Dietary Interventions for Healthy Aging

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Aging is a universal process

**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

Kumar and Lombard
The world is aging rapidly!

Young children and older people as a percentage of global population compared between 2005 and 2030, by age.

2017

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!
NO!

…..but we can alter its onset and progression through interventions
Squaring the survival curve in human populations

Trajectories of Human Lifespan

By half century, 1541–1891
By decade, 1901–1991

Survivors per thousand

Age group
Caloric restriction

Adapted from Weindruch et al., 1979

C3B10RF$_1$ mice
DR increases lifespan in diverse organisms
There’s always a catch

"I'm taking you off calories."
How Does CR Work?

Energy Intake

- Metabolic Rate
- Oxidative Stress
- Hormesis
  - Insulin Signaling
  - GH/IGF1 Signaling
  - Ingestion of AGEs

Body Size

Adiposity

Chronic Inflammation

mTOR Signaling

Sirtuin Activity

AMPK Activity
Molecular Targets for Caloric Restriction and Pharmacological Interventions For Healthy Aging

de Cabo et al. (Cell, 2014)
Adapted from Weindruch et al., 1979

Caloric Restriction Mimetics
(Interventions for Healthy Aging)

% SURVIVAL

AGE (month)

control (n=57)

restricted (n=60)

C3B10RF mice
BUT
Rapamycin: Females better than Males

Acarbose: Longevity Effect Greater in Males
Most CR mimetics are not universal!

- Sex effect
- Diet Composition
- Genetic background
- Age of onset
CR on Body Weight

- DBAM AL
- DBAM 20% CR
- DBAM 40% CR

- DBAF AL
- DBAF 20% CR
- DBAF 40% CR

- CBLM AL
- CBLM 20% CR
- CBLM 40% CR

- CBLF AL
- CBLF 20% CR
- CBLF 40% CR

Age (weeks)

Body Weight (g)
**CR on Survival**

**DBA Females**
- AL
- 20% CR
- 40% CR

**DBA Males**
- AL
- 20% CR
- 40% CR

**C57BL/6 Females**
- AL
- 20% CR
- 40% CR

**C57BL/6 Males**
- AL
- 20% CR
- 40% CR

*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

Time and length of feeding Nutrients, growth factors

Amino acids
insulin/IGF-1
Citrate

AA transporters
AMPK
mTOR
S6K1
ATG
Autophagy
Protein synthesis and translation

IRS1
PI3K
AKT
FOXO
NRF2
p53
PGC-1α
Stress Resistance
Cellular Survival
Mitochondrial Biogenesis

Healthspan and Longevity

NQO1/CytB5R3
NADH
NAD+
SIRT1
PMRS

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

Energy Restriction
Exercise
Intellectual Endeavors

ADAPTIVE STRESS RESPONSES
- Calcium signaling
- CREB, NF-κB
- Neurotrophic factors (BDNF, FGF2)
- Sirtuins
- DNA repair proteins
- Mitochondrial biogenesis
- Protein chaperones

REDUCED PRODUCTION AND ENHANCED CLEARANCE OF PATHOGENIC PROTEINS
- Aβ
- Tau
- TDP-43
- α-Synuclein

Synaptic plasticity
Neuronal survival
Neurogenesis

Optimal Brain Function
AND
Resistance to Injury and Disease

Bolstered Bioenergetics
Improved Calcium Handling
Reduced Oxidative Damage
Enhanced Autophagy
Reduced inflammation

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

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, Zhihong Guo, Michelle Pearson, Yasuji Matsuoka, Roy G. Cutler, Frank M. LaFerla, 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, Terry M. Phillips, DSc, Aiuw Cheng, PhD, Christopher H. Morrell, PhD, Mark P. Mattson, PhD, and Ruiqian Wan, PhD

Neurobiology of Aging 34 (2013) 928–935
Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein
Kathleen J. Griffioen, Sarah M. Rothman, Bruce Ladenheim, Ruiqian Wan, Neil Vranis, Emmette Hutchison, Eitan Okun, Jean Lud Cadet, Mark P. Mattson*a,d,*
Two CR interventions on a mouse model of AD

Hlagappa VK et al (2007)
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
  - Decreases Aβ in the brain of mouse models

Caccamo et al. - JBC 2010
Importantly
Some of these finding are being translated

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. Klickstein1

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 findings are being translated.

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

Graphical Abstract

Authors
Sebastian Brandhorst, In Young Choi, Min Wei, ..., Todd E. Morgan, Tanya B. Dorff, Valter D. Longo

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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!!!
Predictive Mechanism-Related Markers for Aging-Related Outcomes

Adapted from Felipe Sierra
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“See, the problem with doing things to prolong your life is that all the extra years come at the end, when you’re old.”
Domains of the Aging Phenotype

- Healthspan
- Active Life Expectancy

AGING and DISEASES

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

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
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