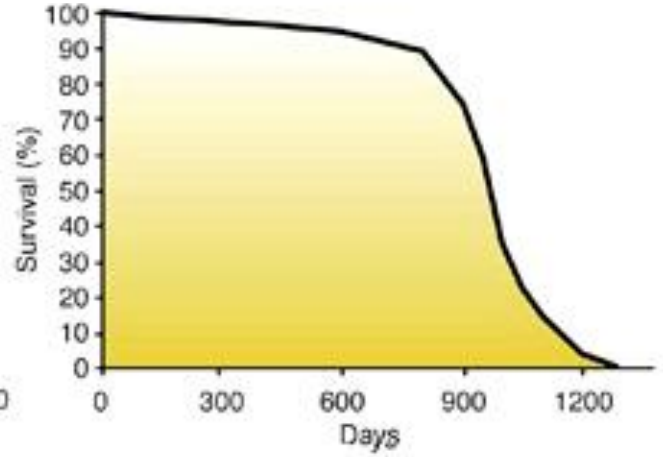
Aging is a universal process

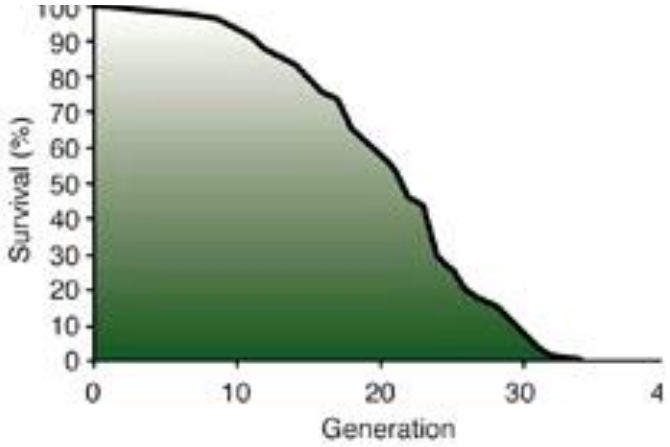
Human



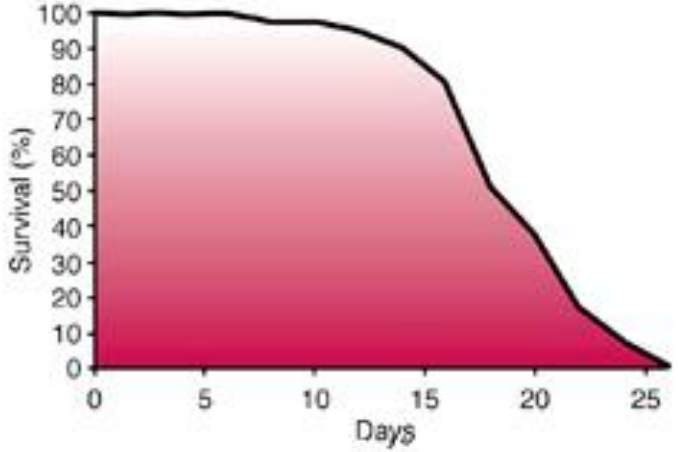
Mouse



Yeast



Worm



AGING: Gradual changes in structure and function of organisms that occur with the passage of time, not as a result from disease or other gross accidents.

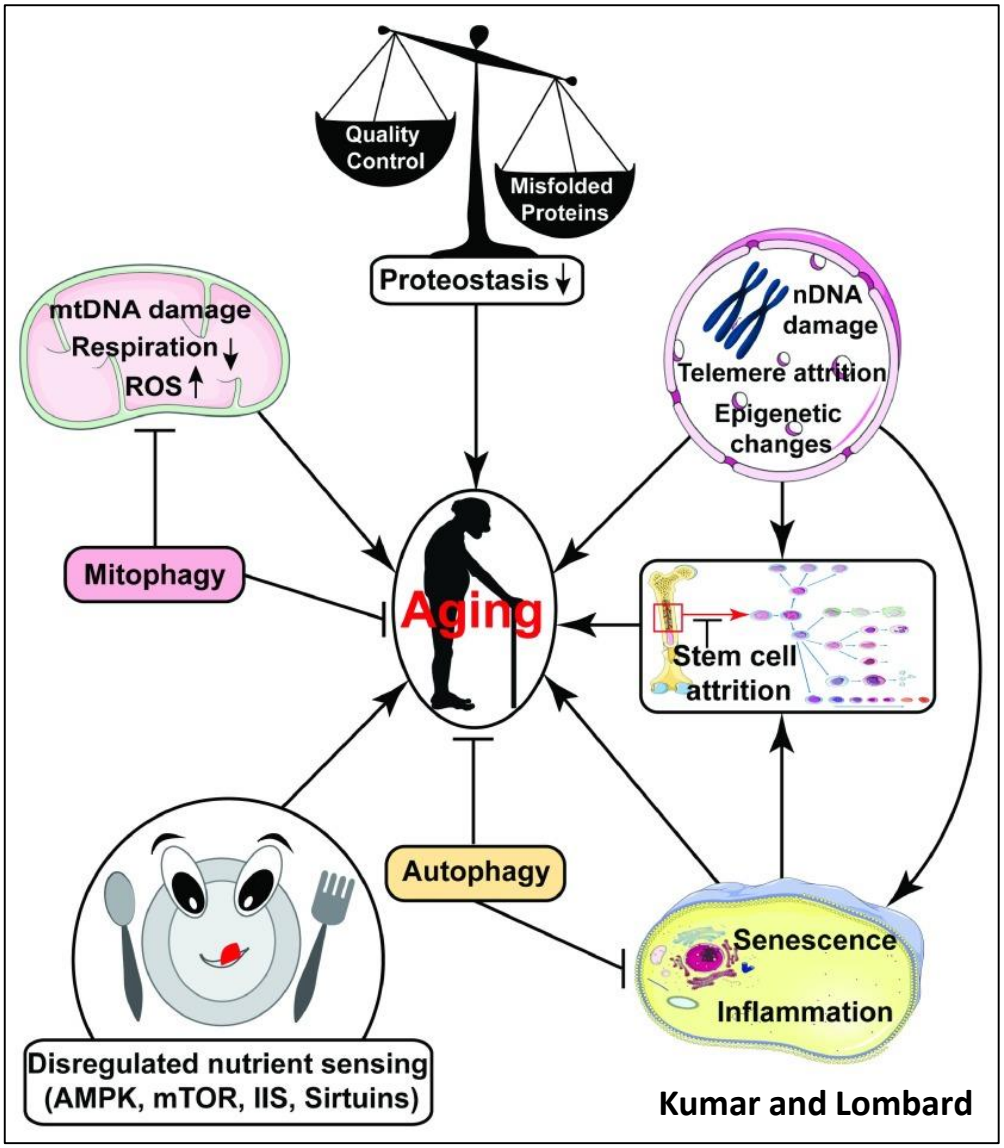
Consequences of Growing Old

Cancer
Breast Cancer
Cervical Cancer
Colon and Rectal Cancer
Prostate Cancer
Lung Cancer
Skin Cancer

Cardiovascular Disease
Heart Attack
Stroke
Hypertension

Vision Impairment
Cataracts
Macular Degeneration

Disability
Osteoporosis
Sarcopenia
Dependency
Arthritis



Dementia
Alzheimer's Disease
Multi-Infarct Dementia

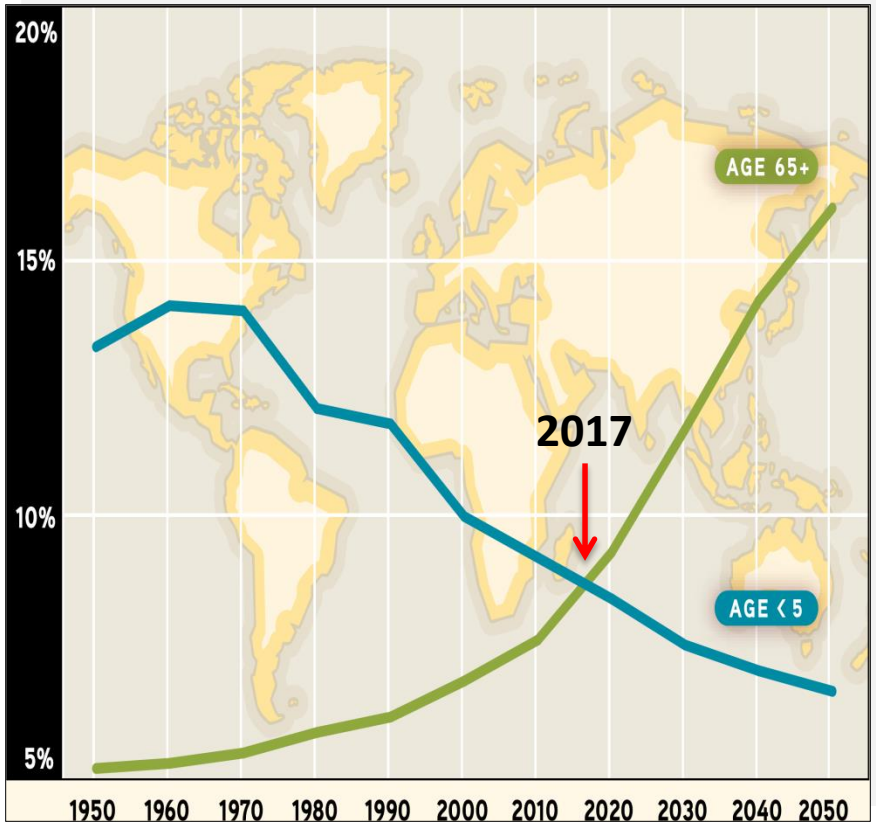
Miscellaneous
Diabetes
Sterility
Urinary Incontinence
Prostate Enlargement
Hearing Impairment

Cosmetic Changes
Hair Loss
Graying Hair
Wrinkles
Age Spots
Altered fat distribution

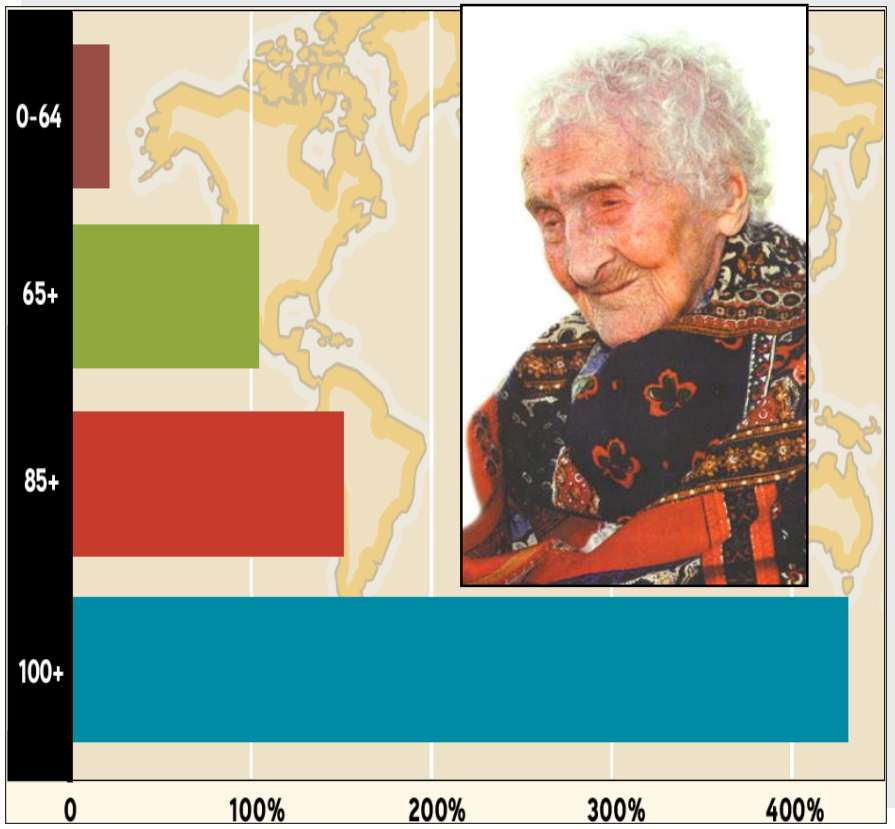
Dental Problems
Gum Disease
Tooth Loss
Tooth Damage

The world is aging……rapidly!

YOUNG CHILDREN AND OLDER PEOPLE AS A PERCENTAGE OF GLOBAL POPULATION

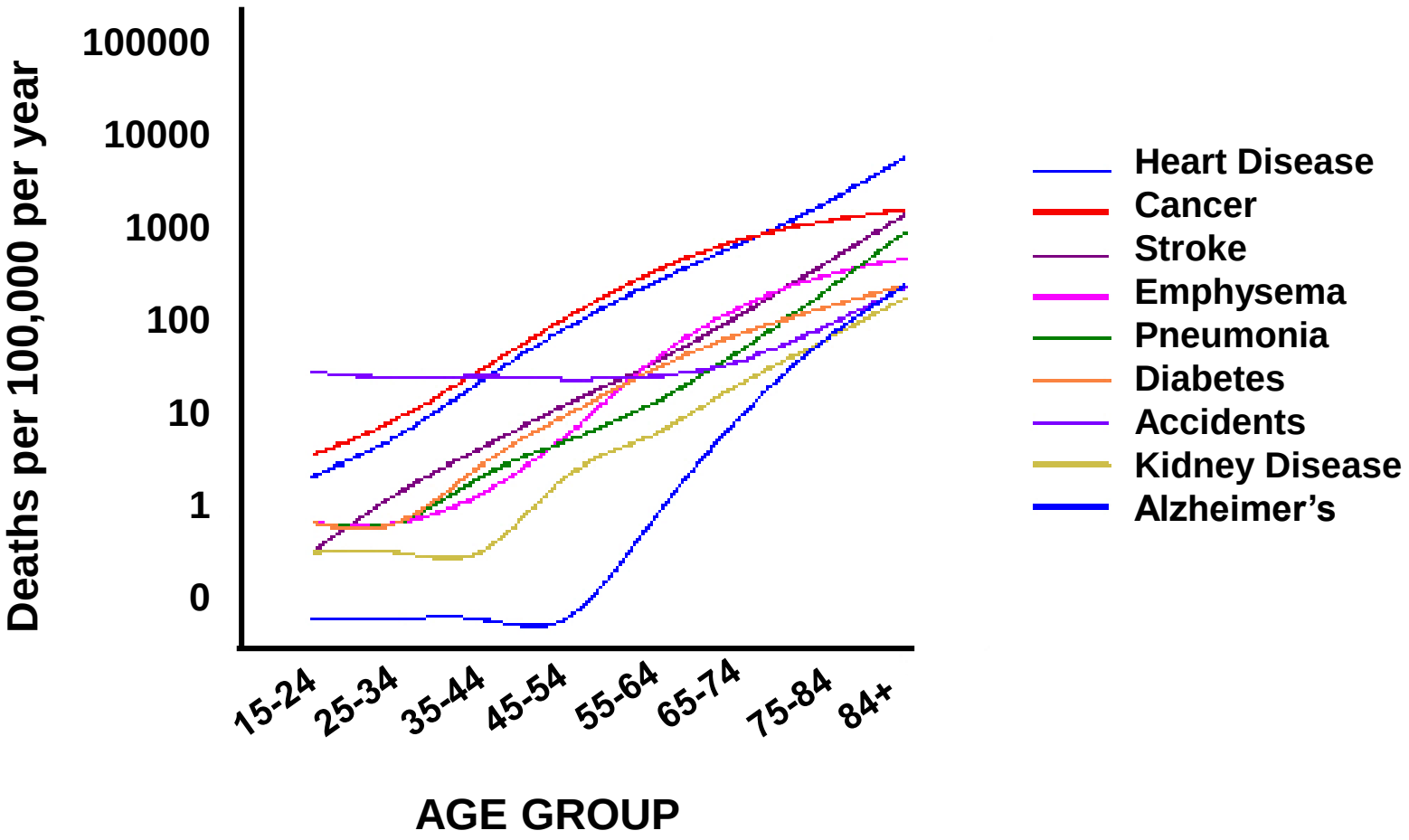


PROJECTED INCREASE IN GLOBAL POPULATION BETWEEN 2005 and 2030, BY AGE



United Nation Department of Economic and Social Affairs, Population Division.*World Population Prospects. The 2004 Revision*. New York: United Nations, 2005 in *Why Population Aging Matters: A Global Perspective* at www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/GlobalAging.htm

Aging is the major risk factor for ALL chronic diseases



Our Bottom Line

- The mission of our biomedical research is to increase the quality of human life

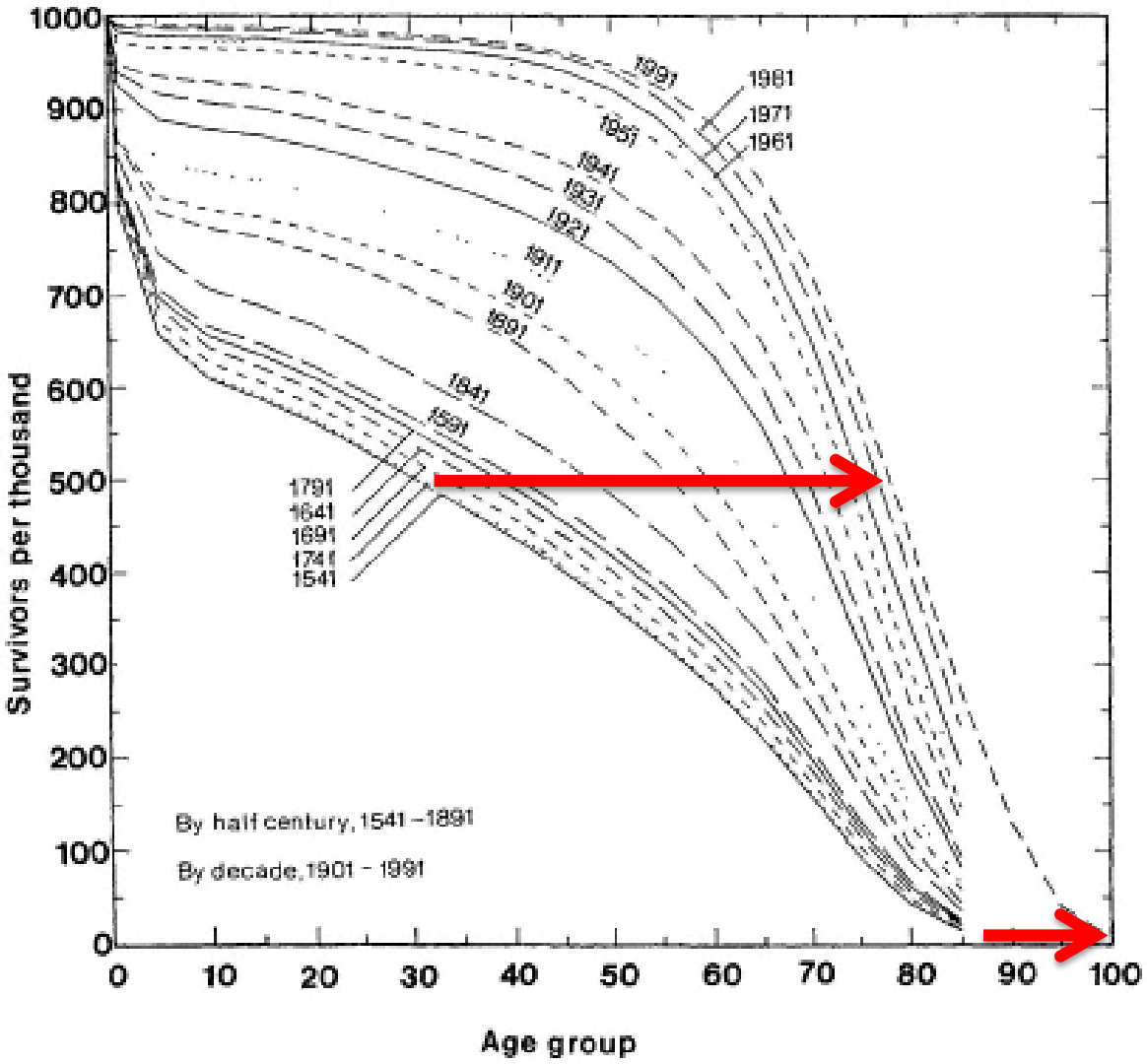
- Chronic diseases of the elderly are currently the main limitation to achieving an increase in the quality of life.

In order to do this, we must address the major risk factor for chronic diseases:

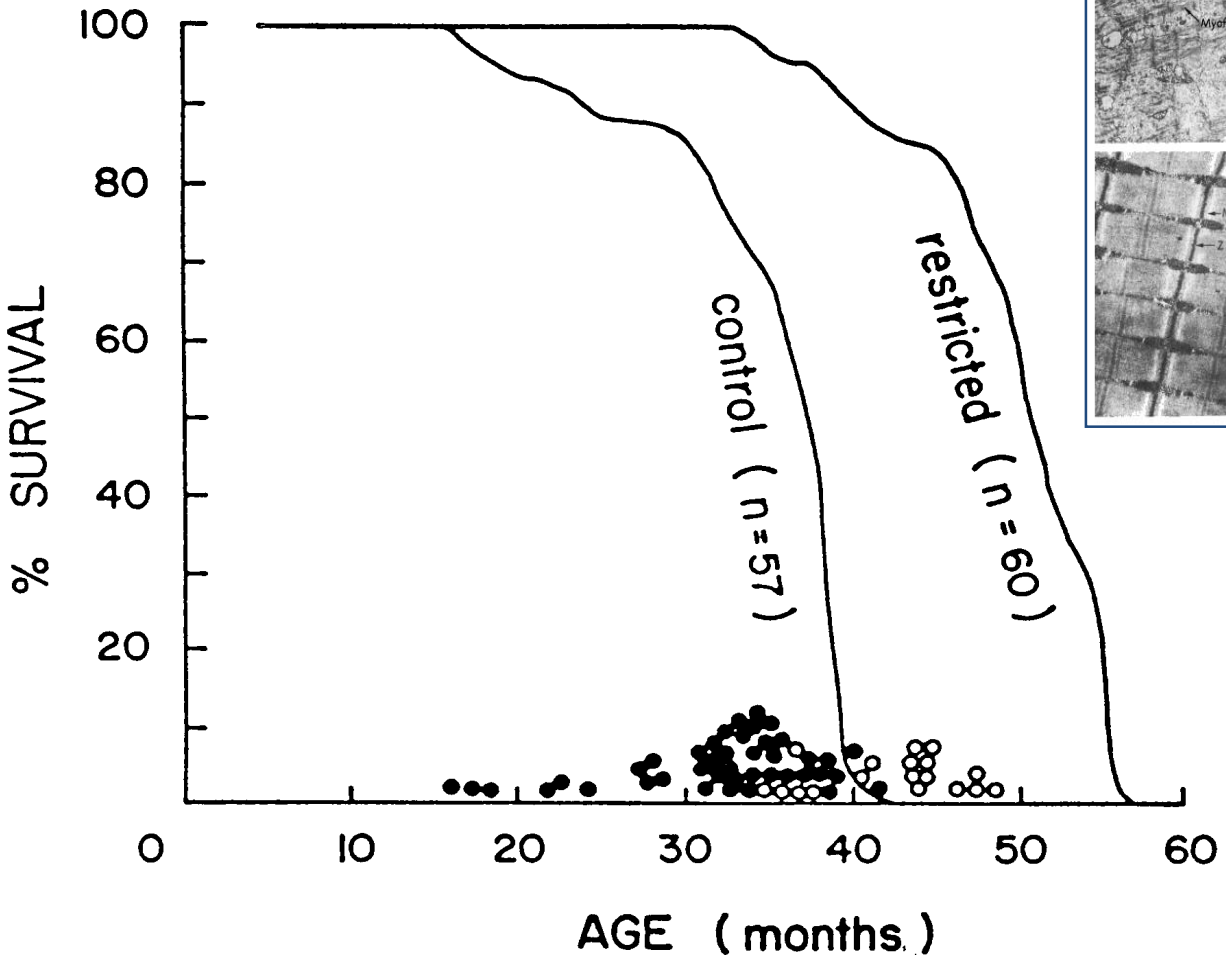
AGING!


OCTOBER 1992/$2.95
LIFE
CAN WE STOP AGING?
NO!
…..but we can alter its onset and progression through interventions
Sally Woodbridge of Berkeley, California, in 1992 and 1944

Squaring the survival curve in human populations



Caloric restriction



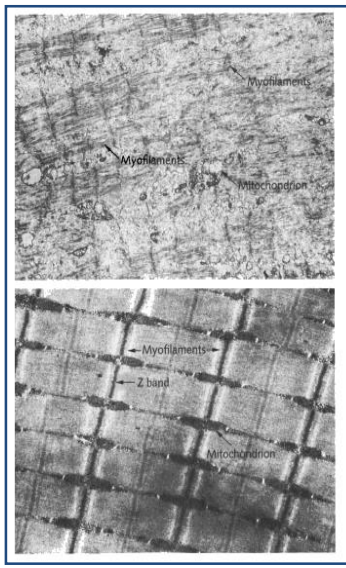


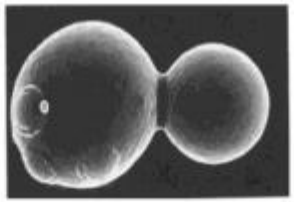
Figure 7.3 The influence of diet on tissue structure. (a) A longitudinal section through the gastrocnemius muscle of a control male Wistar rat aged 1,010 days. Myofibrillar breakdown is significant; only thin, diffuse Z bands remain to support the sparse, degenerated myofibrils. The sarcoplasm contains few mitochondria, vesicles, and fine filamentous remnants. (b) A longitudinal section through the gastrocnemius muscle of a food-restricted male Wistar rat aged 1,284 days. There is no evidence of myofibrillar breakdown or structural abnormalities in mitochondria or T tubules. Abnormal amounts of lipid were not detected. (From Everitt et al. 1985.)

Adapted from Weindruch et al., 1979

$C3B10RF_1$ mice

Rhesus Monkey

Humans ?



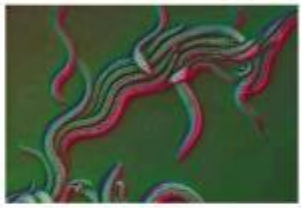
Budding Yeast

Rotifer

Labrador

Daphnia

Rat



C. elegans

DR increases lifespan in diverse organisms

Mouse

Drosophila

Chicken

Medfly

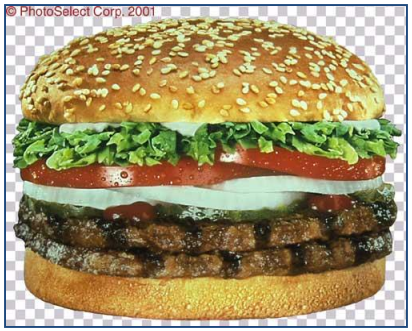
Guppy

Carabid Beetle

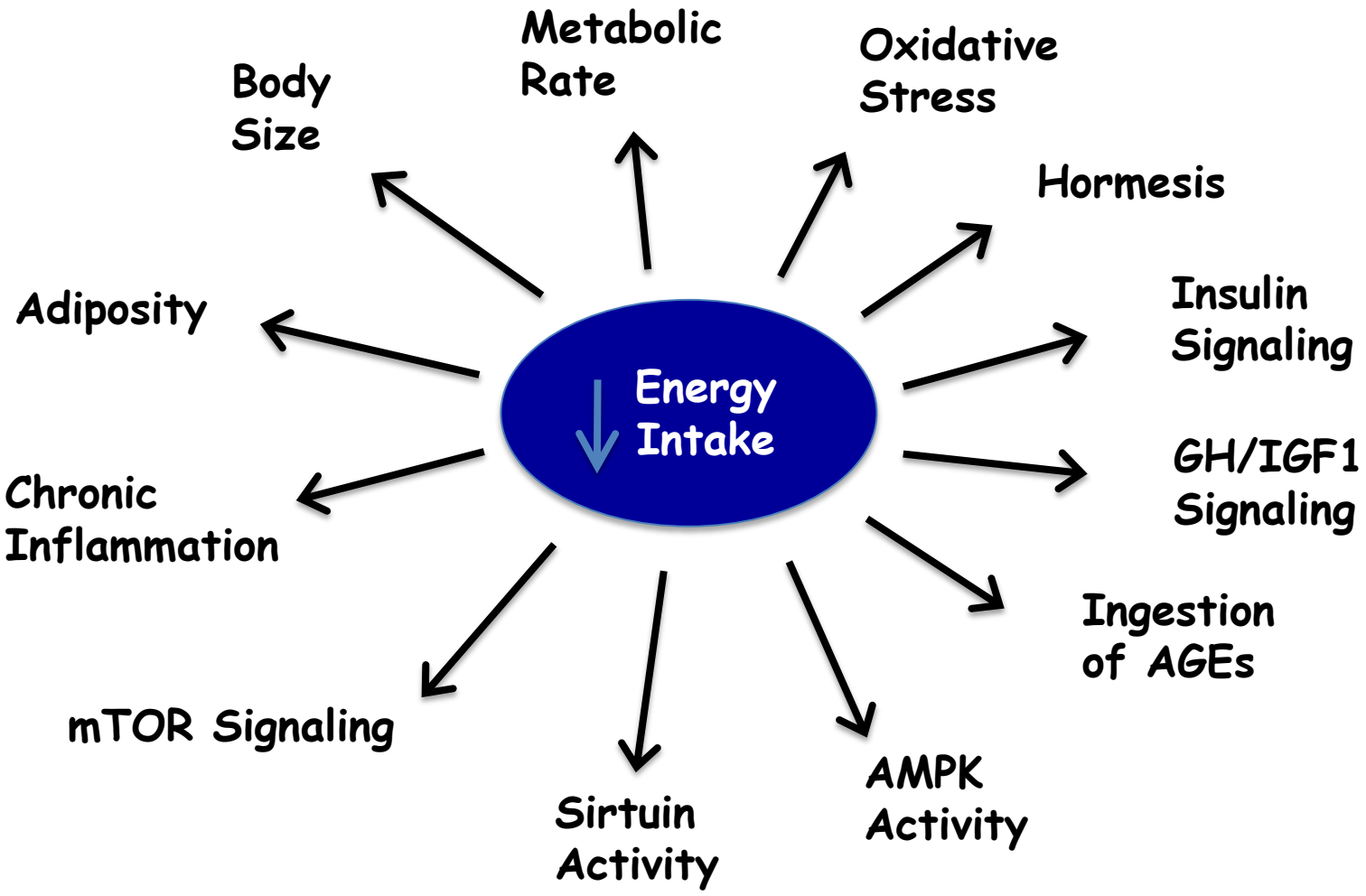
Bowl & Doily Spider

Waterstrider

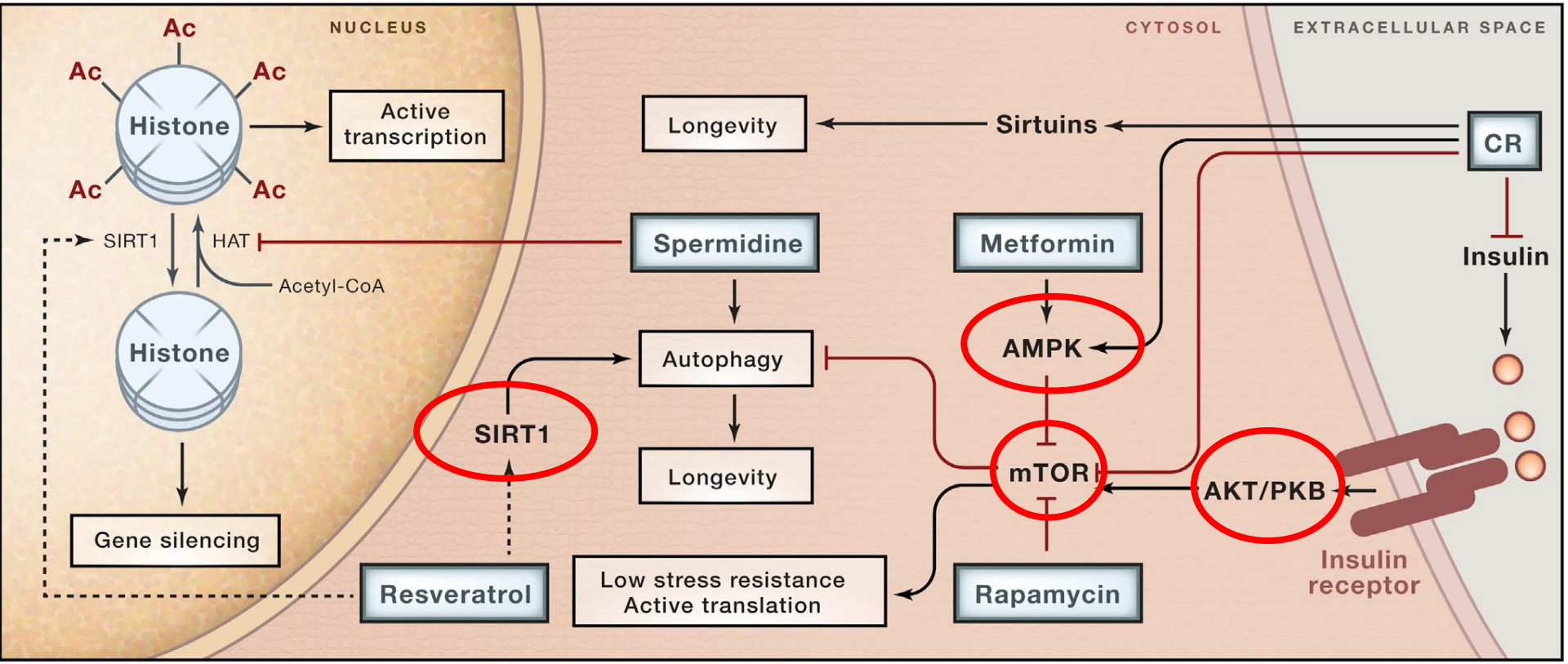
There's always a catch



How Does CR Work?



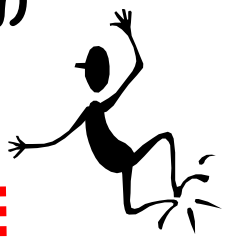
Molecular Targets for Caloric Restriction and Pharmacological Interventions For Healthy Aging

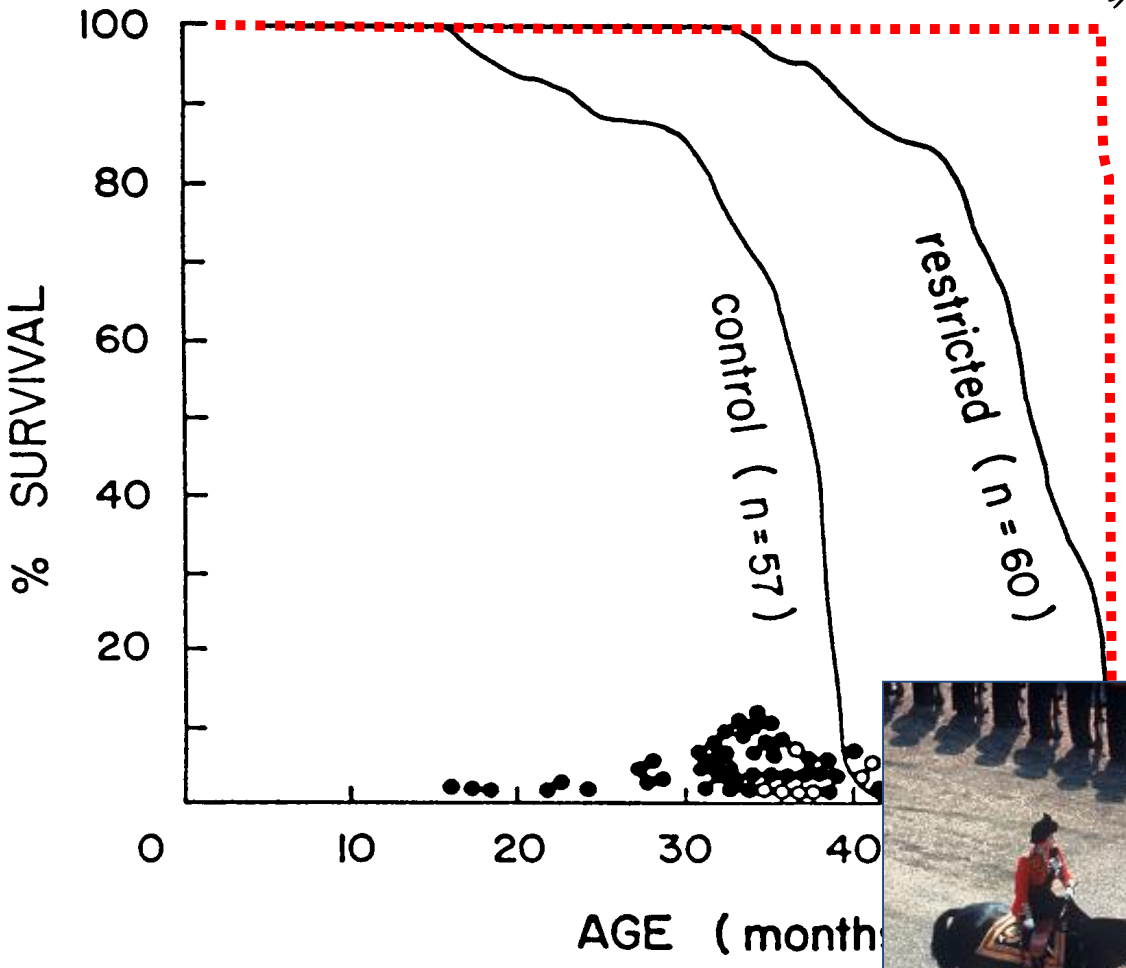


de Cabo et al. (Cell, 2014)

Caloric Restriction Mimetics

(Interventions for Healthy Aging)



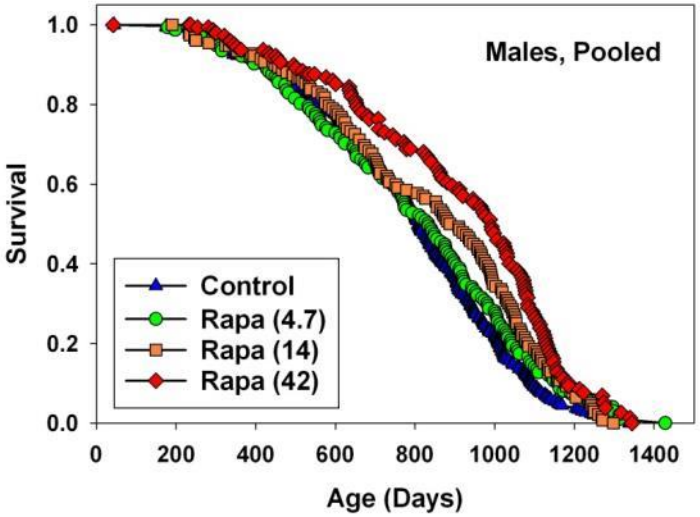


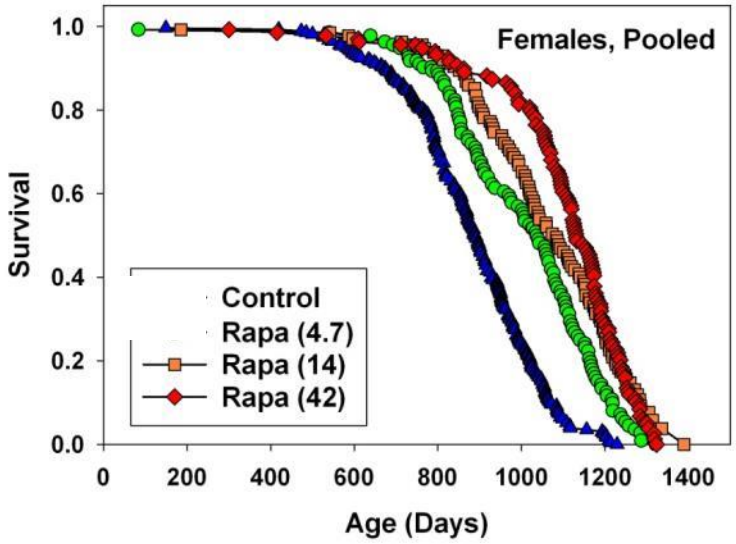
Adapted from Weindruch et al., 1979

C3B10RF$_1$ mice

BUT

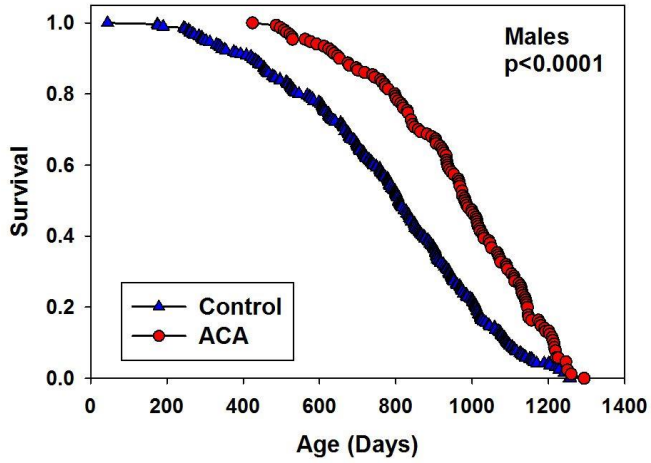
Rapamycin: Females better than Males

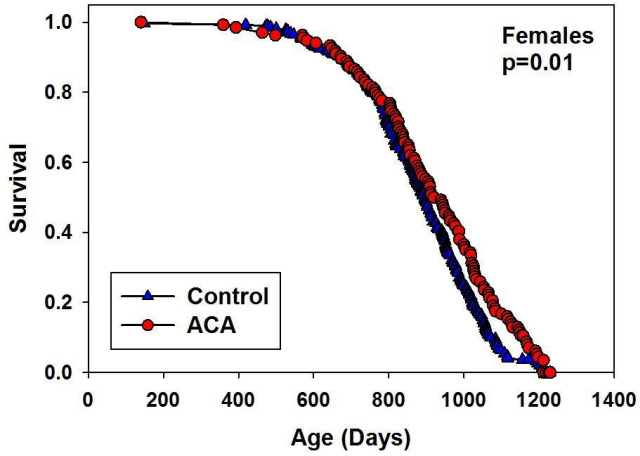




Miller et al., Aging Cell, In Press

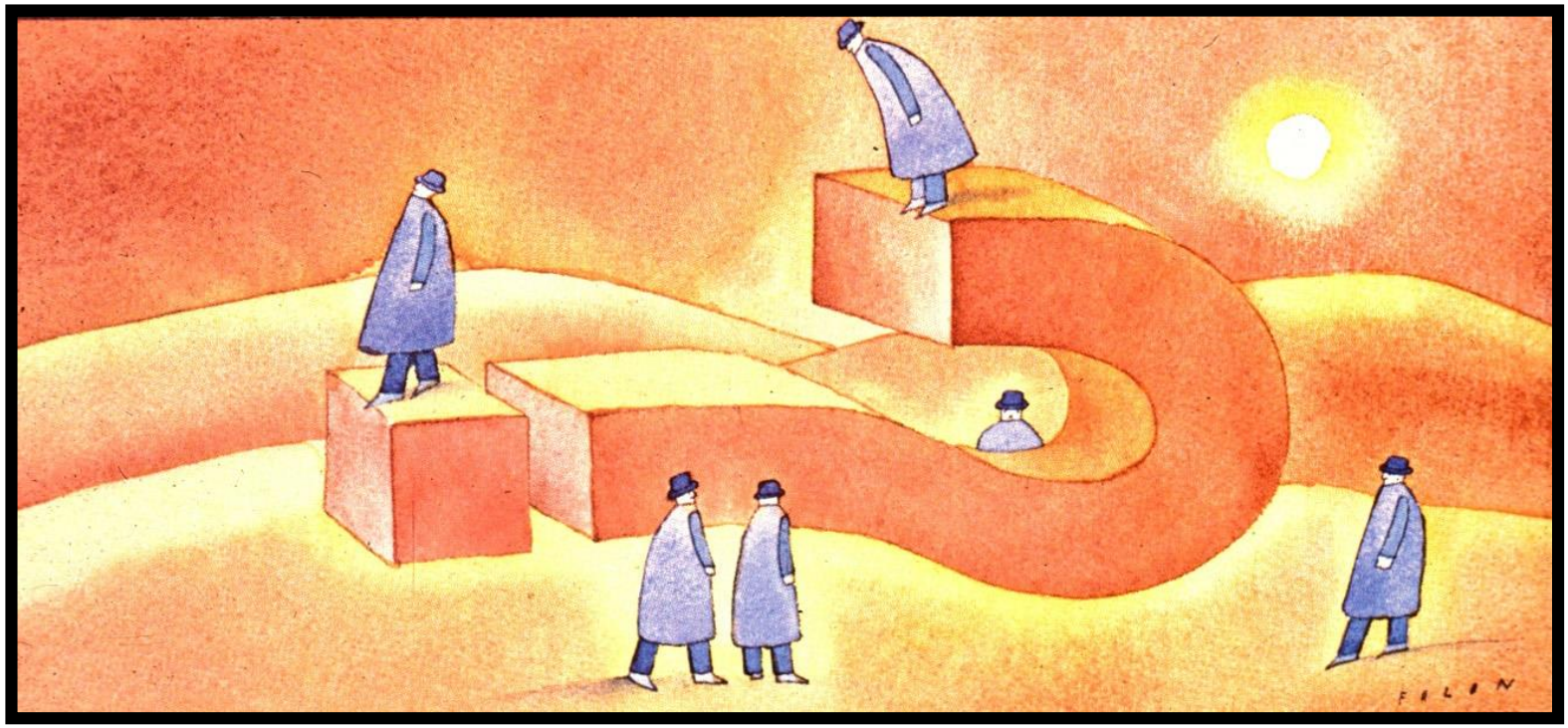
Acarbose: Longevity Effect Greater in Males





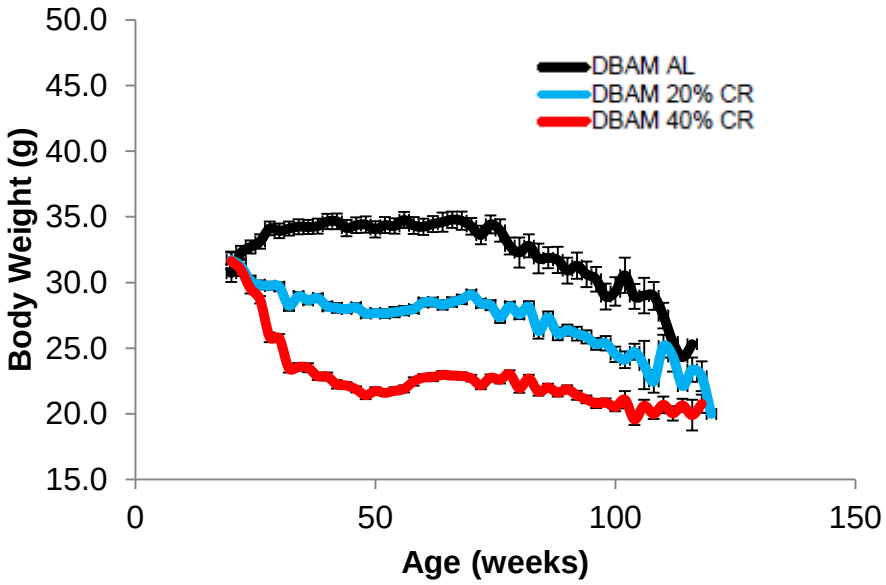
Harrison et al. (Aging Cell, 2014)

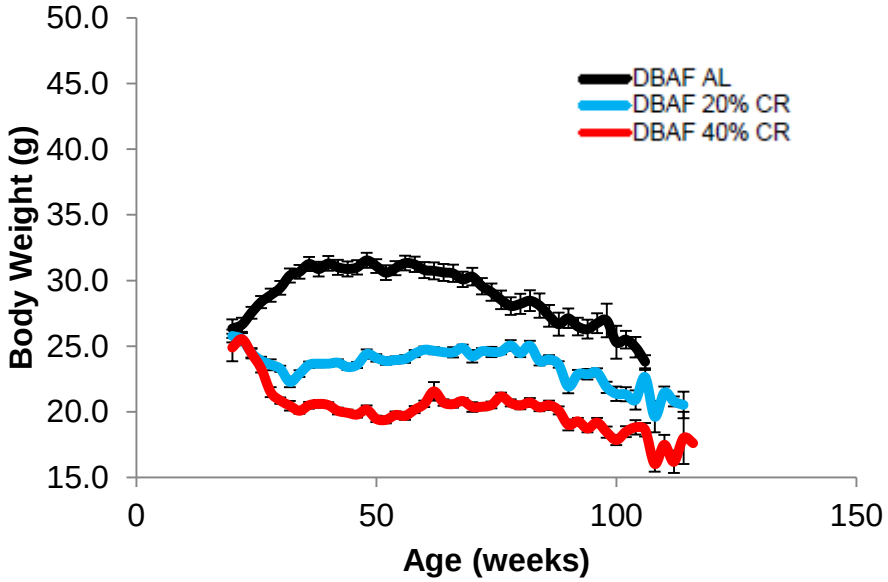
Most CR mimetics are not universal!

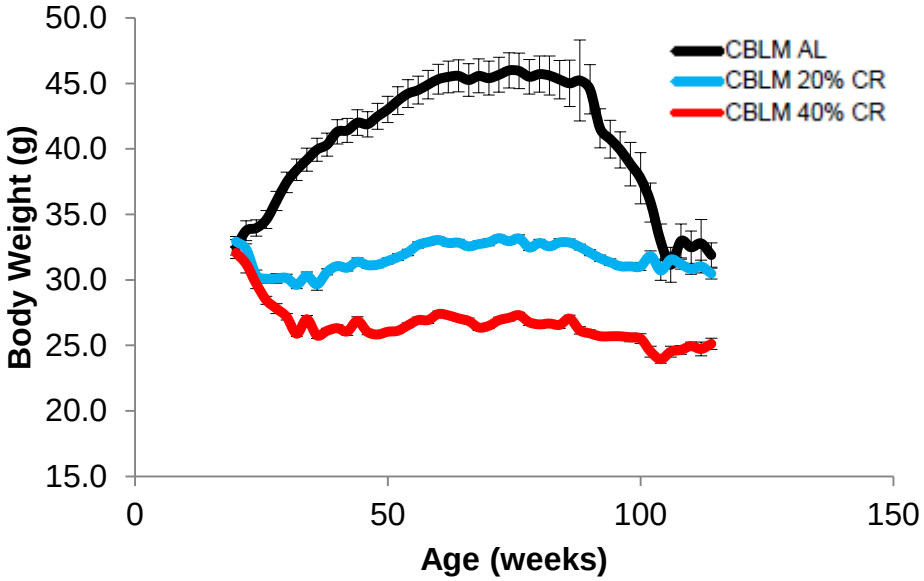


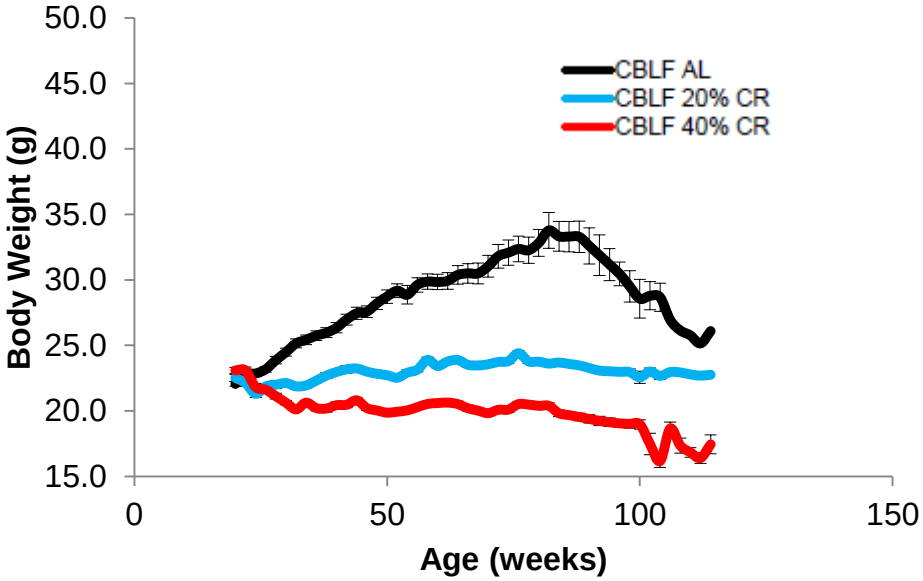
- Sex effect
- Diet Composition
- Genetic background
- Age of onset

CR on Body Weight



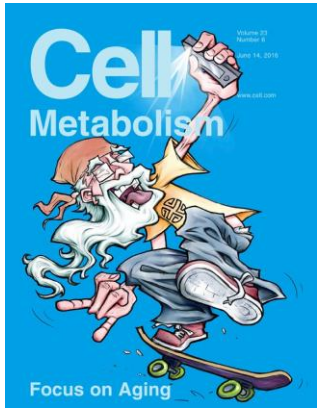




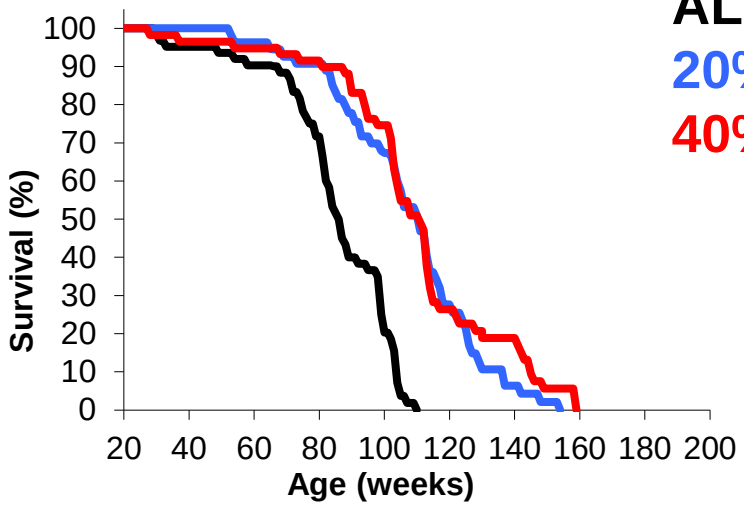


Cell Metabolism 23, 1093–1112, June 14, 2016

CR on Survival

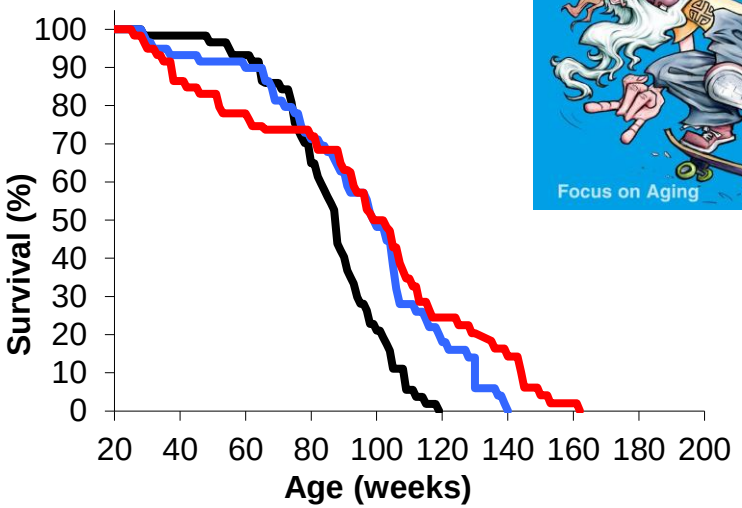


DBA Females

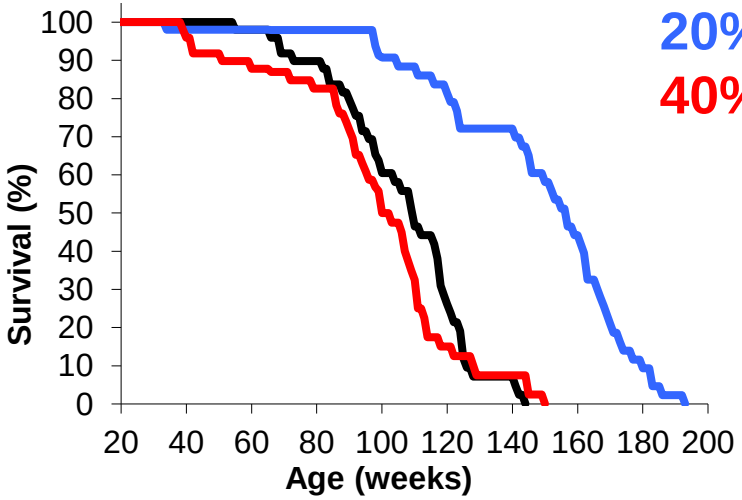


AL
20% CR
40% CR

DBA Males

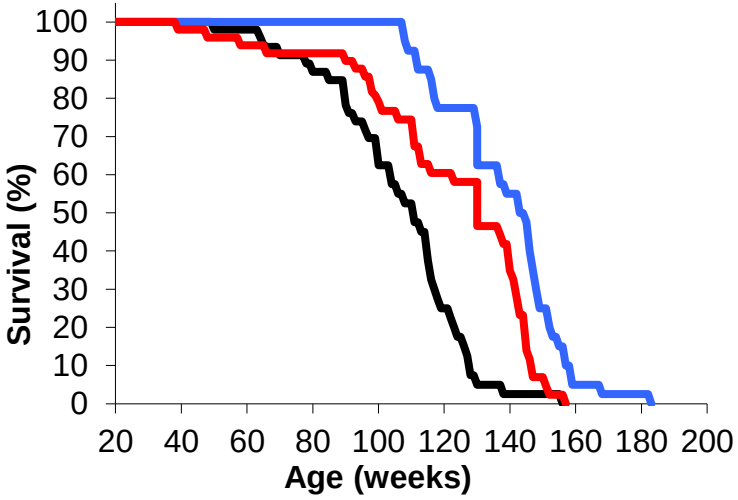


C57BL/6 Females



AL
20% CR
40% CR

C57BL/6 Males

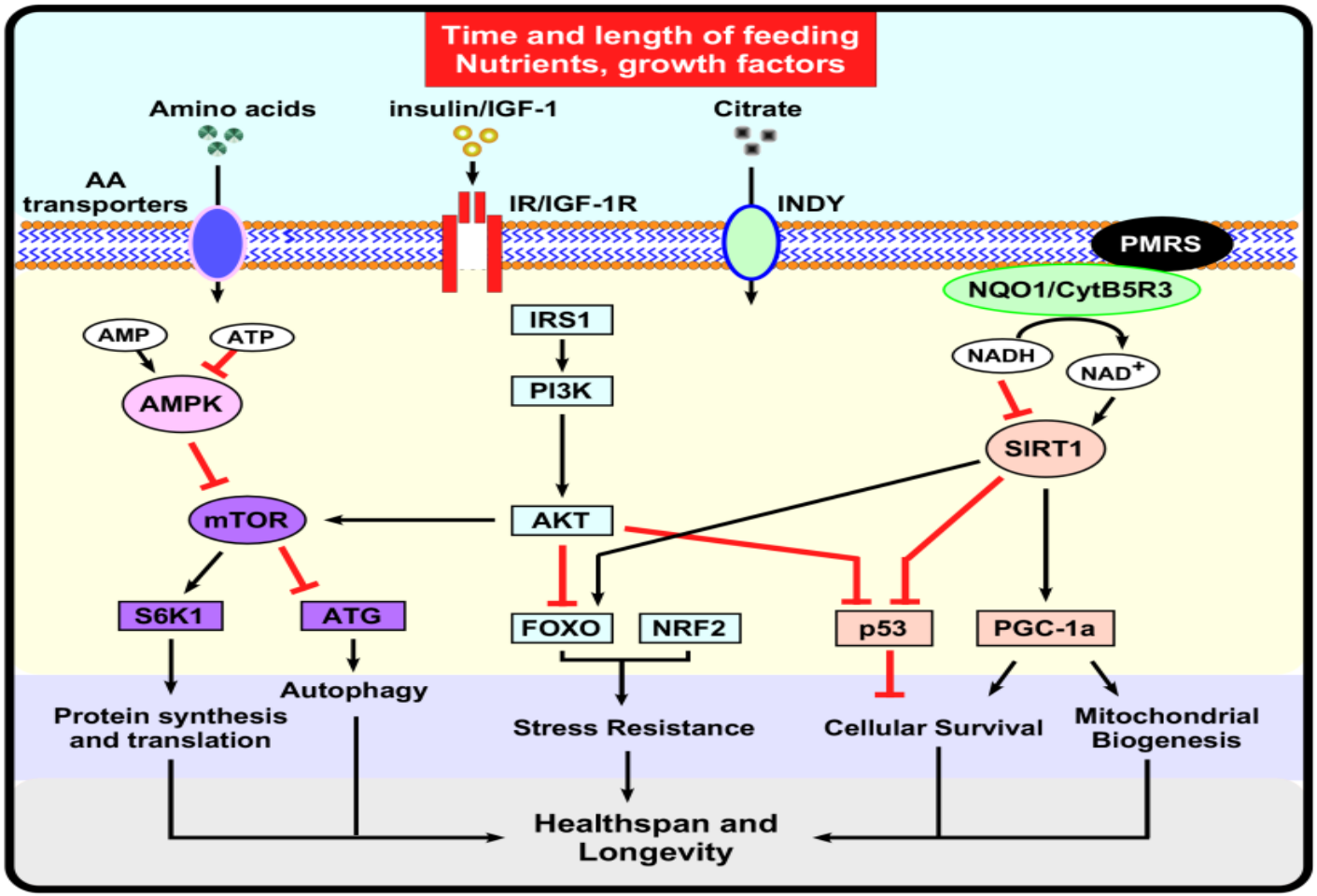


Cell Metabolism 23, 1093–1112, June 14, 2016

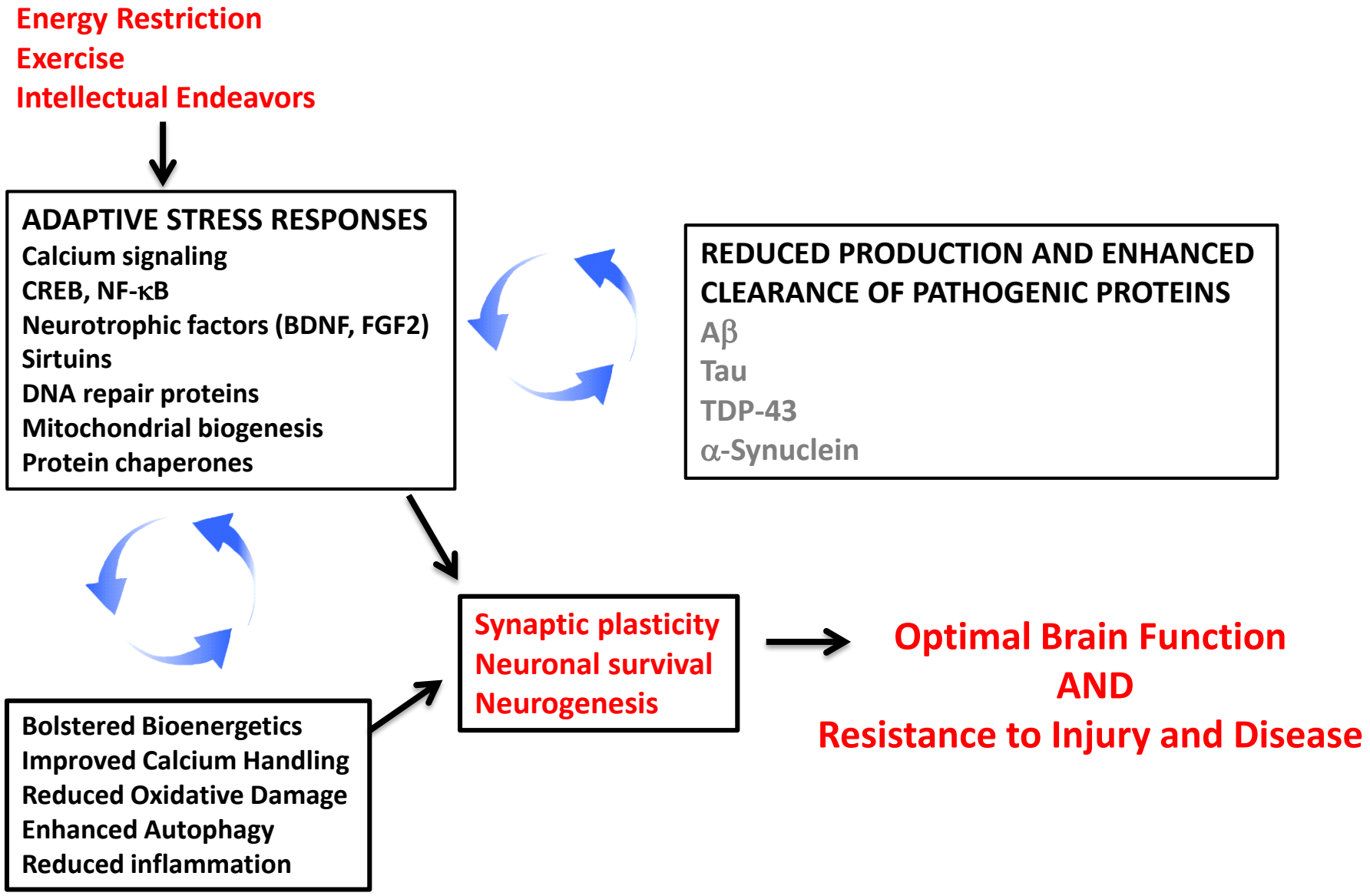
Common Pathways of Diverse CR Strategies

Dietary Manipulations

- Time Restricted Feeding
- Intermittent Fasting
- Amino Acid Restriction
- CR mimetics



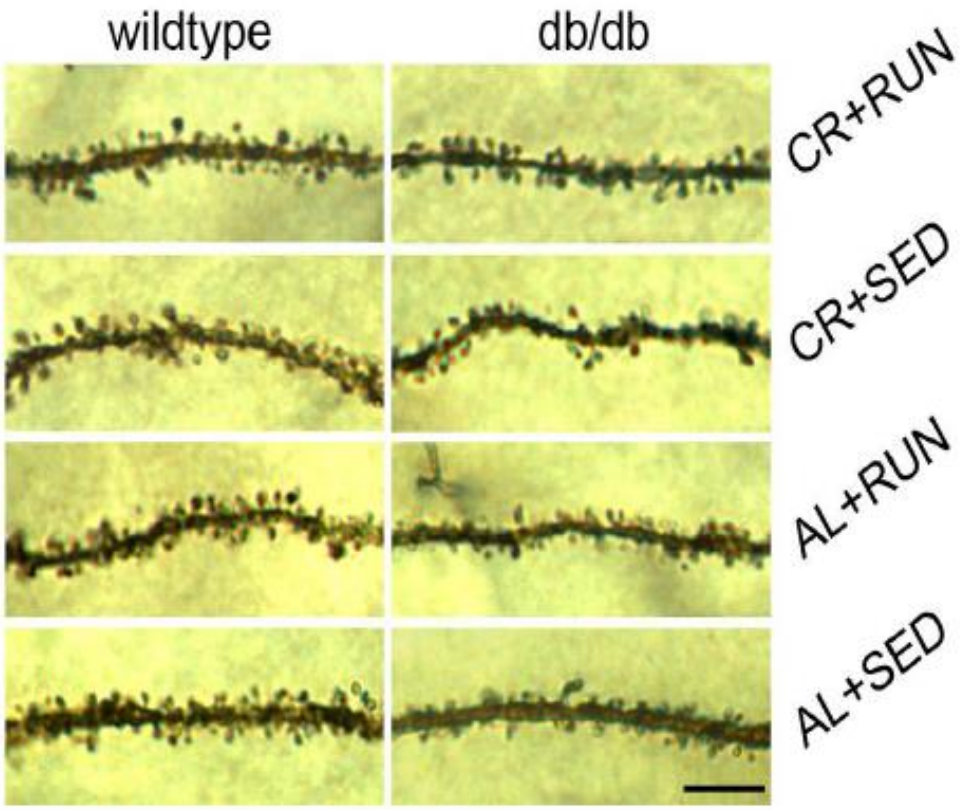
Beneficial effects of intermittent fasting on neurons
Promoting optimal function and resistance to neurodegenerative disorders



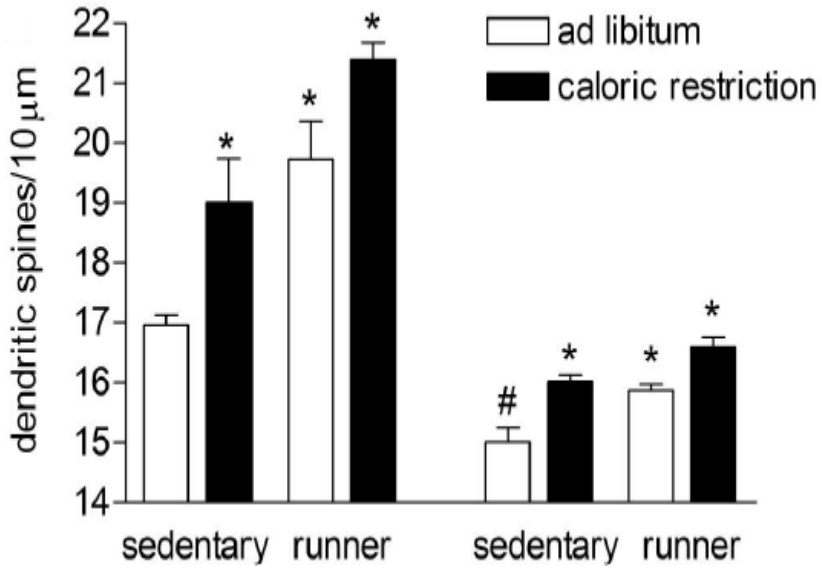
Mattson et al.

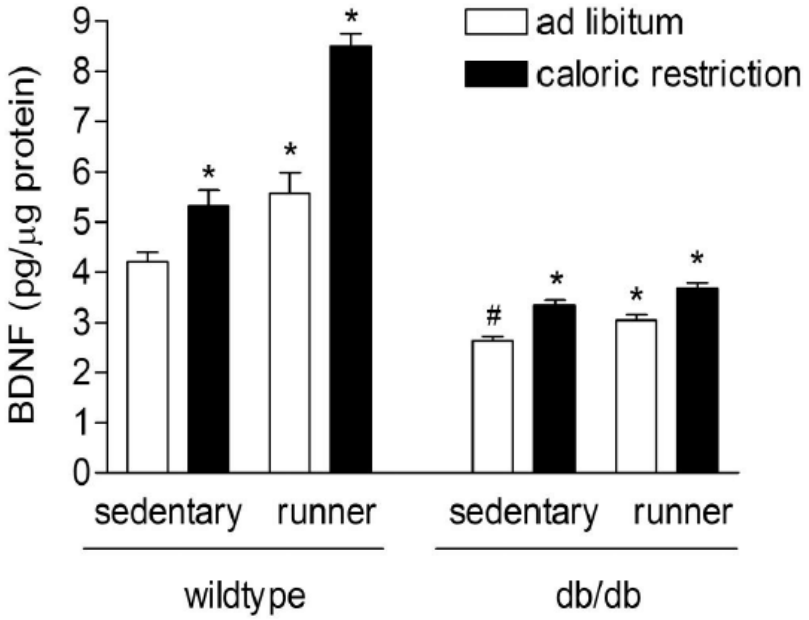
Mice that overeat and are diabetic (db/db mice) exhibit reduced synapse numbers and BDNF levels in the hippocampus, whereas dietary energy restriction and running increase synapse numbers and BDNF levels

Dendritic spines (postsynaptic structures) on hippocampal neurons



3 months of running and/or CR





Stranahan et al. (2008) *Nature Neurosci.* 11: 309-317.
Stranahan et al. (2009) *Hippocampus* 19: 951-961.

Fasting effects on other clinically relevant mouse models.

Annals of Neurology Vol 45 No 1 January 1999

Food Restriction Reduces Brain Damage and Improves Behavioral Outcome Following Excitotoxic and Metabolic Insults

Annadora J. Bruce-Keller, PhD,*† Gloria Umberger, BS, MPH,† Robert McFall, BS,* and Mark P. Mattson, PhD*†

PNAS | March 4, 2003 | vol. 100 | no. 5 | 2911–2916

Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice

Wenzhen Duan*, Zhihong Guo*, Haiyang Jiang*, Melvin Ware†, Xiao-Jiang Li‡, and Mark P. Mattson*§¶

Neurobiology of Disease 26 (2007) 212–220

Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease

Veerendra Kumar Madala Halagappa,[a] Zhihong Guo,[a] Michelle Pearson,[a] Yasuji Matsuoka,[b] Roy G. Cutler,[a] Frank M. LaFerla,[c] and Mark P. Mattson[a,*]

ANN NEUROL 2010;67:41–52

Age and Energy Intake Interact to Modify Cell Stress Pathways and Stroke Outcome

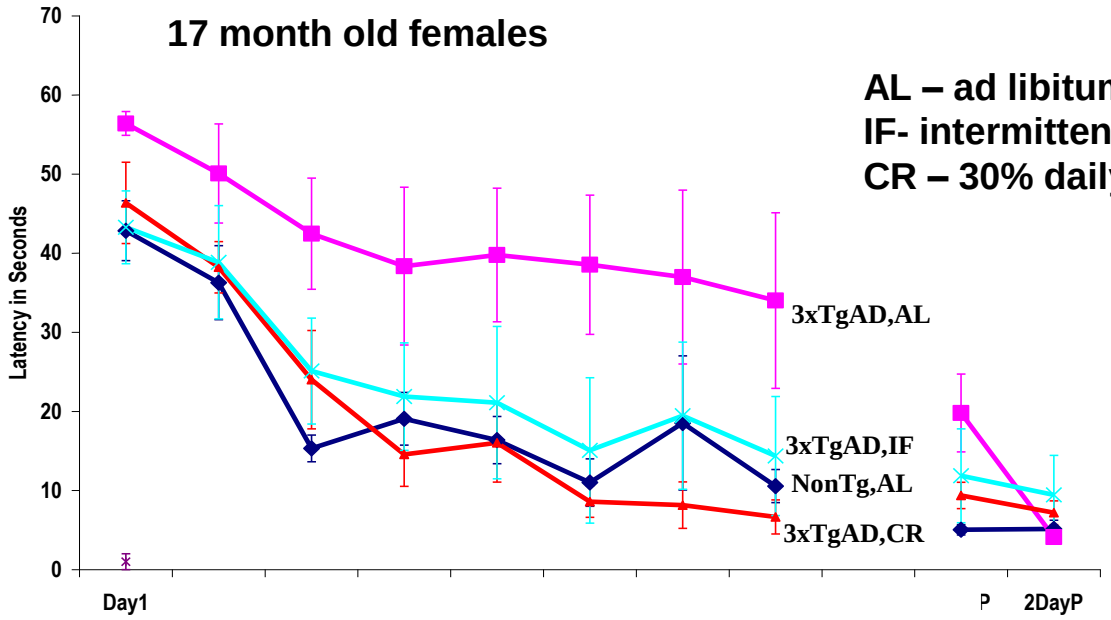
Thiruma V. Arumugam,* PhD,[1,2] Terry M. Phillips,* DSc,[3] Aiwu Cheng, PhD,[1] Christopher H. Morrell, PhD,[4] Mark P. Mattson, PhD,[1,5] and Ruiqian Wan, PhD[1]

Neurobiology of Aging 34 (2013) 928–935

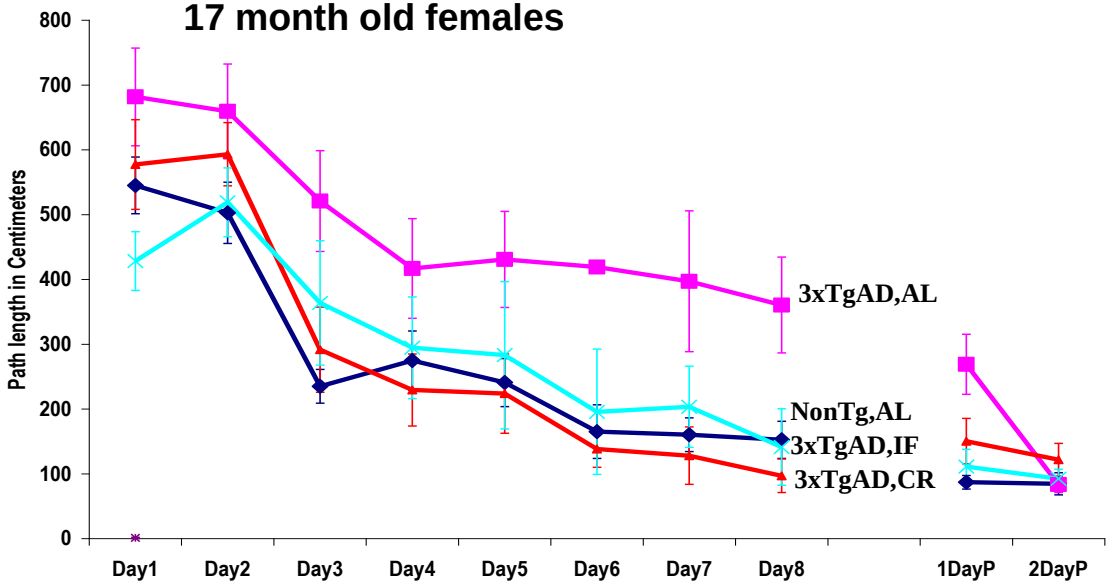
Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein

Kathleen J. Griffioen[a], Sarah M. Rothman[a], Bruce Ladenheim[b], Ruiqian Wan[a], Neil Vranis[a], Emmette Hutchison[a], Eitan Okun[a,c], Jean Lud Cadet[b], Mark P. Mattson[a,d,*]

Two CR interventions on a mouse model of AD



AL – ad libitum
IF- intermittent (alternate day) fasting
CR – 30% daily calorie restriction



Halagappa VK et al (2007)
Neurobiol Dis. 26:212-20.

In summary…

• The lifespan of most species can be extended by calorie restriction (McKay, 1935, and many, many others).

•This lead to the discovery of genes and identification of several molecular pathways which can extend lifespan (IGF, sirtuins, mTOR).

• This in turn has led to non-genetic extension of lifespan (resveratrol, rapamycin, SRT1720, metformin, acarbose and a growing etc).

•There area growing number of CR strategies that seem to recapitulate the original observations (Intermittent fasting, Time restricted feeding, etc)

Adapted from Felipe Sierra

Elucidating CR mechanism should

- Provide a better understanding of basic biological mechanisms of aging

- A better success rate in translating findings into improvements of human health.

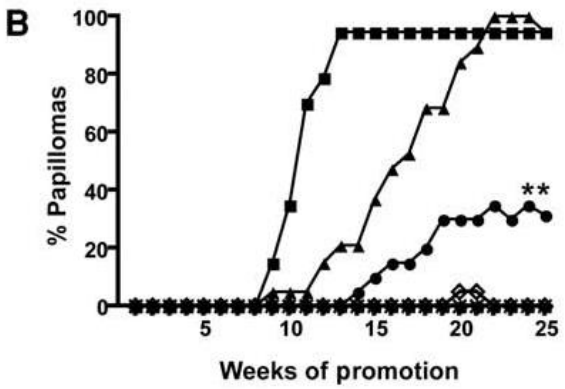
- A better understanding of multiple chronic diseases, including etiology, risk factors, onset, progression and response to treatment.

- An ability to address the most common presentation of diseases in the population: comorbidities.

Healthspan is also improved

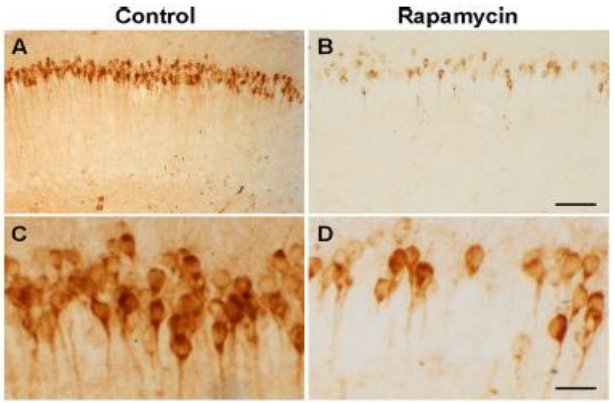
- Well documented in Caloric Restriction over the last 20 years (reduced cell metabolism, ROS production, replicative stress and immune dysfunction, as well as delay in onset of diseases)
- Resveratrol delays the appearance of age- and disease-related inflammation, arterial stiffness, loss of motor coordination, cataract formation and loss of bone mineral density, and protects against ischemic stroke.
- Rapamycin:

Decreases TPA-induced skin tumors



Checkley et al. – Ca Prev. Res (2011)

Decreases Aβ in the brain of mouse models



Caccamo et al. – JBC 2010

Importantly

Some of these finding are being translated

www.ScienceTranslationalMedicine.org 24 December 2014 Vol 6 Issue 268 268ra179

IMMUNOLOGY

mTOR inhibition improves immune function in the elderly

Joan B. Mannick,[1]* Giuseppe Del Giudice,[2] Maria Lattanzi,[2] Nicholas M. Valiante,[3] Jens Praestgaard,[4] Baisong Huang,[1] Michael A. Lonetto,[1] Holden T. Maecker,[5] John Kovarik,[6] Simon Carson,[7] David J. Glass,[1] Lloyd B. Klickstein[1]

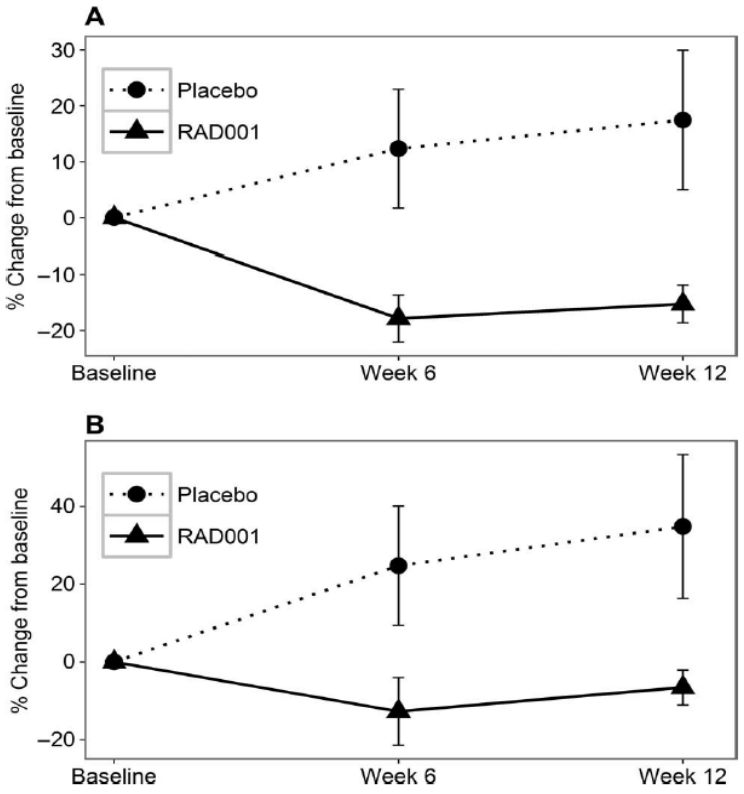


Fig. 3. Decrease in percent of PD-1–positive CD4 and CD8 T cells after RAD001 treatment. The percent of PD-1–positive CD4 and CD8 T cells was determined by fluorescence-activated cell sorting analysis of PBMC samples at baseline, after 6 weeks of drug treatment (week 6), 6 weeks after study drug discontinuation, and 4 weeks after influenza vaccination (week 12). (**A**) There was a significant decrease of 30.2% in PD-1–positive CD4 T cells at week 6 in the pooled RAD001-treated cohort ($n = 84$) compared to the placebo cohort ($n = 25$) [$P = 0.03$ ($q = 0.13$)]. The decrease in PD-1–positive CD4 T cells at week 12 in the pooled RAD001-treated cohort compared to the placebo cohort was 32.7% [$P = 0.05$ ($q = 0.19$)]. (**B**) There was a significant decrease of 37.4% in PD-1–positive CD8 T cells at week 6 in the pooled RAD001-treated cohort ($n = 84$) compared to the placebo cohort ($n = 25$) [$P = 0.008$ ($q = 0.07$)]. The decrease in PD-1–positive CD8 T cells at week 12 in the pooled RAD001-treated cohort compared to the placebo cohort was 41.4% [$P = 0.066$ ($q = 0.21$)].

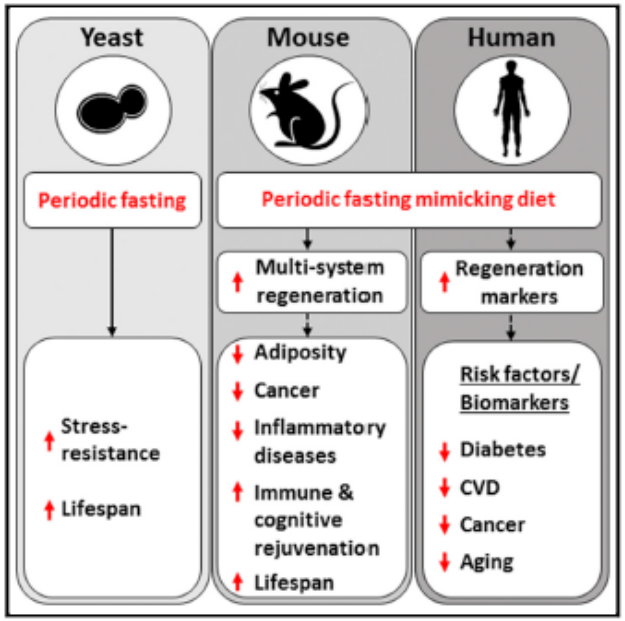
Some of these finding are being translated

Clinical and Translational Report

Cell Metabolism

A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Graphical Abstract



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In Brief

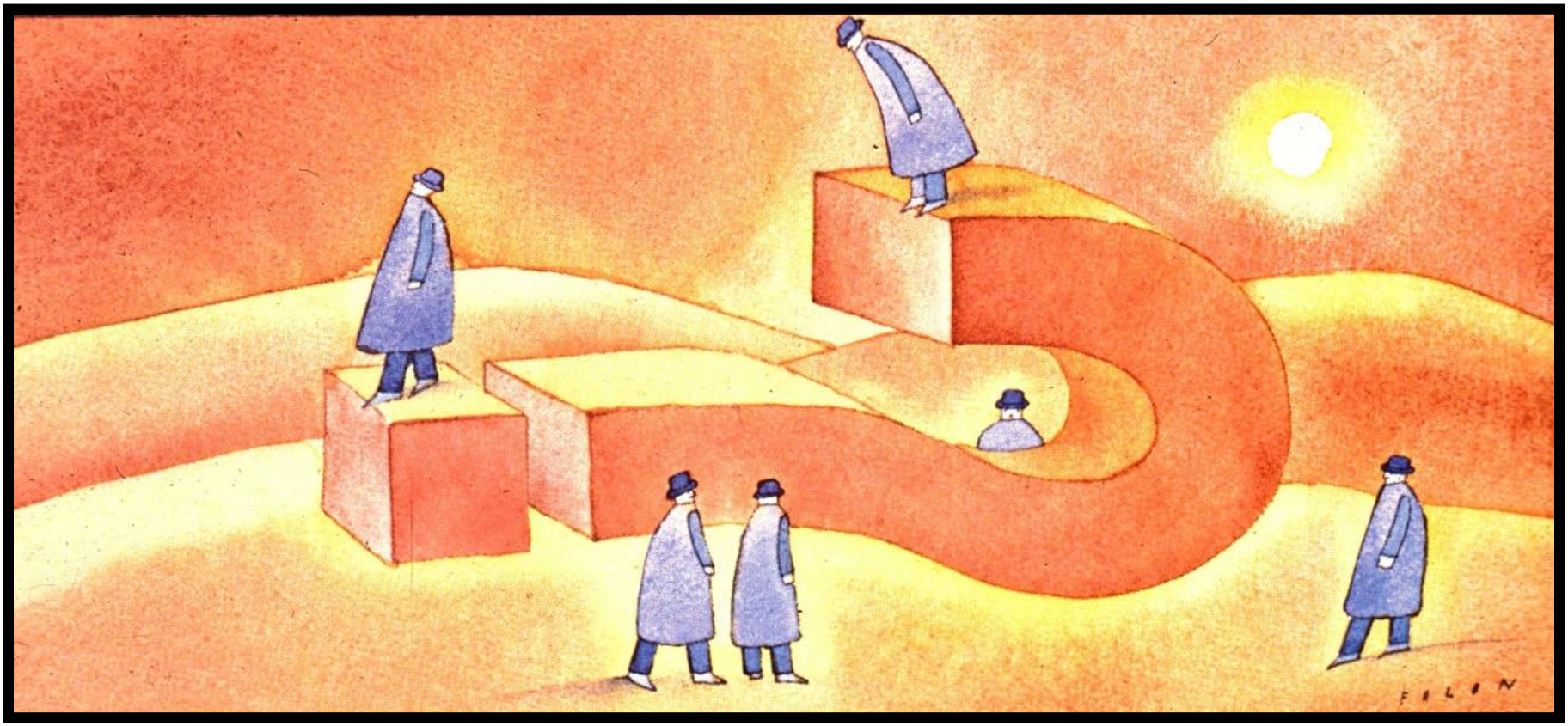
Brandhorst et al. develop a fasting mimicking diet (FMD) protocol, which retains the health benefits of prolonged fasting. In mice, FMD improved metabolism and cognitive function, decreased bone loss and cancer incidence, and extended longevity. In humans, three monthly cycles of a 5-day FMD reduced multiple risk factors of aging

Highlights

- FMD rejuvenates the immune system and reduces cancer incidence in C57BL/6 mice
- FMD promotes hippocampal neurogenesis and improves cognitive performance in mice
- FMD causes beneficial changes in risk factors of age-related diseases in humans

Brandhorst et al., 2015, Cell Metabolism 22, 86–99

Where are we now?

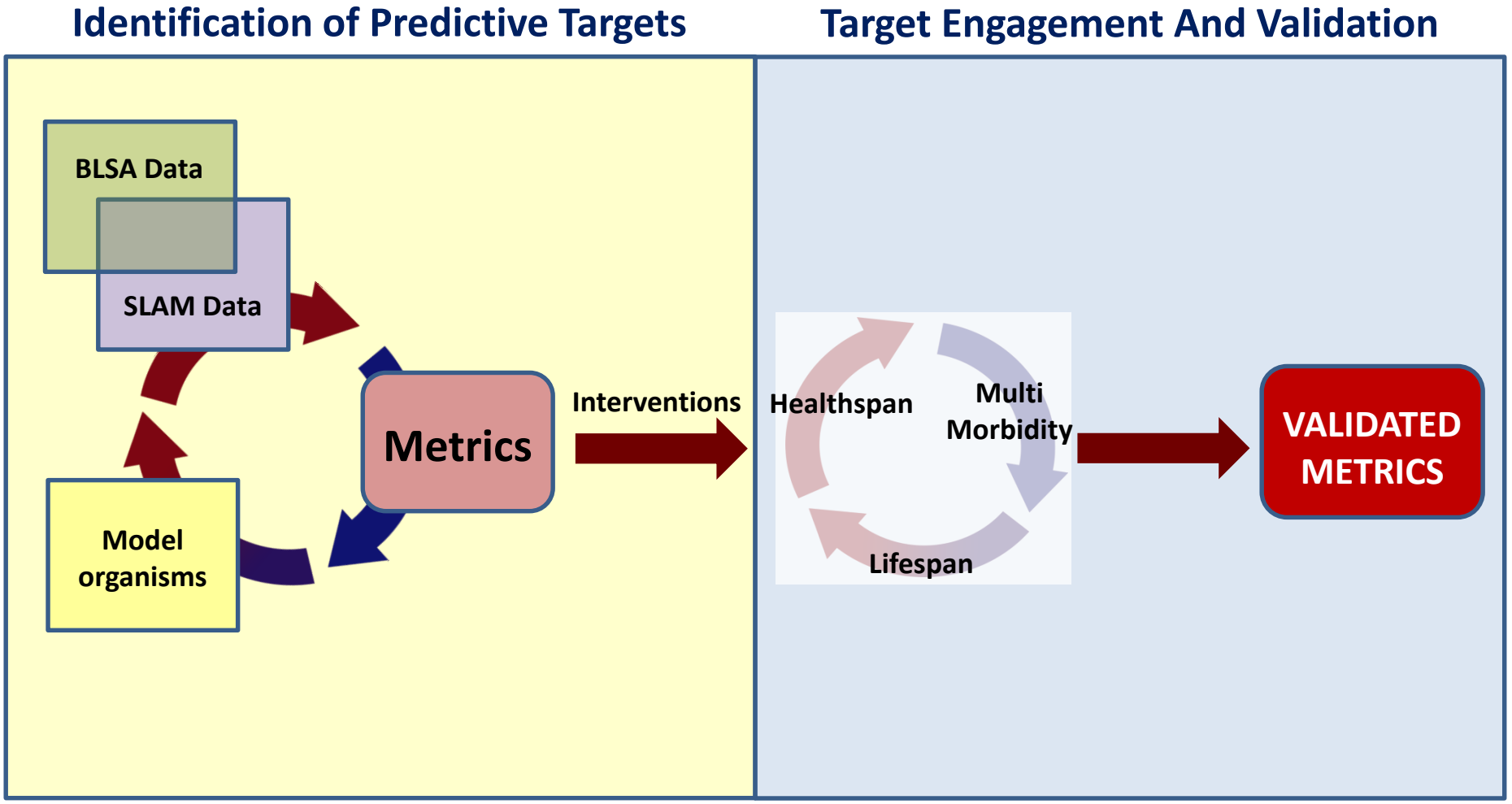


Where are we now?

We are here now

Hope to be here soon!!!

Where are we heading?



Predictive Mechanism-Related Markers for Aging-Related Outcomes

Adapted from Felipe Sierra

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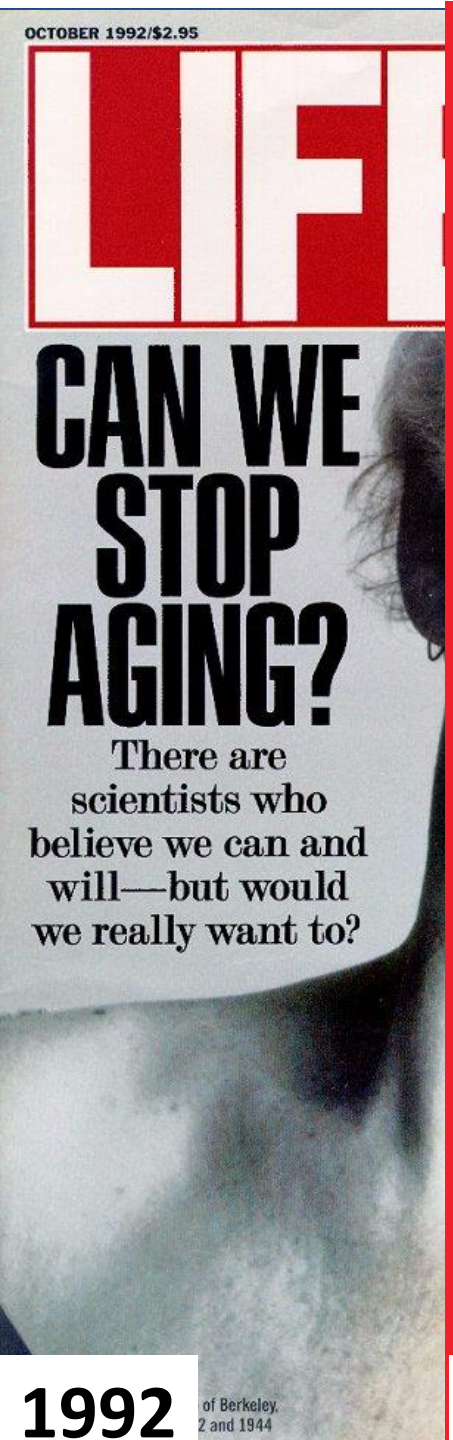
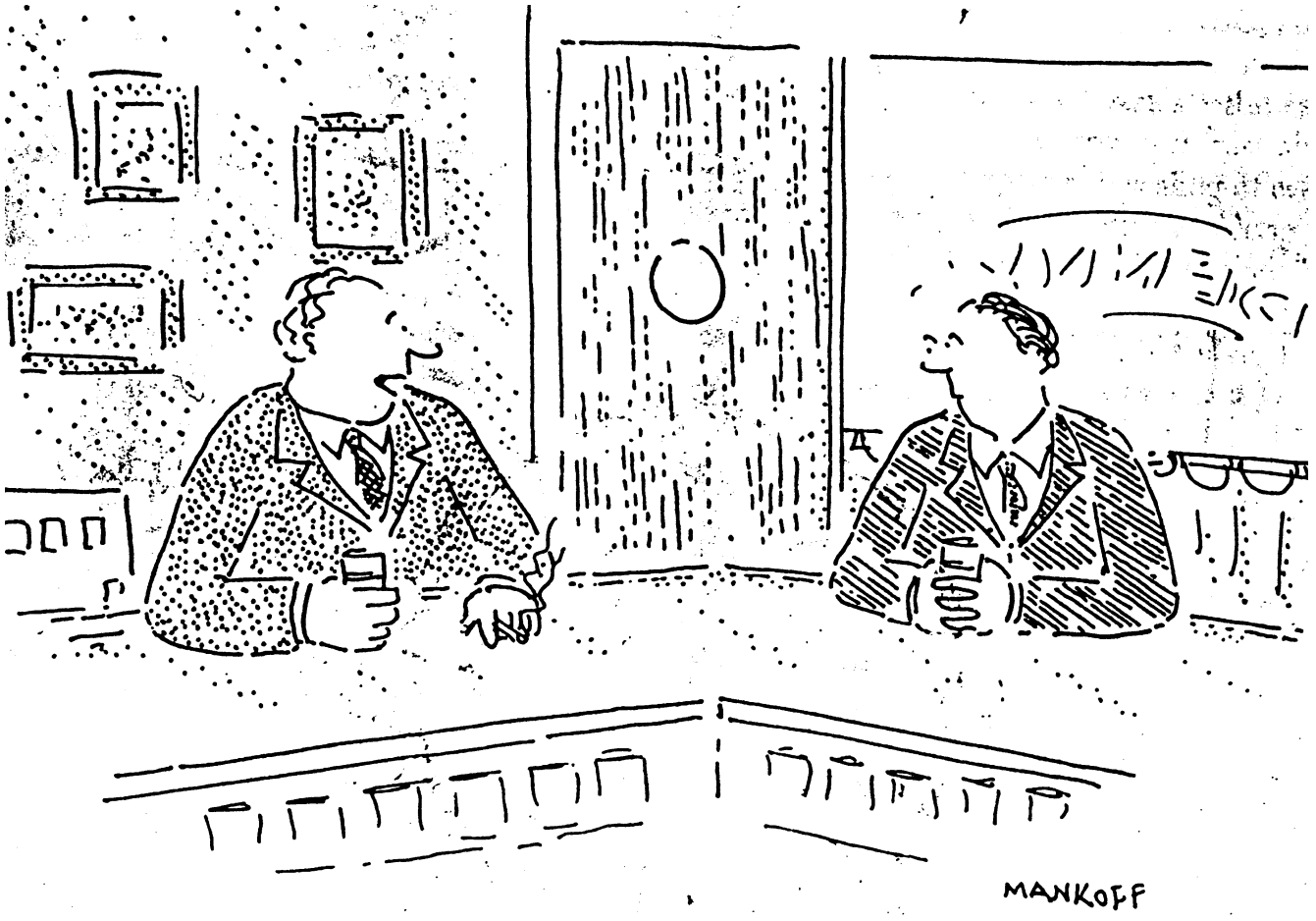


1992

2010

2016

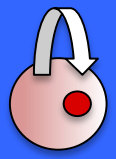


"See, the problem with doing things to prolong your life is that all the extra years come at the end, when you're old."

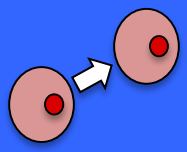
Translational Gerontology Branch
Research Into The Cellular And Molecular Mechanisms For Healthspan and Active Life Expectancy

AGING and DISEASES

Stem Cells Exhaustion

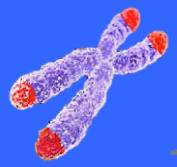


Altered Intercellular Communication

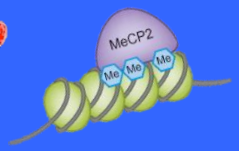


Genomic Instability

Telomere Attrition



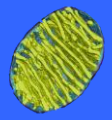
Epigenetic Alterations



Loss of Proteostasis

Deregulated Nutrient Sensing

Mitochondrial Dysfunction



Cellular Senescence

Domains of the Aging Phenotype

- Changes in Body Composition
- Energy Imbalance Production/Utilization
- Homeostatic Dysregulation
- Neurodegeneration

Healthspan And Active Life Expectancy

Consequences

- Disease Susceptibility
- Reduced Functional Reserve:
- Impaired Stress Response and Healing Capacity
- Unstable Health
- Failure to Thrive
- Impaired Physical Function
- Disability
- Dementia

TGB Strategies

- Drug Discovery
- Animal Studies
- Interventions
- Translational studies
- Clinical Trials
- Population Studies

Ferrucci L, Studenski S. Clinical Problems of Aging. In: Harrison's Principles of Internal Medicine, 18th Ed. – 2011
The Hallmarks of Aging López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Cell 3013, 153: 1194

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