**Fast-Mimicking Diets** Therapy to Combat the Relentless Effects of Aging



### Felice L. Gersh, M.D.

Medical Director, Integrative Medical Group of Irvine Consultative Faculty, University of Arizona School of Medicine, Fellowship in Integrative Medicine

# **Aging & Biological Pathways**

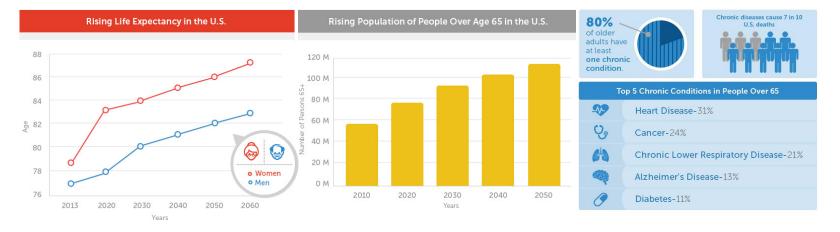
Chronic Conditions: A Growing Problem Evolution of Growth & Aging Pathways Dietary Intervention

# **Fasting's Impact on Aging**

Fasting Mimicking Prevention & Disease Management Clinical Applications

# **Aging & chronic conditions**

People are living longer lives than ever before People over 65 will comprise more than 22% of the population by 2030 Age-associated chronic diseases & conditions are also increasing



(US Census National Population Projections 2012 CDC, National Center for Health Statistics, National Health Interview Survey CDC. National Center for Chronic Disease Prevention & Health Promotion 2

# Cancer, aging, obesity & chronic diseases: growing epidemics with few answers



People worldwide are over 65 years old

# **Aging & chronic conditions**

Why don't young people get Alzheimer's, Diabetes, Cancer, Cardiovascular Disease, or Stroke?

- Because AGING is the catalyst for these diseases
- 67-87% of us will die of one of these diseases Verify Percentage

		Total Deaths		% Share
	🚤 Heart disease		614,348	23.4%
Phil	/ Sancer		591,699	22.5%
	COPD	147,101		5.6%
	Accidents	136,053		5.2%
	Stroke	133,103		5.1%
D.d	Alzheimer's	93,541		3.6%
	Diabetes	76,488		2.9%
	Flu, pneumonia	55,227		2.1%
	Kidney disease	48,146		1.8%
	Suicide	42,773		1.6%
	6	Source: Center for Disease Control &	Prevention	

### Leading Causes of Death 2014

AGING  $\rightarrow$  multiple forms of damage in different tissues as a result of failure of cellular maintenance pathways

# Aging & Biological Pathways An Increasing Problem:

 Age-associated diseases are an enormous challenge & financial burden globally

Average life expectancy has increased dramatically in the last 100 years Healthy life expectancy ("healthspan") has not increased equivalently

• Aging is regulated by Nutrient Sensing Pathways

Targets for nutritional & pharmacological intervention that may **increase longevity & healthspan** 

# So - should we treat aging?



# Aging & Biological Pathways



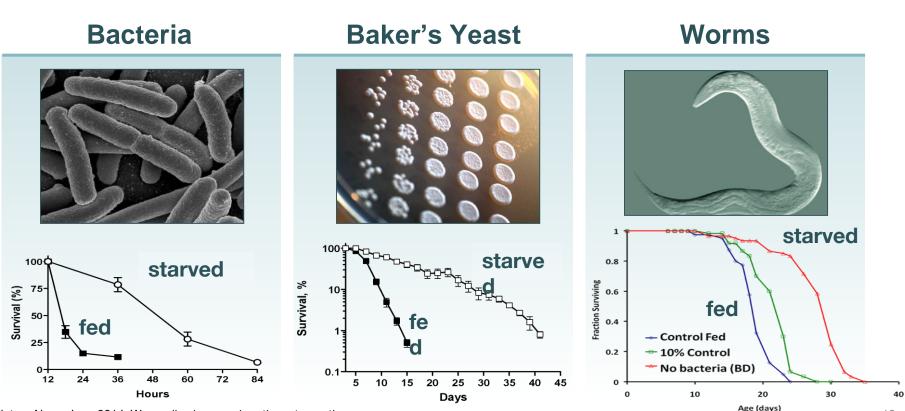
#### Medical News & Perspectives

# Can a Diet That Mimics Fasting Turn Back the Clock?

Jennifer Abbasi

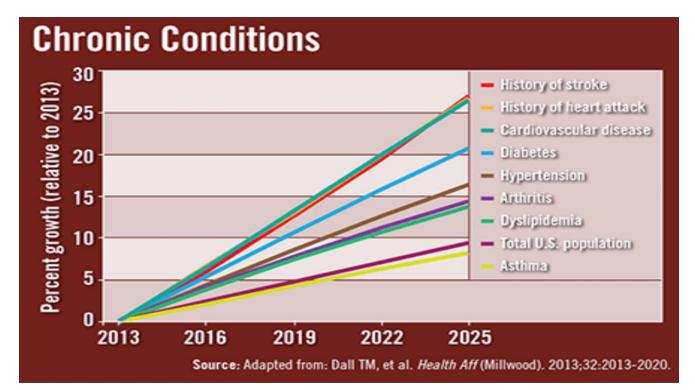


# **Starved organisms live longer**



BBC Nature News June 2014: Worms live longer when they stop eating

## Continuous eating has led to unhealthy aging & early onset of chronic diseases: cancer, Alzheimer's, diabetes & cardio-vascular diseases

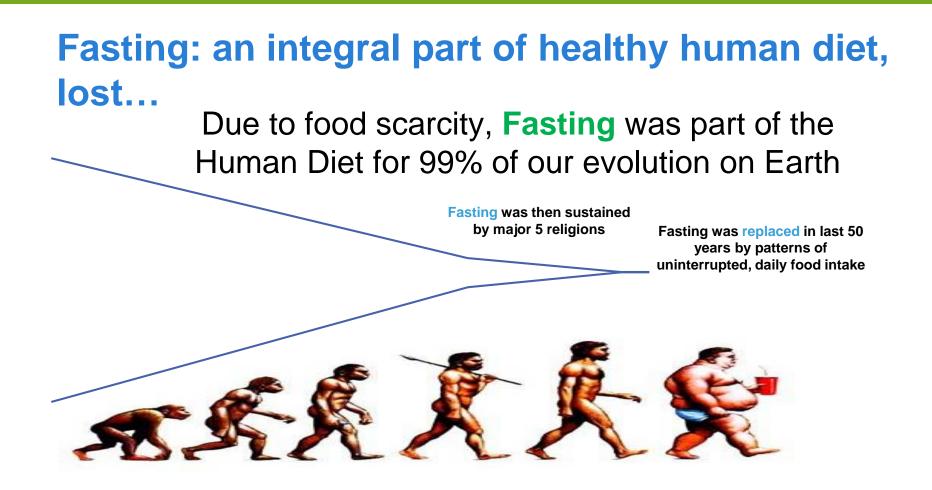


**Evolution of Facting** 

# In the Distant Past, Food was Scarce:

- Dependent on the hunt and the harvest
- Hunger punctuated by intermittent bursts of eating
- These patterns forced strong evolutionary pressures on the body's ability to survive during periods of hunger or fasting.

# Dietary Interventions That Affect Aging & Healthspan



# What does it mean to fast?

Fasting: To abstain from food

**Biological Fasting:** To not consume food that triggers cellular food sensing pathways: PKA, RAS & mTOR. The sensing pathways are triggered up to 24h after the last meal. So biological fasting starts 24h from last meal

**Misconceptions:** Juice fasting is fasting because it does not contain solid food

Time Restricted Eating: No eating for 12 or 16 hours - not biological fasting



# **Evolution of fasting**

Fasting is actually accompanied by an increase in activity and energy

- When hungry, the body is programmed to increase activity to seek nourishment
- In contrast, the body is sedentary when satiated
- Increased energy accompanied by protection from disease and deleterious aging – fasting is truly the miracle "drug"



# **Evolution of fasting**

When food is scarce the body acts to conserve energy by diminishing cellular growth pathways by regulating IGF-1, TOR and PKA (key nutrient sensing pathways), resulting in:

- Increased cellular maintenance and protection
- Increased activation of stress resistance pathways
- Removal and replacement of damaged/dysfunctional cells
- Reduction of inflammation.

Fasting challenges the body, which engages stress response pathways to increase chance of survival

# How fasting works

#### Time Restricted Eating (TRE) and Intermittent Fasting

#### **Prolonged Fasting**

- Few Hours: typically 12-24 hours
- Counterbalance the previous Feeding Period
- Maintains Healthy Weight
- Maintains Healthy Metabolism

- >3 days, typically 5 days
- Induces cellular effects
- Autophagy (Nobel Prize in Medicine, 2016)
- Stem Cell Based Regeneration

- Breakfast is an important meal of the day
- Skipping Breakfast could increase mortality
- Difficult to fast with abundance of food
- Need micronutrients for healthy metabolism

- Very difficult to comply with
- Could be unsafe for some
- Body needs minimal macro and micronutrients for healthy metabolism

- Solutions
- Fasting Mimicking Meal for Healthy TRE
- Fasting Mimicking Diet

### Issues

### Benefits

### Fasting is all about timing of calorie intake, food restriction, or both

### Intermittent Fasting – cyclical fasting in intervals

### Examples of types of fasting Time-restricted eating (TRE) – daily

Sunday	Monday	Tuesday	Wednesda y	Thursday	Friday	Saturday
12-16	12-16	12-16	12-16	12-16	12-16	12-16
hours	hours	hours	hours	hours	hours	hours

### Alternate day fasting





### Prolonged Fasting – fasting days in a row

Periodic fasting – Fasting Mimicking Diet (FMD)<sup>®</sup> few times/year

# The body identifies the presence of food through nutrient-sensing pathways

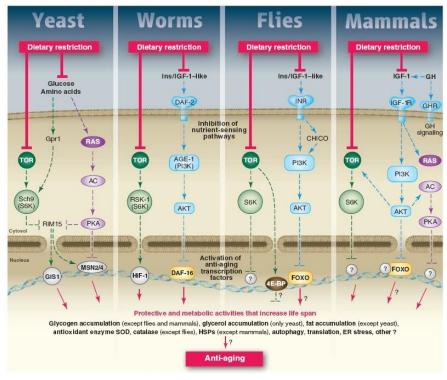
- IGF-1, MTOR, and PKA are 3 key nutrient-sensing pathways
- Nutrient-Sensing Pathways: pro-growth, pro-aging, lead to many common health problems including heart disease and cancer

# **Fasting down-regulates these pathways**

### What are the nutrient sensing pathways on the cells?

# RAS & PKA: Carbohydrate-Insulin pathway

# mTOR: Protein-IGF pathway



Wei et al., 2008; Cheng et al., 2014

**Fasting Mimicking** 

### Fasting Mimicking Diets (FMDs)

downregulate the body's key nutrient-sensing pathways, while still providing needed nourishment

Using a specific combo of low protein, carbohydrates and sugars, and high fat, FMDs shuttle food into the body without releasing the signaling factors for cellular growth & aging

In other words, FMDs allow you to eat but trick the body into acting like it is fasting

\*\*The stomach sees food, while the cells see fasting\*\*

# What is the Fasting Mimicking Diet?

- Macronutrients: high good fat, low in protein, low in Carbs (66 ingredients carefully studied to nourish while not triggering the nutrient sensing pathways) + Minerals & Vitamins
- Comes in a box with food for 5 days soups, bars, crackers, drinks, teas, supplements
- Plant Based, Natural ingredients
- GRAS by FDA
- Scientifically Developed and Clinically Tested at USC, Mayo Clinic, U of Genoa, IFOM, etc.
- Funded by NIH and EU grants: more than \$45MM
- Effective in initial trials against Aging and Multiple Chronic Diseases

### Patented – FIRST EVER FOR PROMOTING LONGEVITY & HEALTHSPAN

Fasting Mimicking Diet: The Only Patent In History Awarded on Regeneration & Longevity

On July 10, 2018, The US Patent and Trademark Office Awarded the Fasting Mimicking Diet a Historical Patent on

## Promoting Tissue/Organ Regeneration, Longevity and Healthspan

https://patents.justia.com/patent/10015980

# Pre-clinical & Clinical Trial –

### Aging, Longevity & Metabolic Health

### **Breakthrough Discoveries Published in top Scientific & Medical Journals**

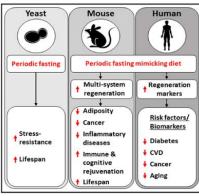
# CellPress

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 acing

### SCIENCE TRANSLATIONAL MEDICINE

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

#### METABOLIC DISEASE

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

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

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.

# **Fasting Mimicking Diet Research**

### **Cell Metabolism**

- Volume 22, Issue 1, p86-99, 7 July 2015

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

- Volume 19, Issue 3, p407-417, 4 March 2014

Low Protein Intake Is Associated with a Major Reduction in IGF-1, Cancer, and Overall Mortality in the 65 and Younger but Not Older Population

Peer-Reviewed Journal 17.565 Impact Factor





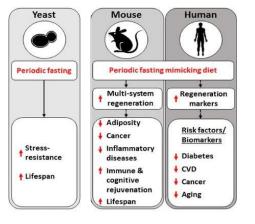












### **The Biological Effects of FMD**

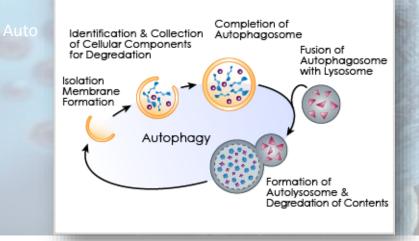


### Prolonged fasting with FMD promotes cellular regeneration to improve body composition

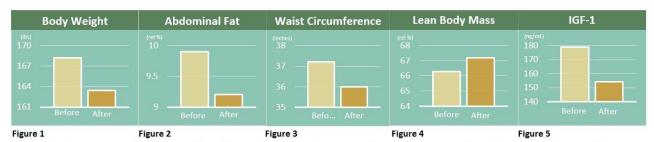
72 hours of continuous fasting promotes stem-cell activation and cellular regeneration. Preclinically, it induces 93.7% in stem cell production

> STEM CELLS (%) 1.6 -1.2 -0.8 -0.4 -0 -BEFORE DURING AFTER

Autophagy plays the key role in the cell rejuvenation process while fasting



### FMD Clinical Trial Results – Longevity, Weight and Metabolic Health



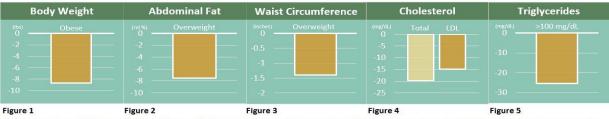
Participants lost an average of 5 lbs (Fig. 1) coming mostly from abdominal fat shown as reduction in abdominal fat mass (Fig. 2) and >1-inch loss in waist circumference (Fig. 3) while preserving lean body mass (Fig. 4). IGF-1, a marker associated with increased mortality and DNA damage in human cells, was reduced by 14% (Fig. 5).



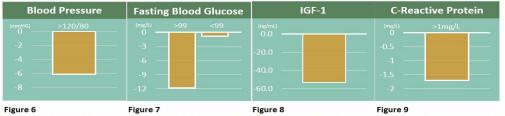
Blood pressure (BP) was significantly reduced from 117.4 to 113.6 mm Hg (systolic) and 75.7 to 72.8 mm Hg (diastolic) (Fig. 6 & 7). Total cholesterol was reduced nearly 10 mg/dL with significant reductions of LDL from 104.9 to 99.2 mg/dL (Fig. 8). C-reactive protein (CRP) levels decreased from 1.5 mg/L to 1.0 mg/L after participants had resumed their normal diet for 5 – 8 days after cycle 3 (Fig. 9). A transient, major and significant elevation of stem cell/regenerative markers was also observed (Fig. 10).

### FMD Clinical Trial Results – Longevity, Weight and Metabolic Health

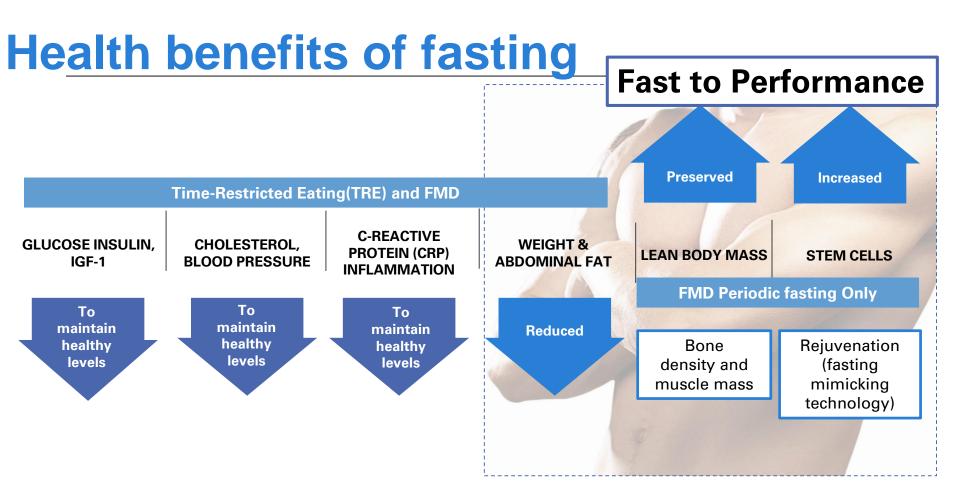
### More significant results for the group of individuals who had elevated health risks



In obese participants (BMI>30), body weight decreased 9 lbs (Fig. 1). Weight remained significantly lower after subjects returned to their normal diet for an average of 3 months. In overweight participants (BMI>25), abdominal fat was reduced by >7% (Fig. 2) with preserved relative lean body mass and decreased waist circumference by approximately >3 cm (Fig. 3). In participants with high triglecards (>109 mg/dl), total cholesterol was reduced by 20 mg/dl and LDL-cholesterol reduced by 15 mg/dl (Fig. 4). In participants with high triglycerides (>100 mg/dl), tryglyceride levels were reduced by >25 mg/dl (Fig. 5).



For participants with high blood pressure (>120/80) systolic and diastolic BPs were reduced by >6 mmHg (Fig. 6). Blood pressure remained significantly reduced after subjects returned to their normal diet for an average of 3 months. In high fasting glucose participants (>99mg/dl), fasting glucose was reduced by >10 mg/dl (Fig. 7) and remained reduced after subjects returned to their normal diet for an average of 3 months; in low glucose participants (<99 mg/dl), fasting glucose remained unchanged (Fig. 7). IGF-1, was reduced by 20% in participants with high IGF-1 levels (Fig. 8). In participants at an average risk for developing cardiovascular disease (C-reactive protein between 1 - 3 mg/L), CRP was lowered >1 mg/L closer to the lowest risk range (Fig. 9).

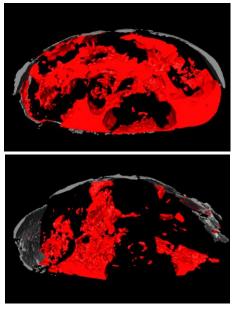


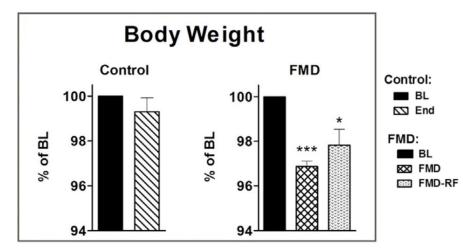
# **Fasting and healthy weight loss**

FMD is clinically proven to help individuals with normal-BMI reading to lose an average of 5.2lbs of fat and 1.2 inches off waist circumference, while overweight/obese may lose >8lbs, mainly with visceral fat reduction while protecting Lean Body Mass:

Visceral fat before FMD

Visceral fat after FMD

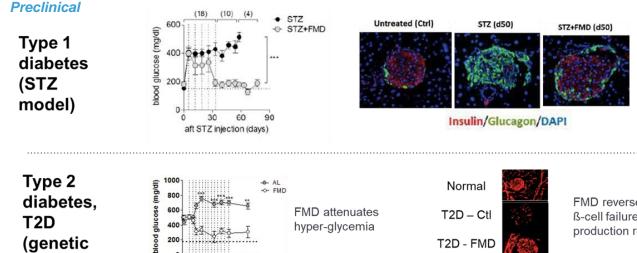




The FMD resulted in a 3% reduction in BW that remained lower even after refeeding.

# **FMD pre-clinical trial on diabetes**

### Reversing Diabetes via Pancreatic Stem Cell Regeneration

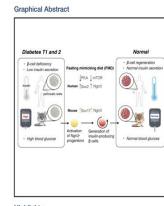


60 90 120 150 days after Bl

model)

#### Cell

### Fasting-Mimicking Diet Promotes Ngn3-Driven $\beta\text{-Cell}$ Regeneration to Reverse Diabetes



#### Authors Chia-Wei Cheng, Valentina Villani, Roberta Buono, ..., Julie B. Sneddon,

Laura Perin, Valter D. Longo

#### Correspondence vlongo@usc.edu

#### In Brief

A periodic short-term diet that mimics fasting modulates β-cell regeneration and promotes insulin secretion and glucose homeostasis with potential to treat both type 1 and type 2 diabetes.

#### Highlights

- Fasting mimicking diet induces prenatal-development gene expression in adult pancreas
- FMD promotes Ngn3 expression to generate insulinproducing β cells
- Cycles of FMD reverse β-cell failure and rescue mice from T1D and T2D

FMD reverses pancreatic ß-cell failure – insulin production restored

Cheng et al. Cell. February 23, 2017

# **Fasting Mimicking Diet:**

# A unique patent on treating diabetes

On July 12, 2016, The US Patent and Trademark Office Awarded the Fasting Mimicking Diet a Historical Patent on Treating Diabetes

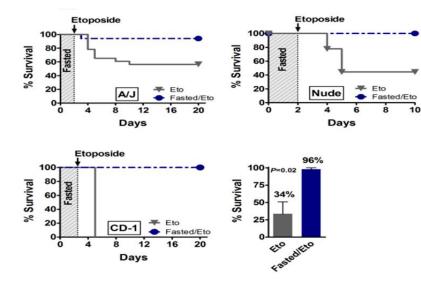
# Fasting condition as dietary treatment of diabetes

https://patents.justia.com/patent/9386790

# **FMD** preclinical trial on cancer

### Intercepting Cancer in Conjunction with and In Between Current Treatment Options

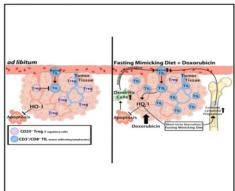
#### Preclinical Results Below. Human Trial expected to be completed in Mid-2019



### **Cancer Cell**

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

#### Graphical Abstract



Article

#### Authors

Stefano Di Biase, Changhan Lee, Sebastian Brandhorst, ..., Min Wei, Todd E. Morgan, Valter D. Longo

#### Correspondence vlongo@usc.edu

#### In Brief

Di Biase et al. show that combining a fasting-mimicking diet with chemotherapy increases the levels of bone marrow common lymphoid progenitor cells and cytotoxic CD8\* tumor-infiltrating lymphocytes, delaying tumor progression. In breast tumors, this effect is partially mediated by downregulating HO-1.

# The Fasting Mimicking science drove fasting to the **#1 category in nutrition in US (May 2018)**

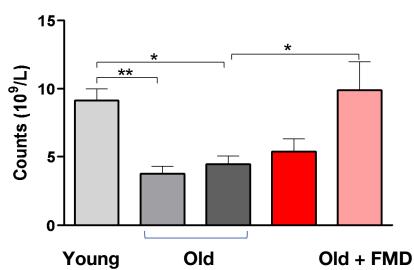
2018 Food and Health Survey



The top eating pattern cited was intermittent fasting (10 percent). Diets considered at least somewhat restrictive of carbohydrates were wellrepresented, including Paleo (7 percent), low-carb (5 percent), Whole30 (5 percent), high-protein (4 percent), and ketogenic/high-fat (3 percent)" 20%

Fasting Mimicking Diet (FMD) started at middle age reverses the effect of aging on white blood cell number

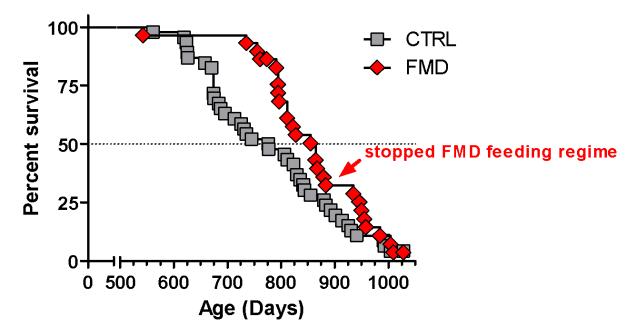
FMD activates blood stem cells resulting in regeneration and rejuvenation of the immune system



White Blood Cells

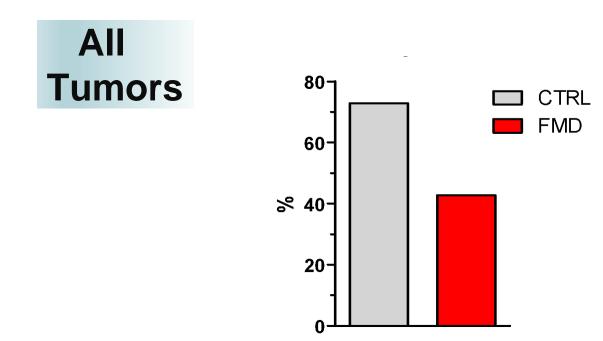
### Periodic Fasting Mimicking Diet (FMD) Started at Middle Age Extends Longevity

## Mice placed on a 4 day FMD twice a month starting at 16 month of age



### **Fasting Mimicking Diet cycles reduce & delay cancer**

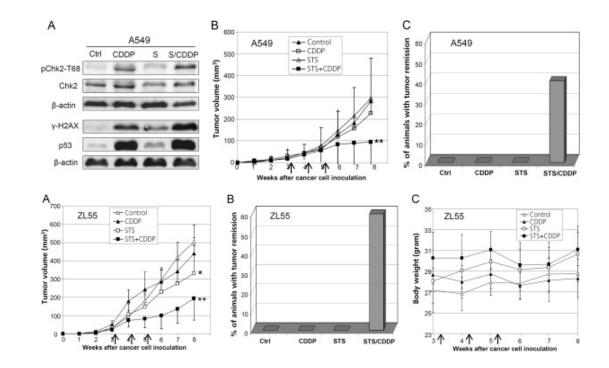
Mice placed on a 4 day FMD twice a month starting at 16 month of age



# **Increased cancer**-**free rates in mice**

Multiple fasting cycles

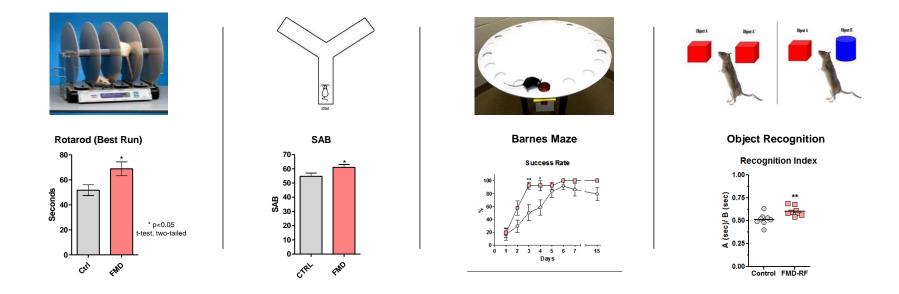
 chemotherapy
 promote cancer free
 survival in 35-55% of
 mice with human lung
 adenocarcinoma and
 mesothelioma
 xenografts



Shi Y,et al BMC Cancer 2012

## **FMD™s and Neuro-cognition**

### Improves cognitive performance in mice

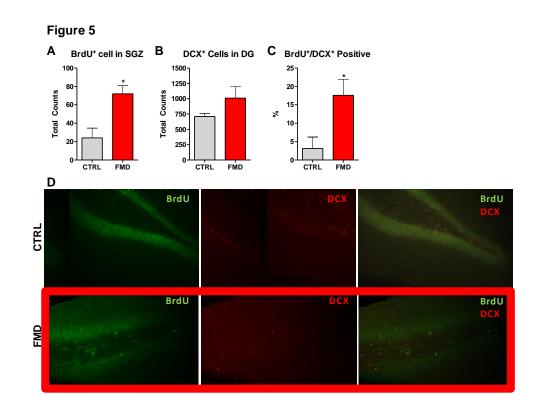


### FMDs & Neurogenesis FMD™s Improve neurogenesis

Cell Metabolism Volume 22, Issue 1, p86-99, 7 July 2015; A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan; Volume 19, Issue 3, p407-417, 4 March 2014

Demonstration of re-growth of new cells in mouse models:

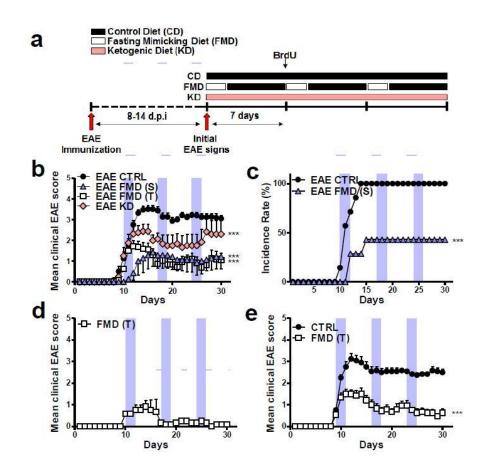
Bromodeoxyuridine (BrdU) &



### **FMD Autoimmune**

Reduces autoimmunity & alleviates MS symptoms

- Weekly cycles of FMD are effective in ameliorating cellular and disability measures in mice
- FMD reduced clinical severity in all mice, and caused complete recovery in 20% of the animals



### **FMD** Autoimmune

## **Regenerates damaged** nerve tissue

 FMD promoted oligodendrocyte precursor cell regeneration and re-myelination in axons in mice

EAE FMD

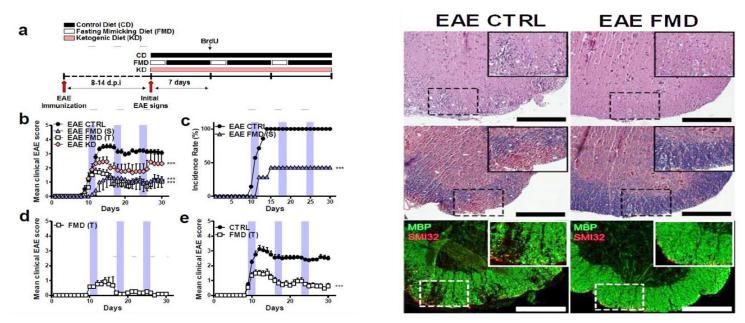
EAE CTRL

Choi, Y et al. Cell Reports 2016



### **FMD preclinical trial on Multiple Sclerosis**

## Reversing/Intercepting Auto-Immune Diseases: Multiple Sclerosis Preclinical Results



FMD promoted oligodendrocyte precursor cell regeneration and re-myelination in axons in mice

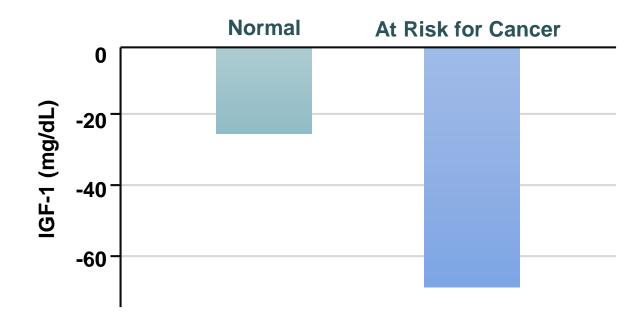
### **Rejuvenation from within – periodic FMD is more effective in at risk patients**

Blood glucose drops in pre-diabetic patients after 3 cycles of the FMD



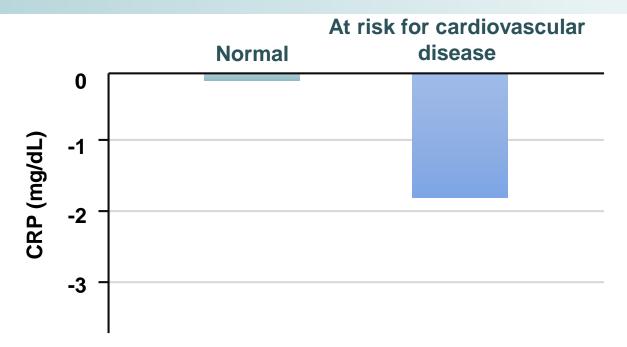
#### **Rejuvenation From within – periodic FMD Is more effective in at risk patients**

IGF-1, associated with aging and cancer, is reduced after 3 cycles of the FMD

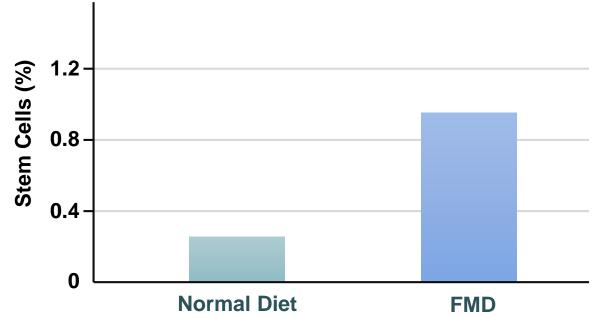


## Rejuvenation from within – periodic FMD Is more effective in at risk patients

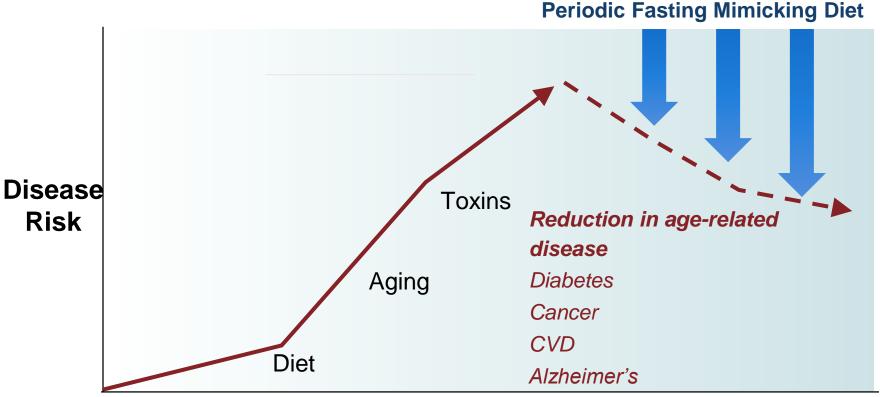
CRP, a risk factor for cardiovascular disease, is reduced after 3 cycles of the FMD



### Circulating stem cells in humans undergoing FMD cycles



## **Rejuvenation from within**





Look Backwards to Provide the Solutions for Optimal Longevity and HealthSpan

Thank you for your kind attention!

Felice L. Gersh, M.D felicelgershmd.com <u>felicelgershmd@felicelgershmd.com</u> @DrFeliceGersh

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