USC Davis School of Gerontology

USU Uniformed Services University

Low Calorie Diets for Chemotherapy Augmentation

State of the Science Symposia Series

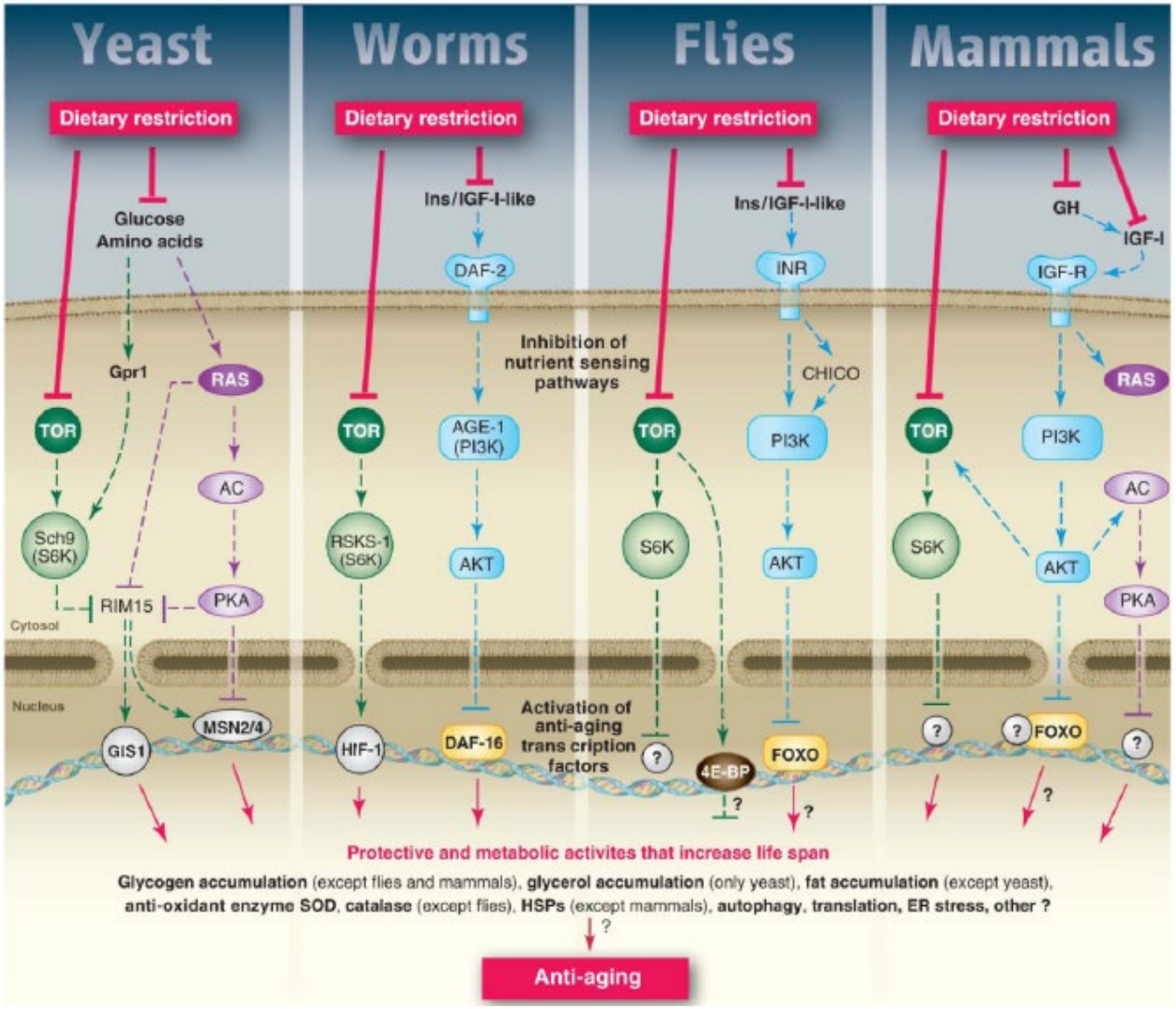
Metabolic Pathways and Therapeutics to Promote Resilience, Rehabilitation and Delayed Aging

Friday, October 25th 2019

Sebastian Brandhorst, PhD
Longevity Institute
University of Southern California

USC Davis
School of Gerontology

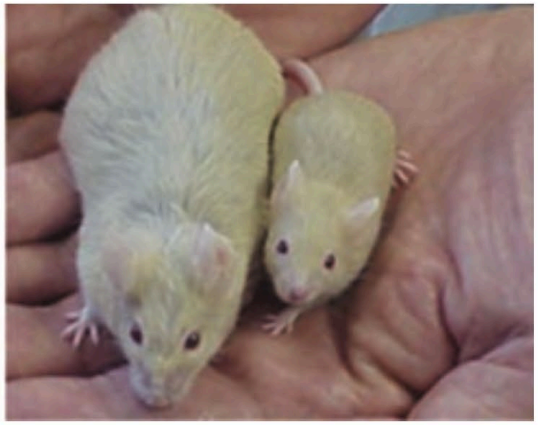
Nutrient-Sensing Pathways Present a Target to Delay the Onset of Aging-Related Diseases and Aging.



Fontana et al. Science. 2010 Apr 16;328(5976):321-6.

USC Davis
School of Gerontology

Yeast, Flies, and Mice with Similar Genetic Mutations Live Healthier and Longer.

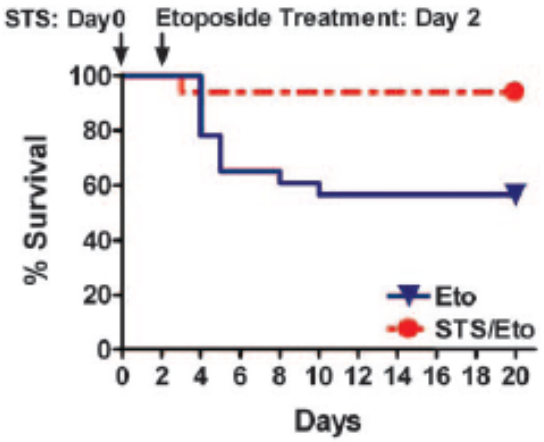


Fontana et al. Science. 2010 Apr 16;328(5976):321-6.

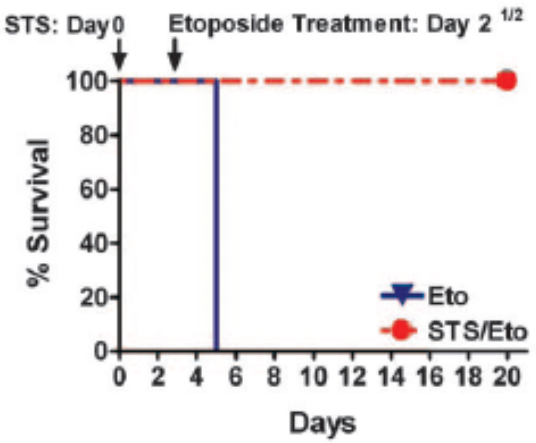
USC Davis
School of Gerontology

Starvation Increases Resistance to a Variety of Toxins.

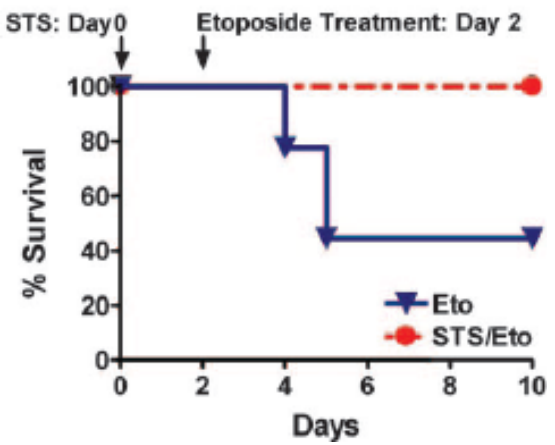
A/J



CD-1



Nude

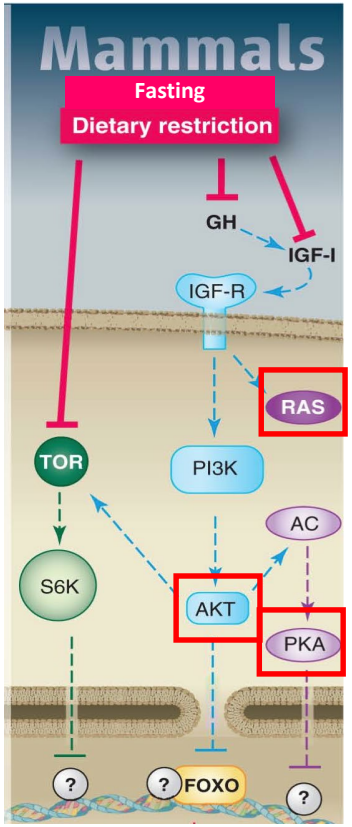


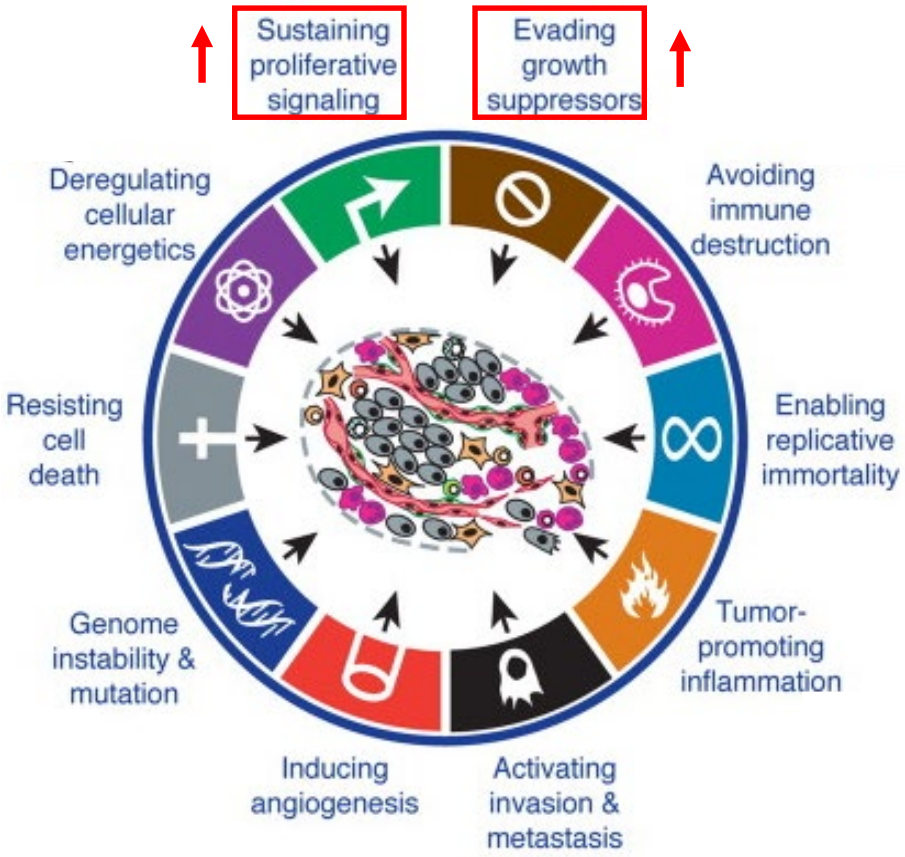
→ **Detrimental if fasting induces similar protection in cancer cells**

Cancer Res. 2010 Feb 15;70(4):1564-72. Lee et al

USC Davis
School of Gerontology

The Hallmarks of Cancer: Oncogenes in Pro-aging Pathways.



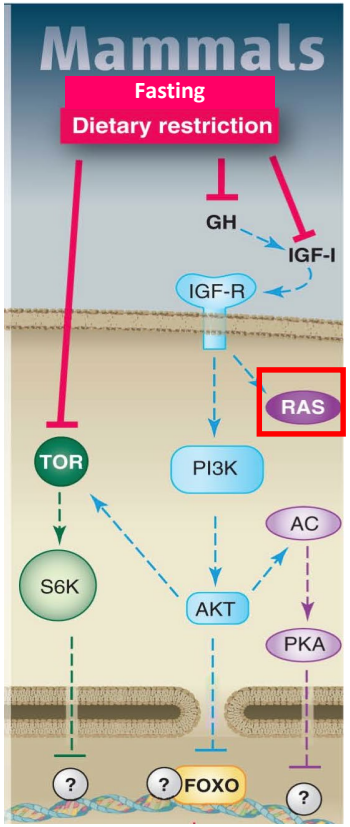


Fontana L, Partridge L, Longo VD. Science. 2010 Apr 16;328(5976):321-6.

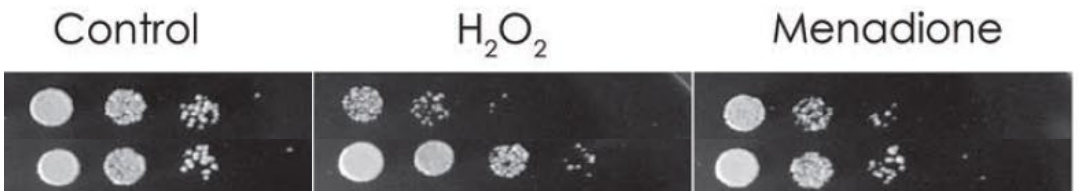
Hanahan D, Weinberg RA. Cell. 2000 Jan 7;100(1):57-70.

USC Davis School of Gerontology

Fasting induced Differential Stress Sensitization.



WT- reg. medium
24h water



Fontana L, Partridge L, Longo VD. Science. 2010 Apr 16;328(5976):321-6.

Sci Transl Med. 2012 Mar 7;4(124):124ra27; Lee et al

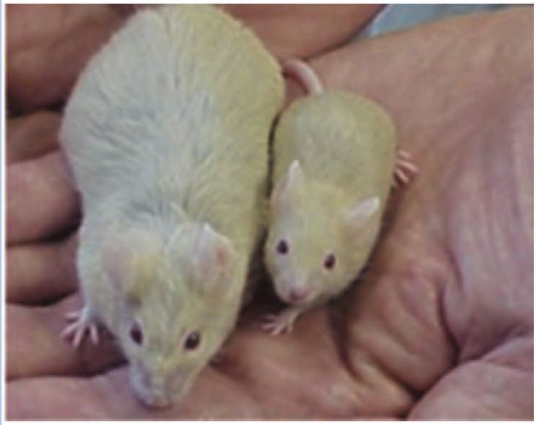
USC Davis
School of Gerontology

video

Safdie, Brandhorst et al. **PLoS One** 2012

USC Davis
School of Gerontology

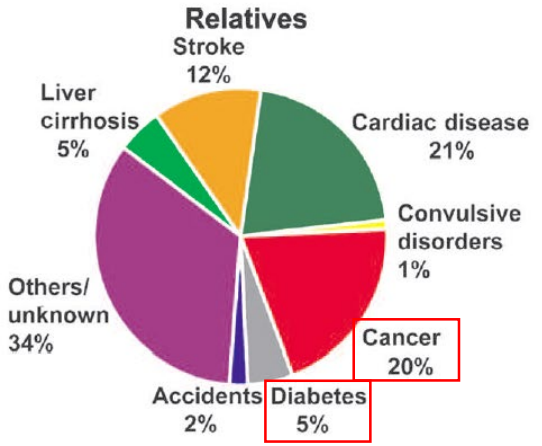
Fasting:
Translation to Humans?

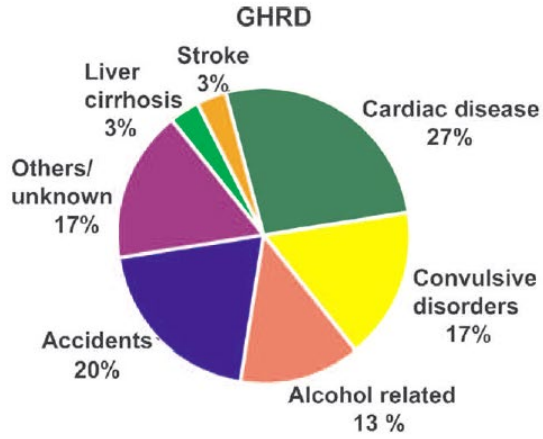


Fontana et al. Science. 2010 Apr 16;328(5976):321-6.

USC Davis
School of Gerontology

Growth Hormone Receptor Deficiency is Associated with a Major Reduction in Pro-aging Signaling, Cancer and Diabetes in Humans.

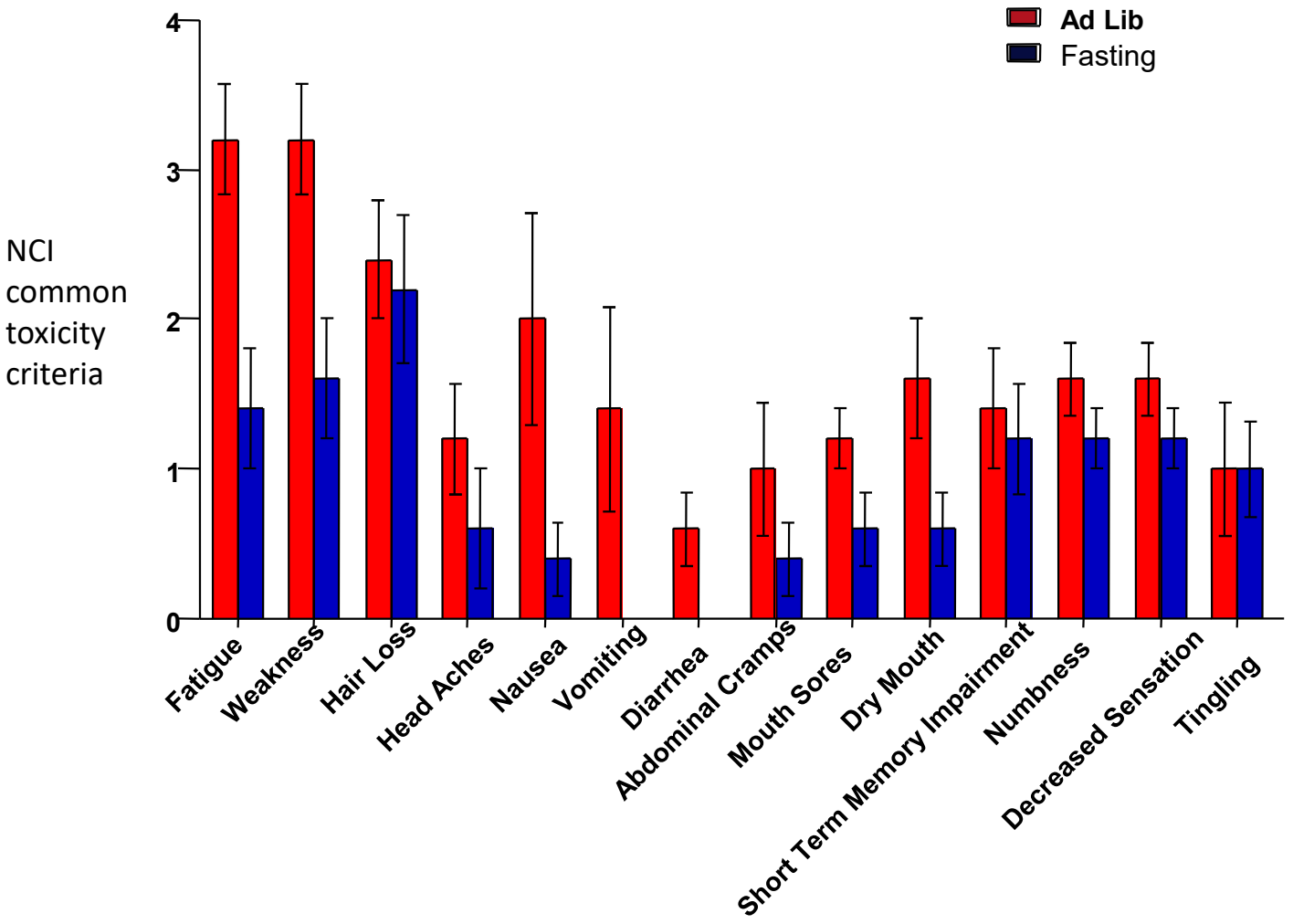




Sci Transl Med. 2011 Feb 16;3(70):70ra13. Guevara-Aguirre J et al.

USC Davis
School of Gerontology

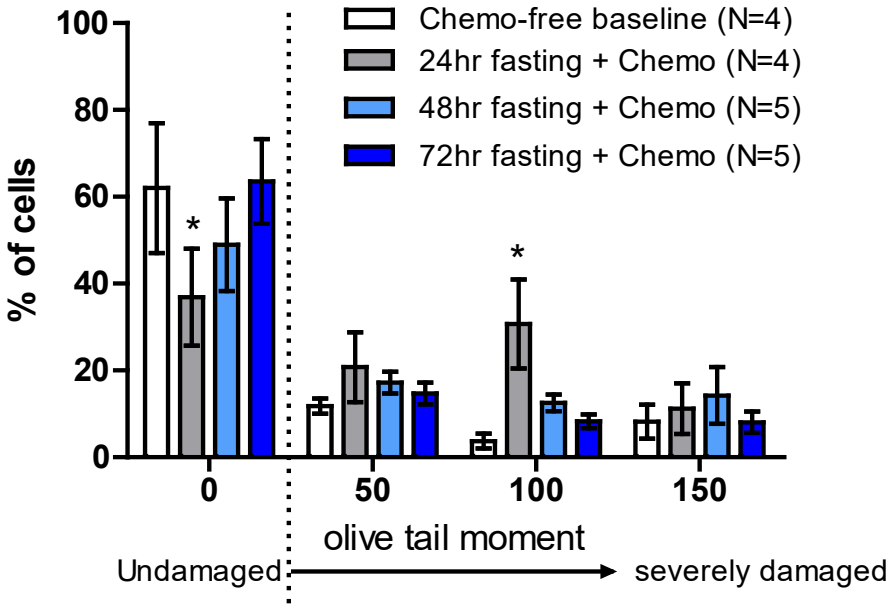
Translation: Fasting Reduces Self-reported Severity of Symptoms in Patients that have Received Chemotherapy.

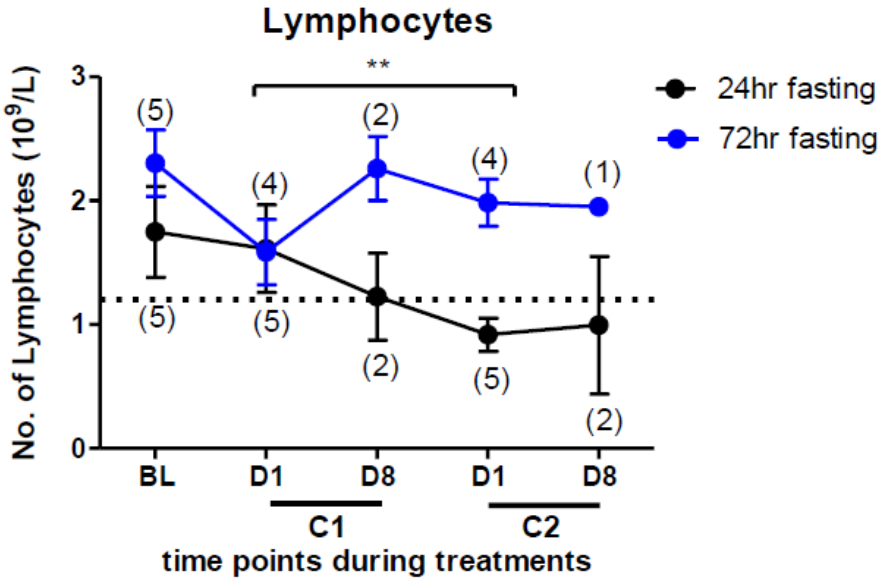


Safdie et al, Aging 2009

USC Davis
School of Gerontology

Translation: Fasting reduces DNA Damage and Lymphocytopenia.





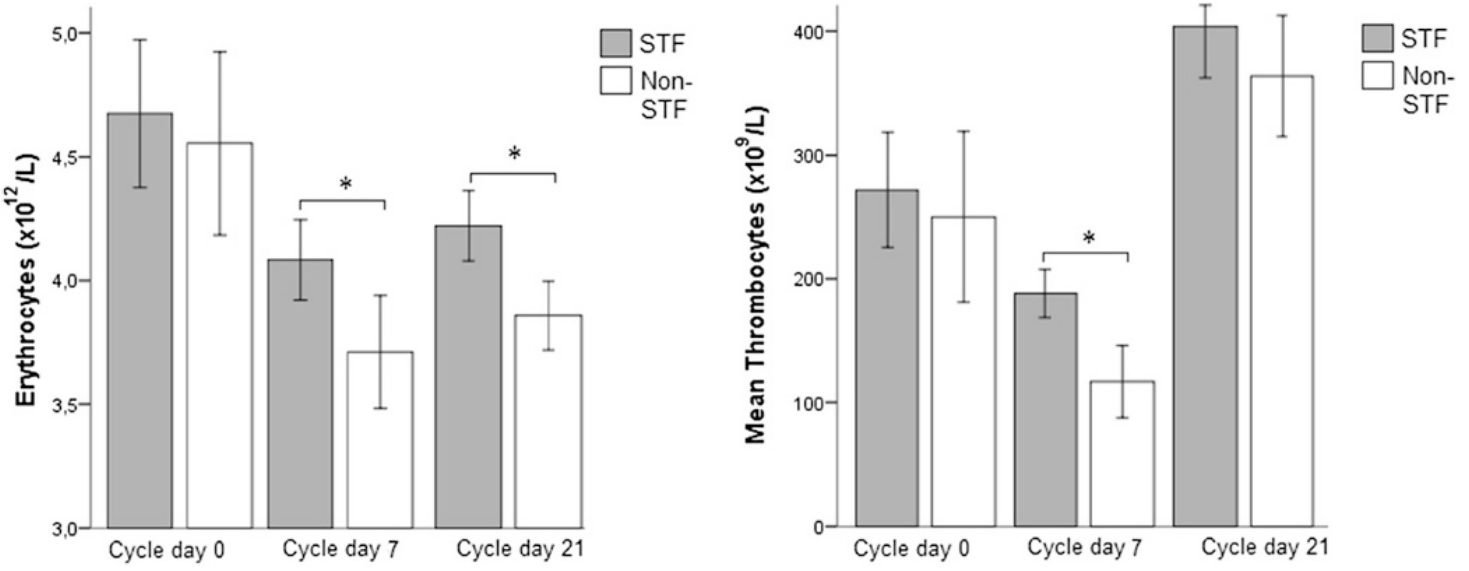
Completed Phase I Clinical trial: 72 hours of fasting is associated with reduced DNA damage and reversal of lymphocytopenia in patients receiving gemcitabine/cisplatin, carboplatin/taxol

BMC Cancer. 2016 Jun 10;16:360. Dorff et al.

USC Davis
School of Gerontology

Translation: Fasting attenuates Bone Marrow Toxicity.

- confirmed diagnosis of HER2-negative stage II and III breast cancer
- receiving (neo) adjuvant TAC-chemotherapy



➢ decreased breakdown of circulating cells and/or less severe bone marrow suppression

Values are measured on day 0 of cycle 1 immediately before the chemotherapy infusion, on day 7 of cycle 1–5 combined and day 21 of cycle 1–5 combined.

BMC Cancer. 2015 Jun 15;652. de Groot et al.

USC Davis School of Gerontology

Clinical Adaptation: FMDs to Overcome the Limitations of Fasting.

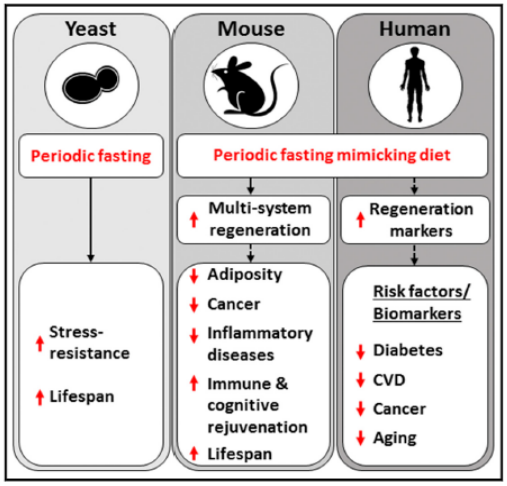
- ✓ Plant Based, Natural ingredients
- ✓ Effective in initial trials against Aging and Multiple Chronic Diseases

Clinical and Translational Report

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

Correspondence

vlongo@usc.edu

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

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

METABOLIC DISEASE

Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease

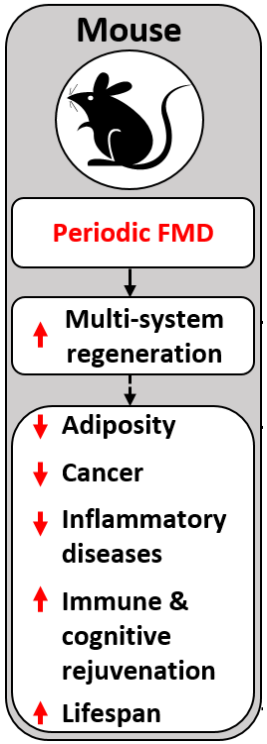
Min Wei,[1]* Sebastian Brandhorst,[1]* Mahshid Shelehchi,[1] Hamed Mirzaei,[1] Chia Wei Cheng,[1] Julia Budniak,[1] Susan Groshen,[2] Wendy J. Mack,[2] Esra Guen,[1] Stefano Di Biase,[1] Pinchas Cohen,[1] Todd E. Morgan,[1] Tanya Dorff,[3] Kurt Hong,[4] Andreas Michalsen,[5] Alessandro Laviano,[6] Valter D. Longo[1,7†]

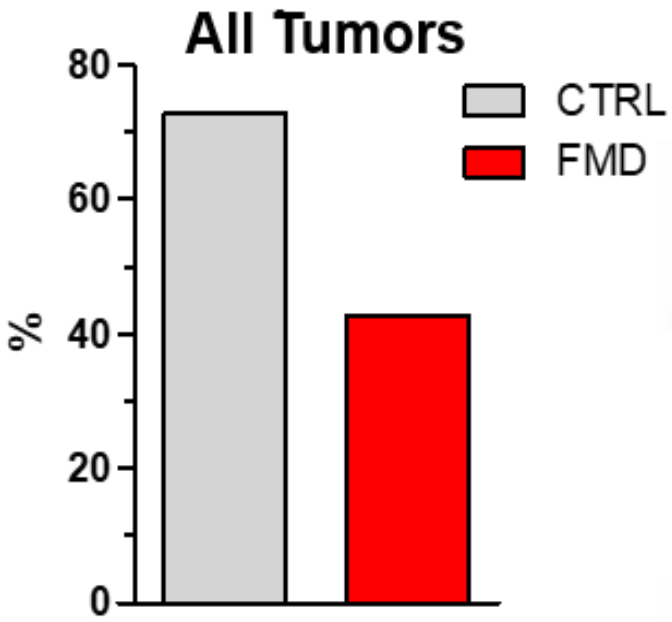
Calorie restriction or changes in dietary composition can enhance healthy aging, but the inability of most subjects to adhere to chronic and extreme diets, as well as potentially adverse effects, limits their application. We randomized 100 generally healthy participants from the United States into two study arms and tested the effects of a fasting-mimicking diet (FMD)—low in calories, sugars, and protein but high in unsaturated fats—on markers/risk factors associated with aging and age-related diseases. We compared subjects who followed 3 months of an unrestricted diet to subjects who consumed the FMD for 5 consecutive days per month for 3 months. Three FMD cycles reduced body weight, trunk, and total body fat; lowered blood pressure; and decreased insulin-like growth factor 1 (IGF-1). No serious adverse effects were reported. After 3 months, control diet subjects were crossed over to the FMD program, resulting in a total of 71 subjects completing three FMD cycles. A post hoc analysis of subjects from both FMD arms showed that body mass index, blood pressure, fasting glucose, IGF-1, triglycerides, total and low-density lipoprotein cholesterol, and C-reactive protein were more beneficially affected in participants at risk for disease than in subjects who were not at risk. Thus, cycles of a 5-day FMD are safe, feasible, and effective in reducing markers/risk factors for aging and age-related diseases. Larger studies in patients with diagnosed diseases or selected on the basis of risk factors are warranted to confirm the effect of the FMD on disease prevention and treatment.

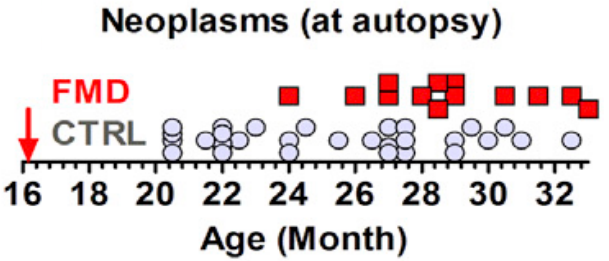
USC Davis
School of Gerontology

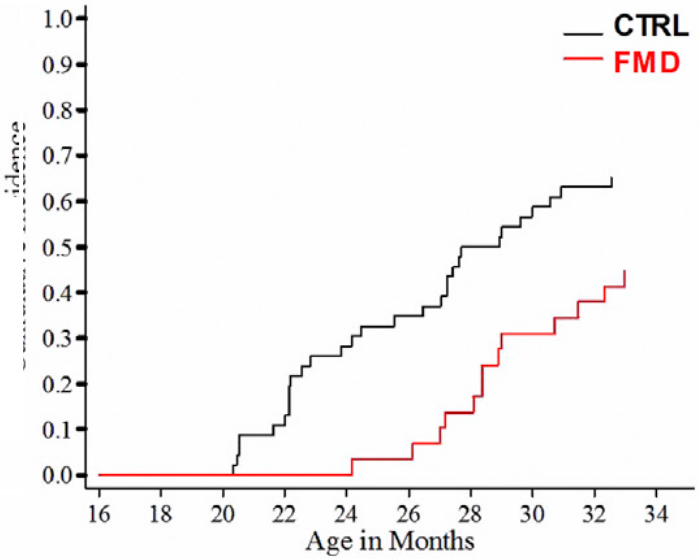
A periodic FMD reduces Cancer Incidence in Mice

	72h fasting		96h FMD	
	Effect	*Change*	*Effect*	*Change*
Fasting glucose	↓	~ 45 %	↓	~ 40 %
Ketone bodies	↑	~ 10 fold	↑	~ 10 fold
IGF-I	↓	~ 40-70 %	↓	~ 45 %
IGFBP-I	↑	~ 7-11 fold	↑	~ 8 fold





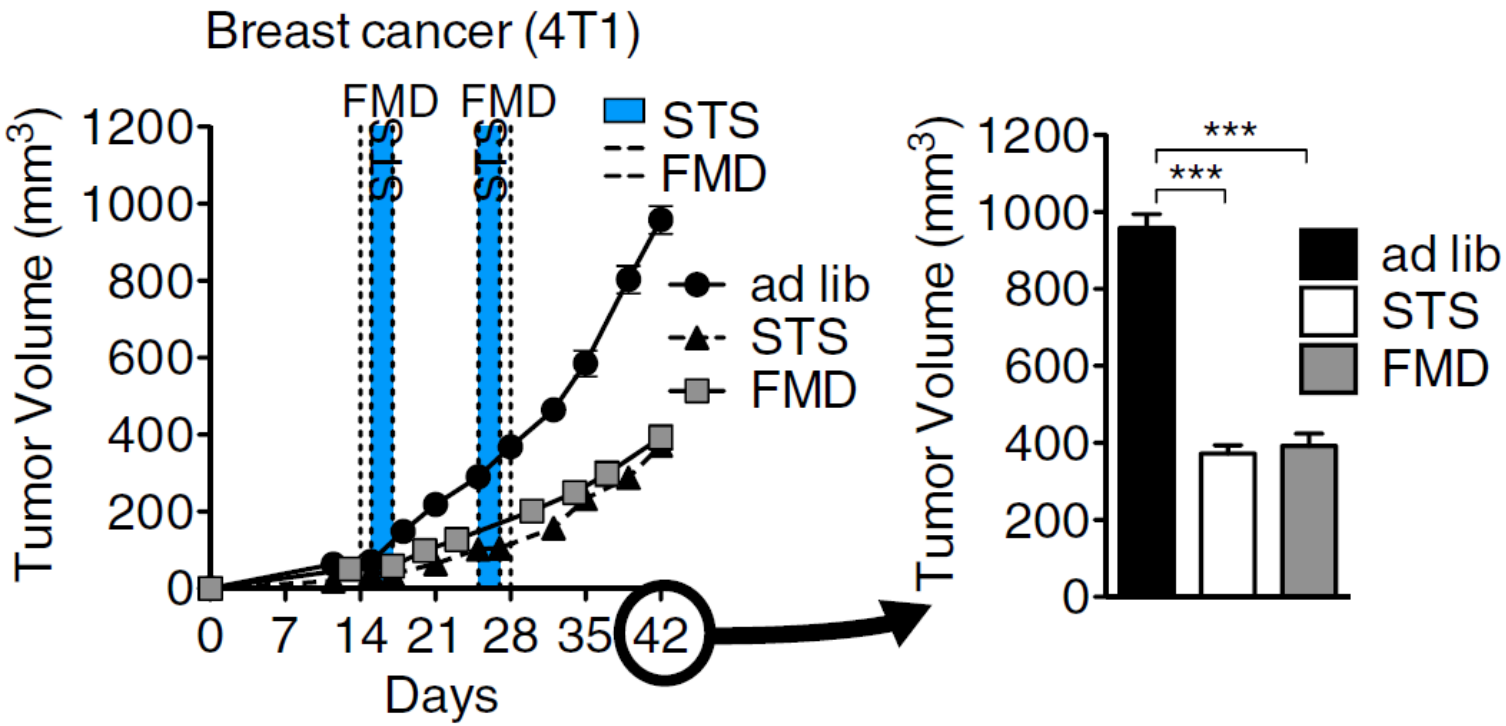




Brandhorst et al. **Cell Metab**. 2015 Jul 7;22(1):86-99.

USC Davis
School of Gerontology

FMDs are as Effective as Fasting in Reducing Tumor Progression



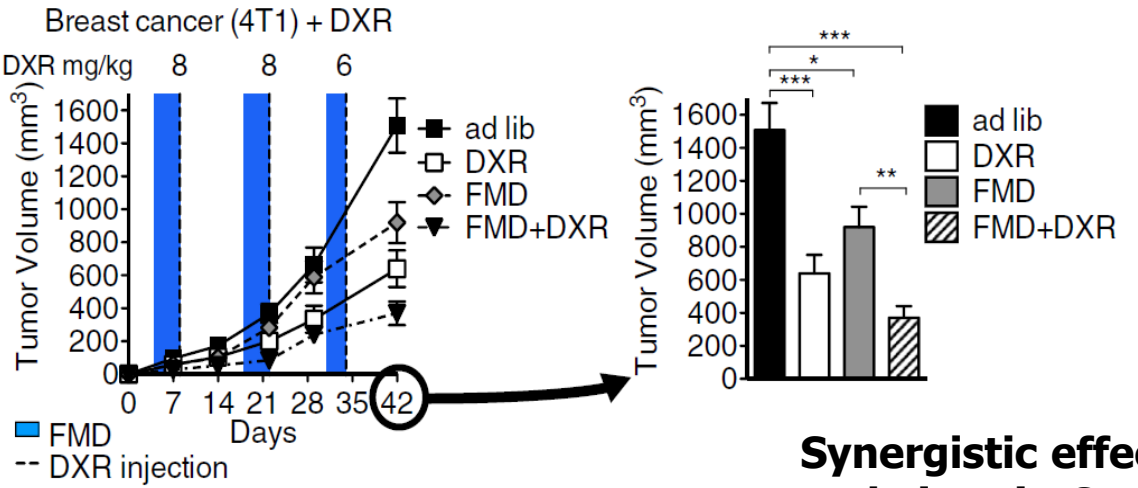
Di Biase et al, **Cancer Cell**, 2016

USC Davis
School of Gerontology

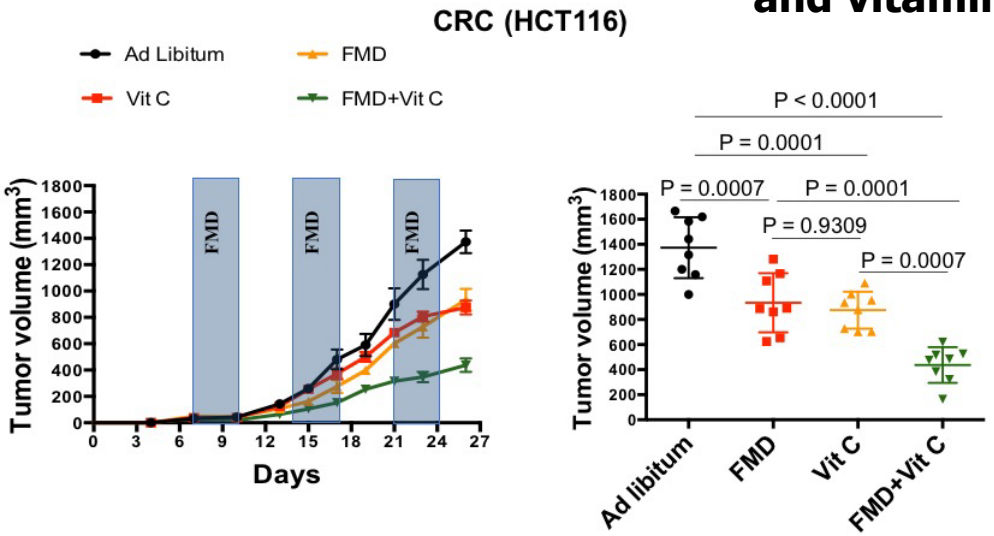
Cancer Cell
Article

Fasting-Mimicking Diet Reduces HO-1 to Promote T Cell-Mediated Tumor Cytotoxicity

Stefano Di Biase,[1,4] Changhan Lee,[1,4] Sebastian Brandhorst,[1] Brianna Manes,[1] Roberta Buono,[1] Chia-Wei Cheng,[1] Mafalda Cacciottolo,[1] Alejandro Martin-Montalvo,[2] Rafael de Cabo,[2] Min Wei,[1] Todd E. Morgan,[1] and Valter D. Longo[1,3,*]
[1]Longevity Institute, Leonard Davis School of Gerontology and Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089, USA
[2]Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA
[3]IFOM, FIRC Institute of Molecular Oncology, Milan 20139, Italy



Synergistic effect of Fasting-mimicking diet and vitamin C against *KRAS* mutated cancers



Di Tano et al, **Nature; under review**

USC Davis
School of Gerontology

Clinical Application of FMDs in Chemotherapy Augmentation?

Variable	N=	Baseline Mean ± SD (95% CI)		After Completion of 1st FMD cycle Mean ± SD (95% CI)		p-value§	Δ*
Body Weight							
kg	71	76.3 ± 16.9	(72.30 - 80.32)	73.8 ± 16.3	(69.98 - 77.66)	< 0.0001	-2.5 ± 1.1
Body-mass Index‡							
All Subjects	71	26.7 ± 4.8	(25.58 - 27.86)	25.9 ± 4.7	(24.76 - 26.96)	< 0.0001	-0.8 ± 0.3
< 25	27	22.4 ± 1.7	(21.68 - 23.03)	21.6 ± 1.6	(20.98 - 22.25)	< 0.0001	-0.7 ± 0.3
25- 30	30	27.1 ± 1.4	(26.58 - 27.60)	26.3 ± 1.5	(25.71 - 26.78)	< 0.0001	-0.8 ± 0.3
> 30	14	34.4 ± 3.5	(32.37 - 36.36)	33.2 ± 3.2	(31.37 - 35.10)	< 0.0001	-1.2 ± 0.4
Total Body Fat¥							
abs. Volume	70	21648 ± 8594	(19598 - 23697)	20320 ± 9326	(17582 - 23058)	0.075	-1328 ± 1714
rel. Volume %	70	30.8 ± 9.5	(28.55 - 33.06)	30.1 ± 10.2	(27.05 - 33.06)	0.047	-0.7 ± 1.6
Lean Body Mass¥							
abs. Volume	70	46281 ± 11997	(43240 - 49142)	44469 ± 11554	(41077 - 47862)	< 0.0001	-1812 ± 1997
rel. Volume %	70	66.3 ± 9.1	(64.15 - 68.50)	66.9 ± 9.9	(63.99 - 69.79)	0.020	0.9 ± 9.5
Waist Circumference							
cm	52	94.6 ± 13.5	(90.86 - 98.38)	91.8 ± 14.5	(86.66 - 96.91)	< 0.0001	-2.8 ± 13.1
Fasting Glucose							
mg/dL	66	91.0 ± 9.0	(88.78 - 93.19)	80.1 ± 9.2	(77.78 - 82.31)	< 0.0001	-10.9 ± 10.1
beta-Hydroxybutyrate							
mM	69	0.4 ± 0.3	(0.36 - 0.52)	1.3 ± 0.9	(1.12 - 1.54)	< 0.0001	0.9 ± 0.9
IGF-1							
ng/ml	69	178.8 ± 72.2	(161.5 - 196.1)	134.5 ± 67.6	(118.2 - 150.7)	< 0.0001	-44.3 ± 51.6
IGFBP-1							
ng/ml	69	28.5 ± 36.6	(19.73 - 37.32)	48.3 ± 43.6	(37.79 - 58.73)	< 0.0001	19.7 ± 32.7
Systolic Blood Pressure							
mmHg	70	117.4 ± 13.0	(114.2 - 120.4)	115.7 ± 13.8	(112.4 - 118.9)	0.076	-1.7 ± 7.8
Diastolic Blood Pressure							
mmHg	70	75.7 ± 8.8	(73.59 - 77.78)	73.3 ± 9.7	(70.98 - 75.62)	0.0003	-2.4 ± 5.3
Triglycerides							
mg/dL	55	97.4 ± 50.4	(83.74 - 111.0)	74.1 ± 28.2	(66.47 - 81.71)	< 0.0001	-23.3 ± 39.3
Cholesterol							
Total, mg/dL	55	186.1 ± 32.5	(177.3 - 194.9)	189.8 ± 38.1	(179.5 - 200.1)	0.12	3.7 ± 17.7
LDL, mg/dL	55	104.9 ± 32.0	(96.23 - 113.5)	112.4 ± 39.2	(101.8 - 123.0)	0.0026	7.5 ± 17.8
HDL, All subjects	55	61.7 ± 16.9	(57.12 - 66.26)	62.5 ± 16.5	(58.06 - 67.00)	0.29	0.8 ± 5.8
C-reactive Protein							
mg/L	69	1.5 ± 2.2	(0.95 - 2.02)	1.6 ± 1.9	(1.10 - 2.03)	0.75	0.1 ± 2.1

↓ 12%
↑ 3-fold
↓ 25%
↑ 60%

‡ *The body-mass index is the weight in kilograms divided by the square of the height in meters.*

¥ *Analysed by dual energy x-ray absorptiometry.*

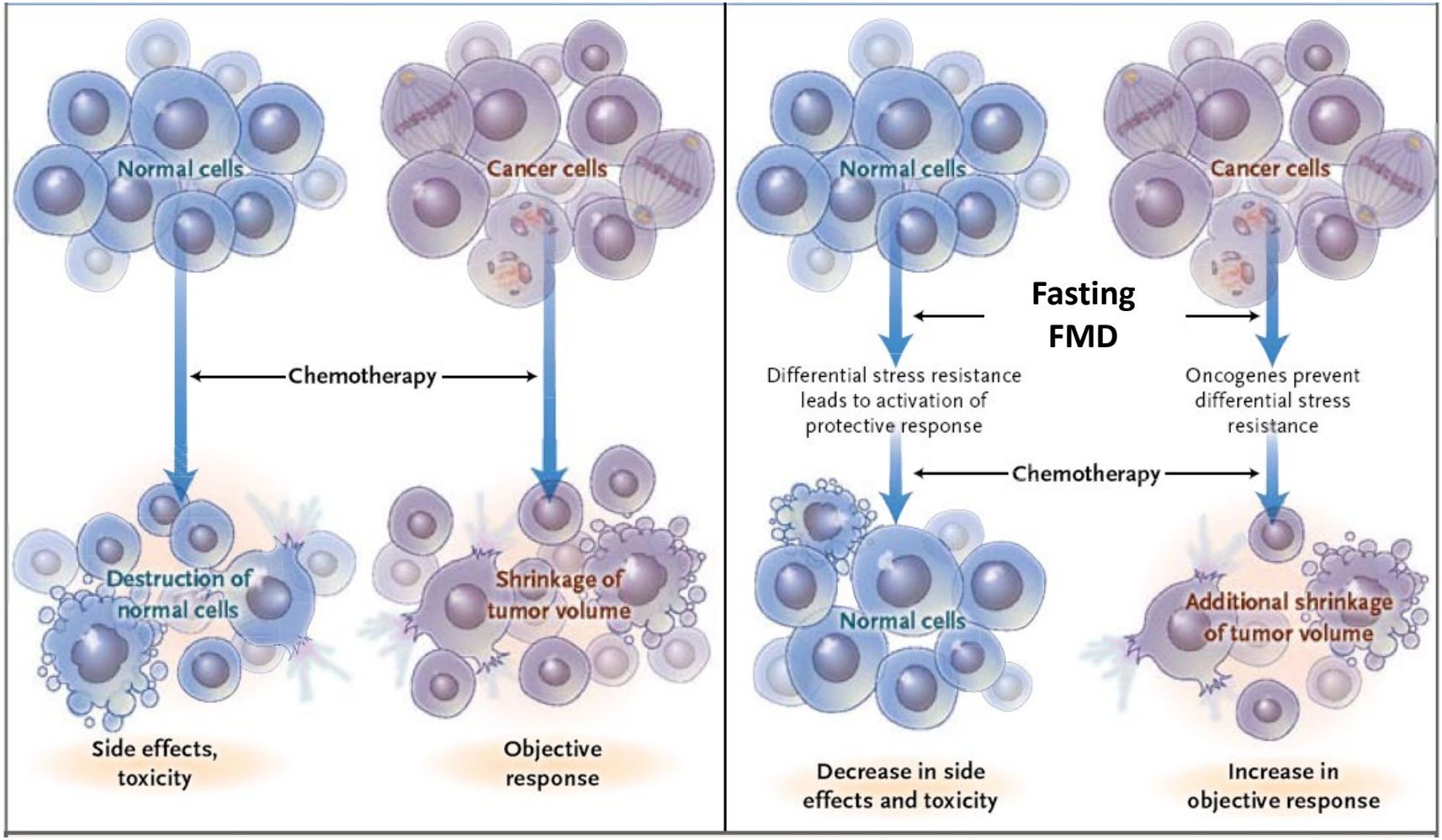
§ *p-values comparing within-group changes were calculated using paired two-tailed Student's t-test.*

* *Plus-minus values are mean± SD rounded to the nearest tenth.*

Wei, Brandhorst et al. *Sci Transl Med. 2017 Feb 15;9(377)*

USC Davis
School of Gerontology

FMDs to Optimize Cancer Management?

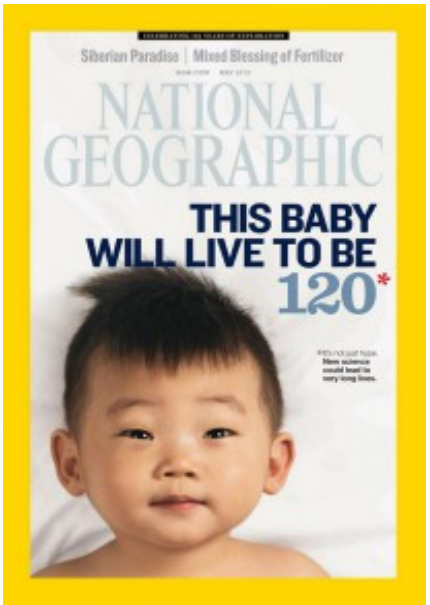


Modified based on: Laviano A, Rossi Fanelli F. **Toxicity in chemotherapy--when less is more.** N Engl J Med. 2012 Jun 14;366(24):2319-20.

USC Davis School of Gerontology

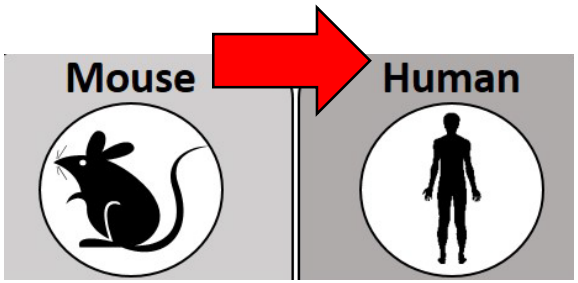
Conclusions

- Fasting and FMDs protect normal cells against chemotoxicity BUT sensitize cancer cells to chemotherapy.
- Clinical adoption is largely restricted by time & cost associated with large scale clinical trials.
- Clinical trials remain the biggest funding gap for us and should be a priority for future investments.



Preclinical findings:

- Reverses Type 1, Type 2 diabetes
- Reduces symptoms of MS
- Protects again chemo-toxicity
- Sensitizes cancers to chemotherapy



Clinical findings

?

Disclaimer and Acknowledgements

USC

Valter Longo, PhD
Min Wei, PhD
In Young Choi, PhD
Todd Morgan, PhD
Tanya Dorff, MD
David Quinn, MD
Pinchas Cohen, MD

Others

Brian Kennedy, PhD Buck Institute

Jaime Guevara, MD Quito Ecuador

Rafael de Cabo, PhD NIA

Sebastian Brandhorst, PhD
Davis School of Gerontology
University of Southern California
Los Angeles, CA, USA
brandhor@usc.edu

The experimental FMD was provided by L-Nutra, Inc.

The University of Southern California has licensed intellectual property to L-Nutra that is under study in this research. As part of this license agreement, the University has the potential to receive royalty payments from L-Nutra.

Thank you!

MD
"How much longer do I have before I have to change to a healthy lifestyle?"