The Cellular Stability Hypothesis:

Role of Essential Fatty Acid C15:0 in Supporting Our Healthspan & Longevity

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Presentation to the Homeopathic Board of Nevada and the American Osteopathic Society of Integrative Medicine

July 16, 2024

Learning objectives:

1. Understand ferroptosis and the implications of this newly discovered type of cell death on aging and chronic diseases.

2. Describe C15:0 (pentadecanoic acid), why it meets the criteria of being an essential fatty acid, its mechanisms of action relevant to metabolic, heart and liver health.

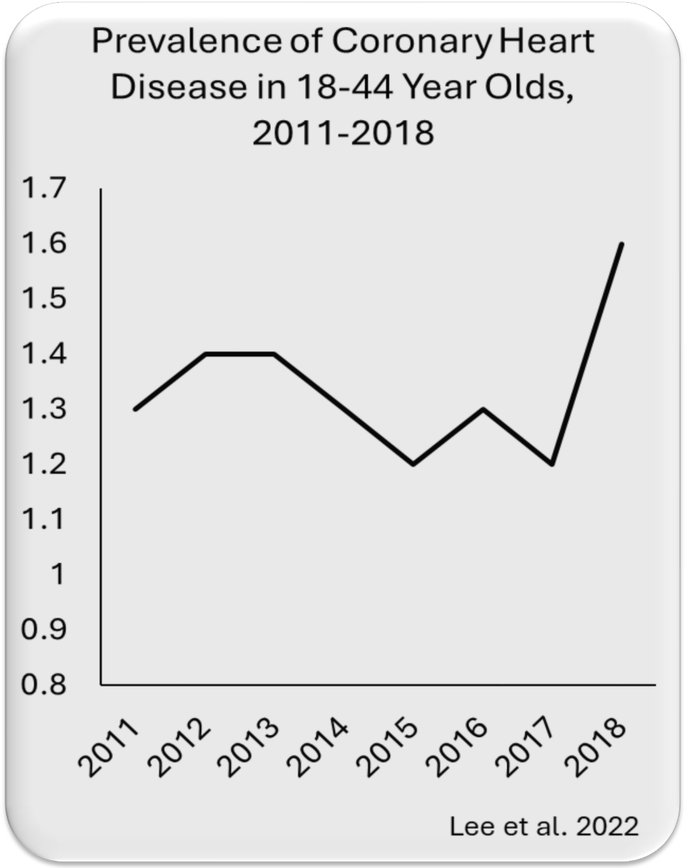
3. Understand C15:0's evolutionary role in supporting mammalian longevity, and how the Cellular Stability Hypothesis explains how C15:0 can extend longevity in individuals.

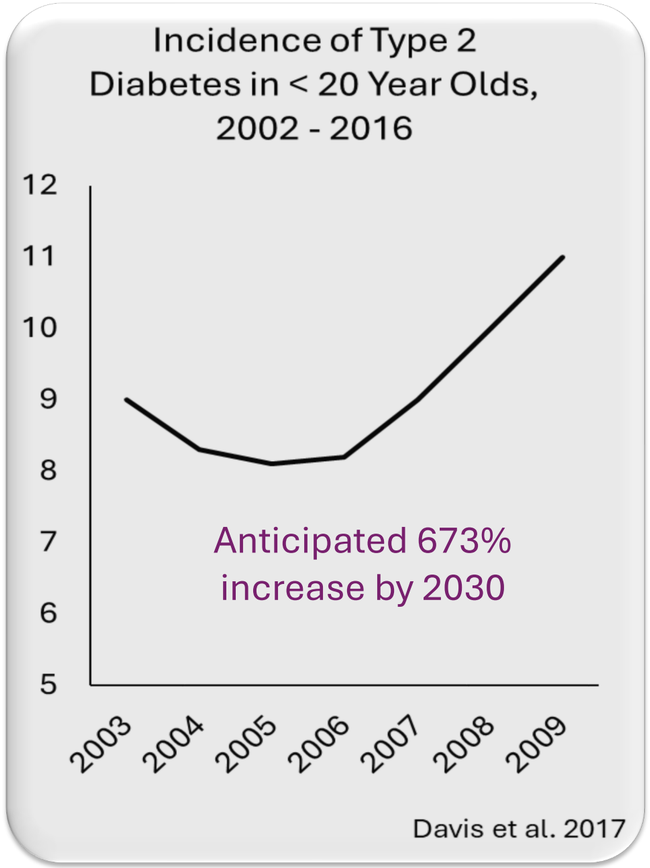
4. Describe Cellular Fragility Syndrome (a nutritional C15:0 deficiency syndrome), its pathophysiology, relevant diagnostics, and how it accelerates aging & onset/progression of metabolic, liver and cardiovascular diseases.

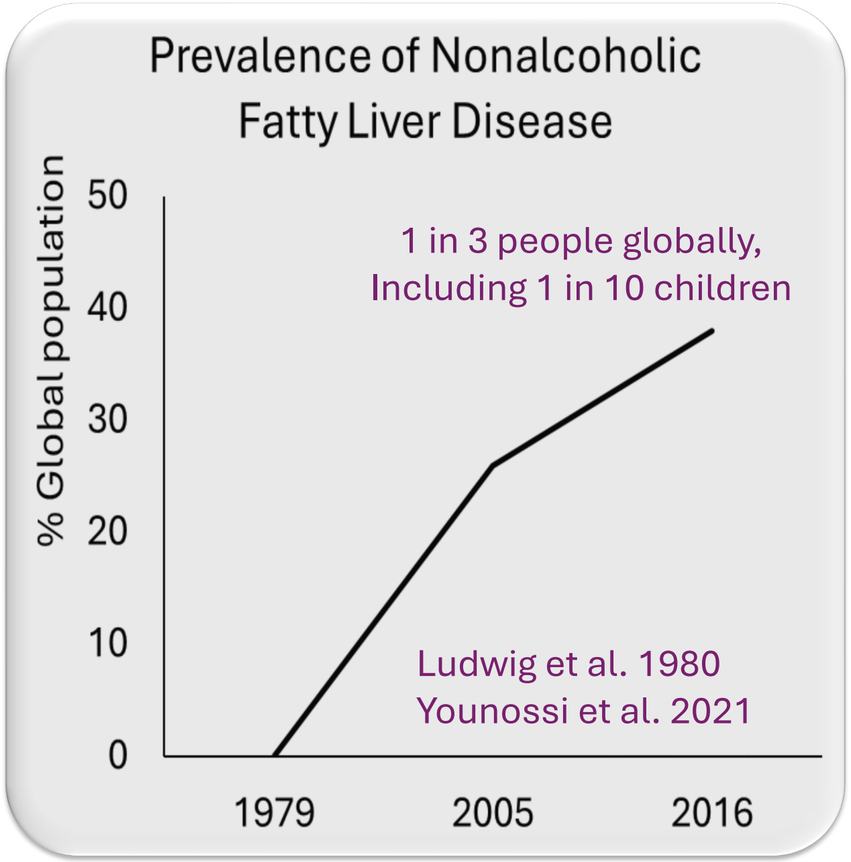
5. Understand why nutritional C15:0 deficiencies have been increasing, how to test for low/healthy/optimal levels, and how to fix them.

Our health is heading in the wrong direction.

Aging-associated diseases are increasing in prevalence among younger people.



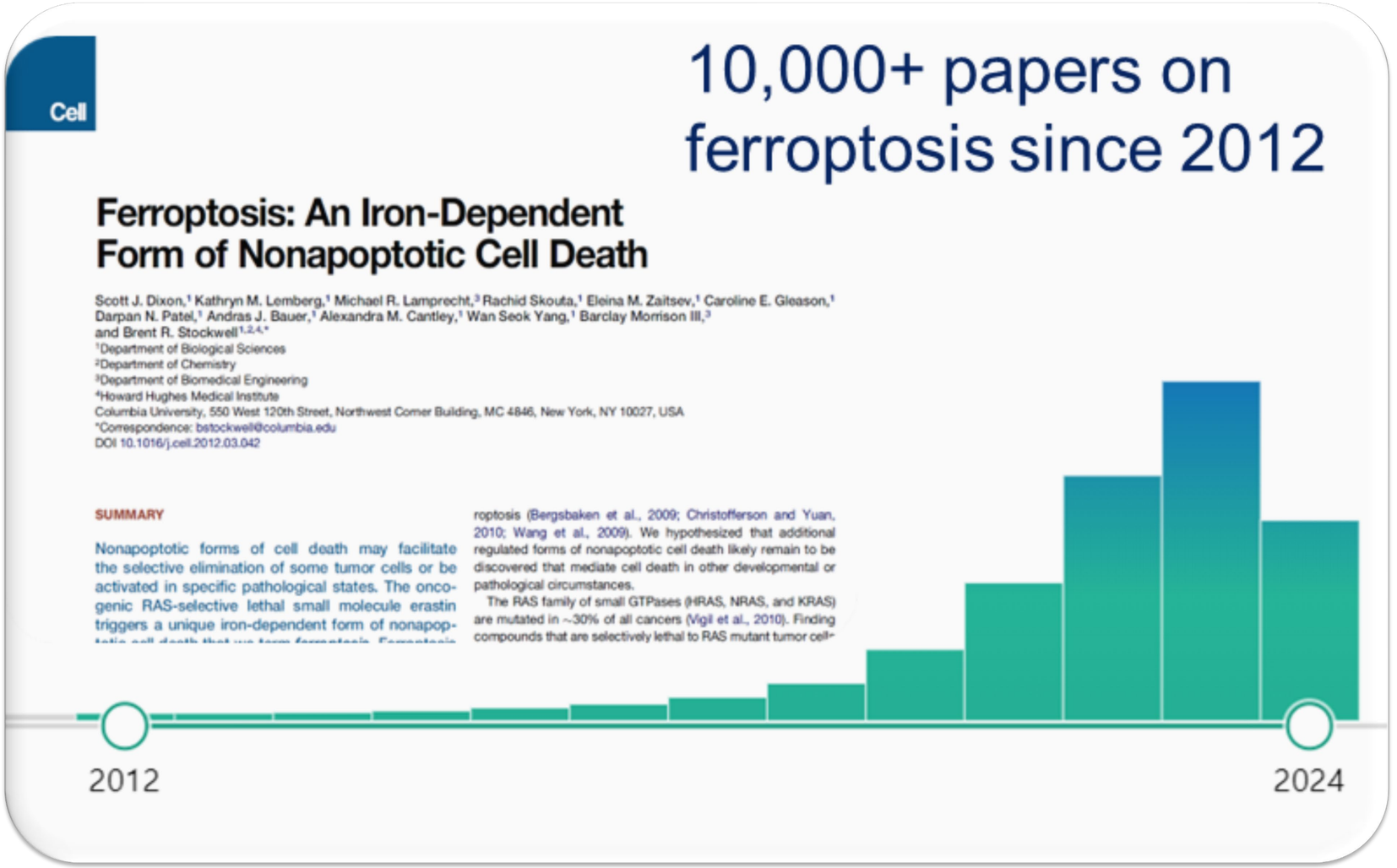




A new type of cell death has emerged.

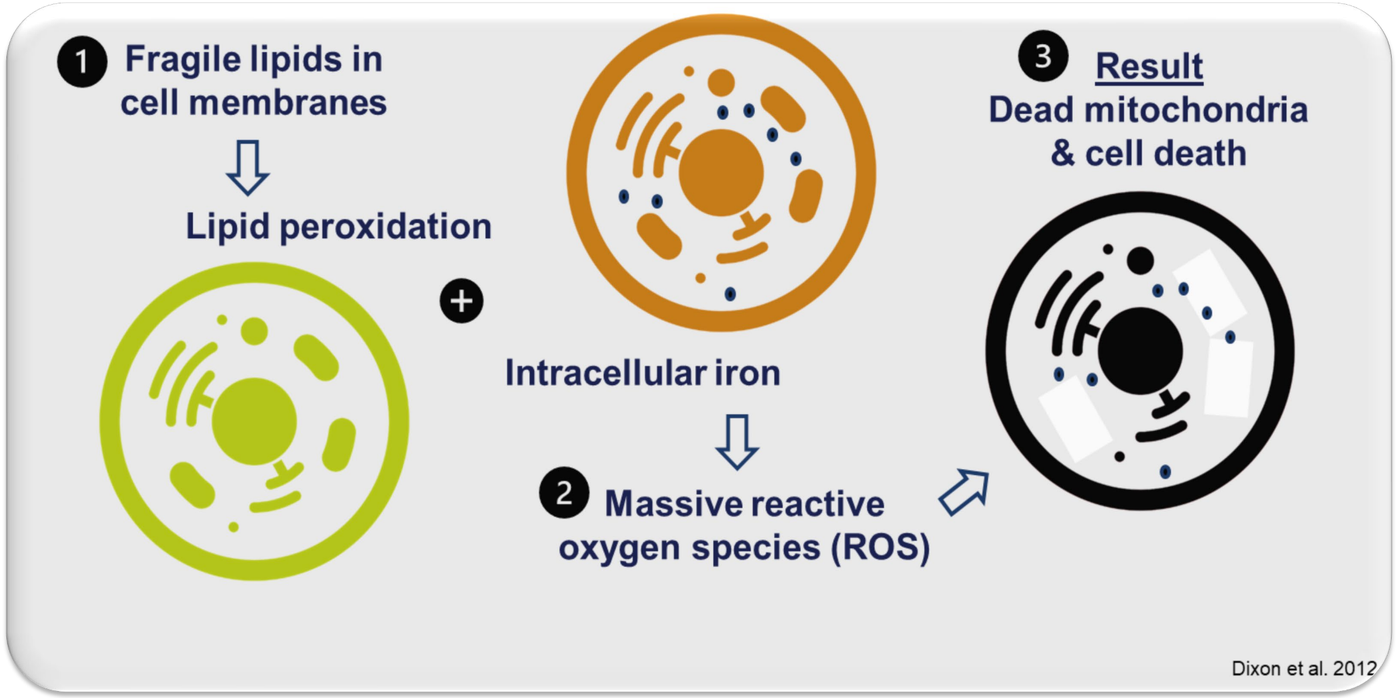
It’s called ferroptosis

- ❑ Apoptosis
- ❑ Necrosis
- ❑ Autophagy
- ❑ **Ferroptosis**



The 101 on ferroptosis.

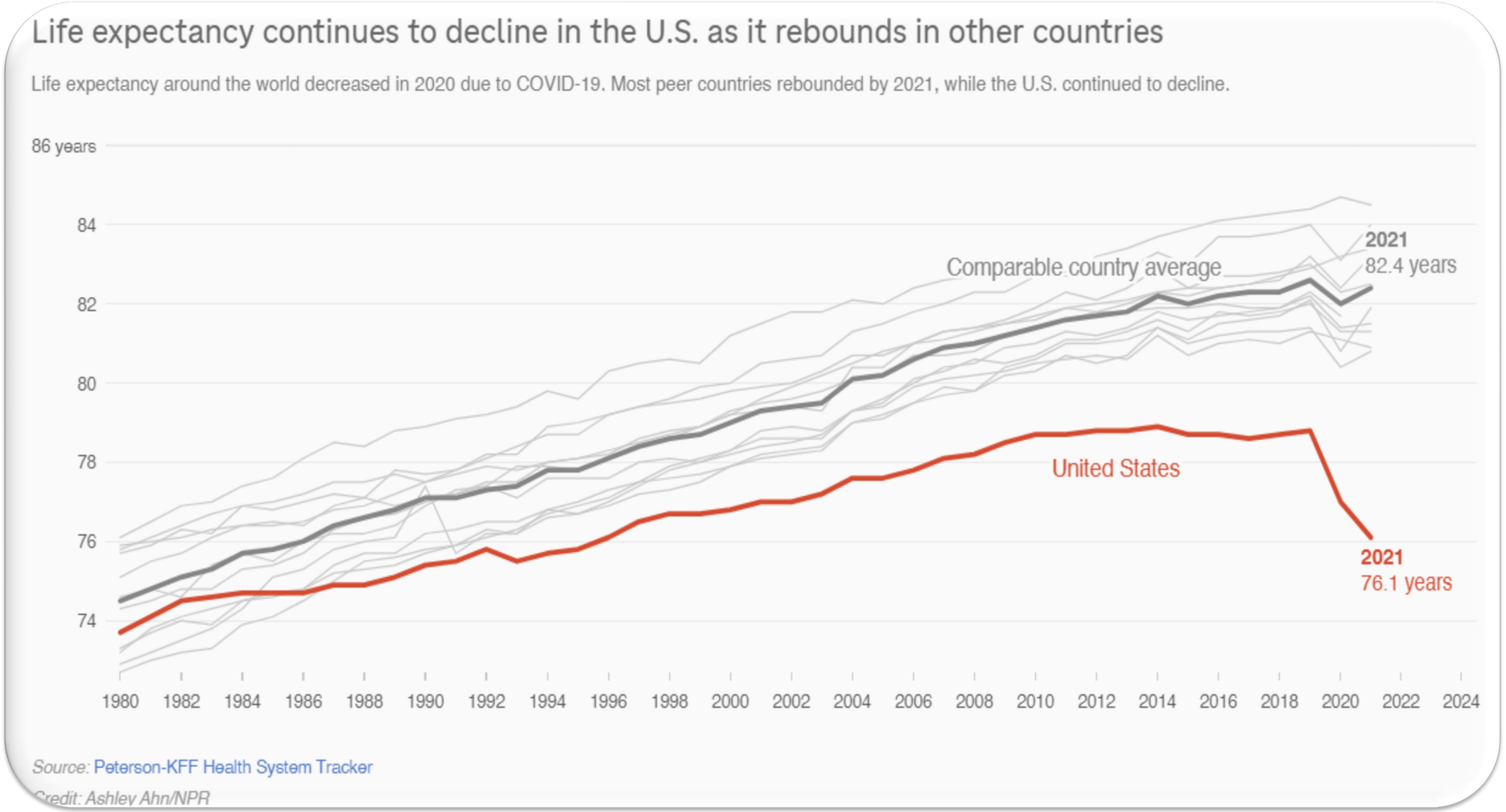
A nonapoptotic form of cell death



- Accelerated aging
- Earlier onset & more aggressive chronic conditions
  - ✓ Type 2 diabetes
  - ✓ Cardiovascular disease
  - ✓ NAFLD/NASH

Our lifespans are decreasing.

This trend is most pronounced in the United States



Age-related conditions were rising in dolphins, too.

Dolphins & humans are susceptible to similar chronic conditions

- NAFLD & NASH
- Dyslipidemia
- Insulin resistance
- Metabolic syndrome
- Dysmetabolic iron overload syndrome
- Chronic inflammation
- Anemia
- Alzheimer’s disease

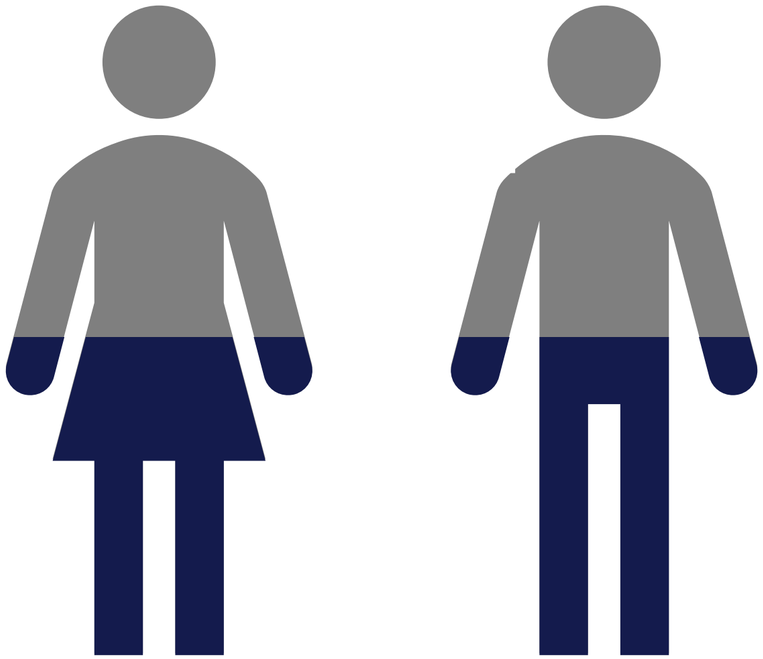
Venn-Watson et al. 2012, 2013, 2015, 2020

A common denominator.

Low dietary & circulating C15:0 (pentadecanoic acid)

People with lower C15:0 are more likely to have or to develop

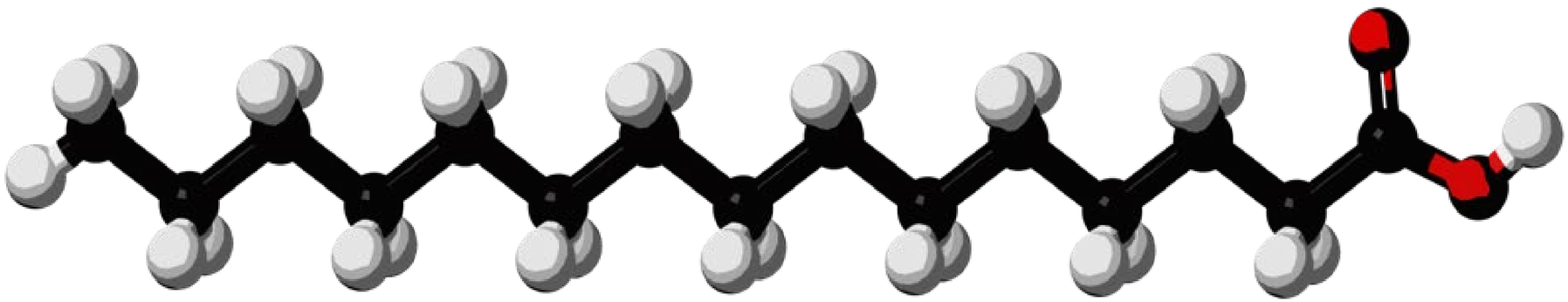
- Type 2 diabetes
- Cardiovascular disease
  - Coronary heart disease
  - Heart failure
- NAFLD/NASH
- Certain cancer types
- Anemia



Venn-Watson et al. 2020, Huang et al. 2019. Trieu et al. 2021, Sawh et al. 2021, Lu et al. 2023, Soboleva et al. 1994

The first essential fatty acid to be discovered in 90+ years.

Our bodies require adequate C15:0 to maintain physiological health



pentadecanoic acid

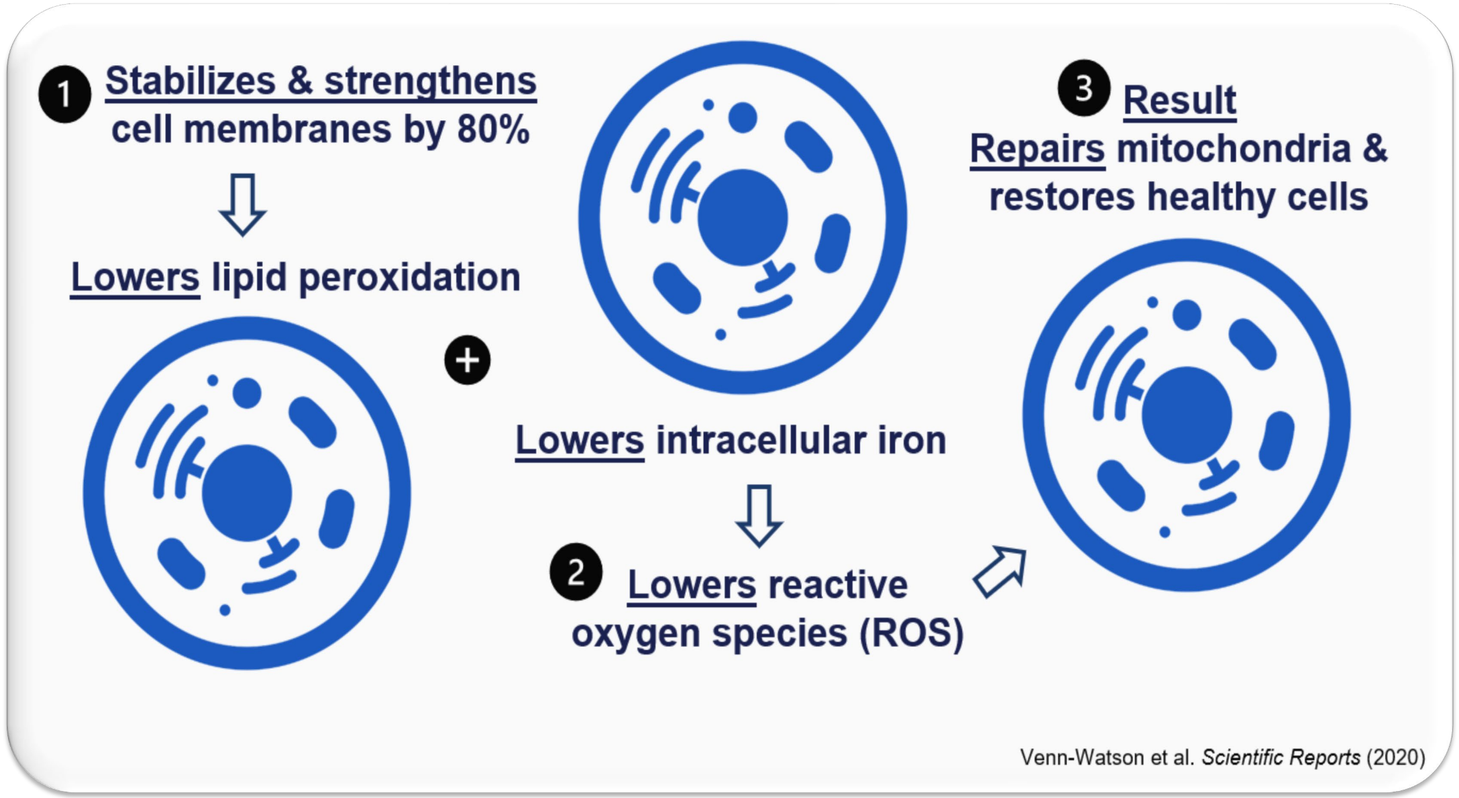
C15:0 (pentadecanoic acid)

- Dietary odd-chain saturated fatty acid
- Stable fatty acid with no double bonds
- Resistant to lipid peroxidation
- Strengthens cell membranes

Venn-Watson et al. 2020

C15:0 reverses ferroptosis.

Effectively stops all core components

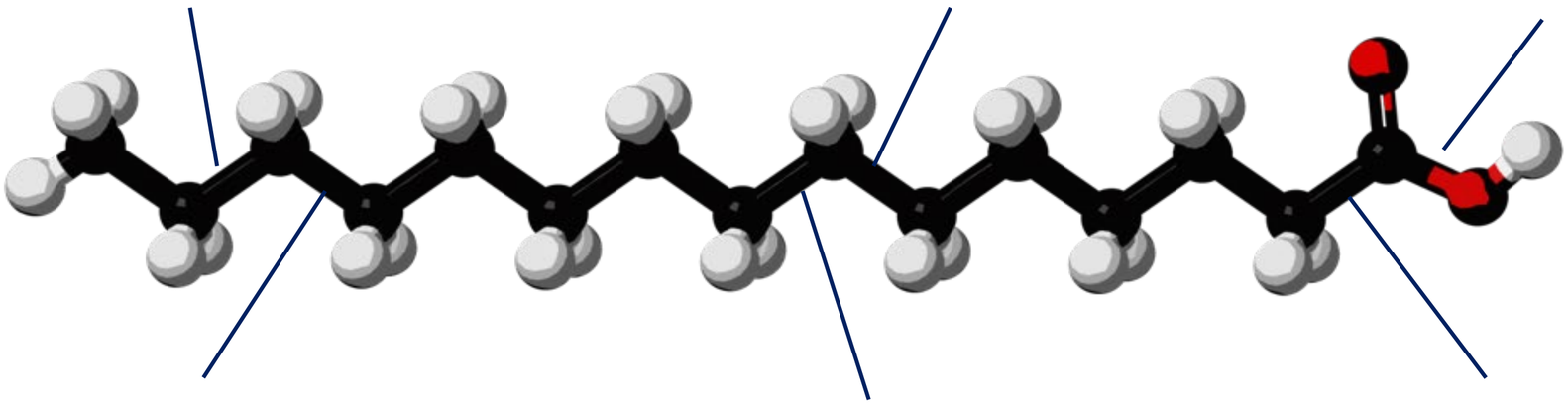


- ✓ Stabilizes cell membranes
- ✓ Lowers lipid peroxidation
- ✓ Stops iron deposition
- ✓ Repairs mitochondria
- ✓ Lowers ROS

Venn-Watson et al. 2020, 2024

C15:0 has multiple mechanisms to enhance health & longevity.

Pleiotropic activities with broad effects



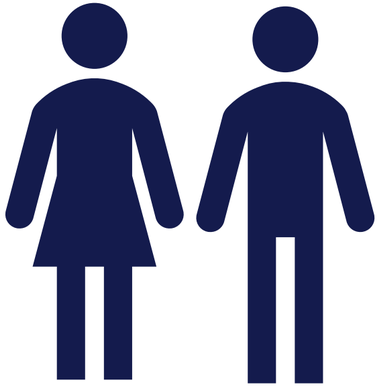
- Anti-inflammatory
- Antioxidant
- Antifibrotic
- Anticancer
- Antimicrobial

Venn-Watson et al. 2020, 2023, Fu et al. 2021, Bishop et al. 2023, Ediweera et al. 2021, To et al. 2020, To et al. 2022

C15:0 has clinical efficacy that improves health.

Including double-blinded and controlled clinical trials

- Alleviated anemia
- Lower liver enzymes
- Lower cholesterol
- Lower glucose
- Alleviated liver iron deposition
- Less liver fibrosis



- Higher hemoglobin
- Lower liver enzymes
- Lower LDL-cholesterol
- Improved gut microbiome

Venn-Watson et al. 2020,2023, To et al. 2020, Wei et al. 2023, Chooi et al. 2024, Schwimmer et al. 2024

C15:0 is the first ***essential fatty acid*** to be discovered in over 90 years.

Venn-Watson et al. 2020

3x more cellular benefits than pure omega-3 (EPA).

Broad efficacy across 12 human cell systems mimicking various diseases

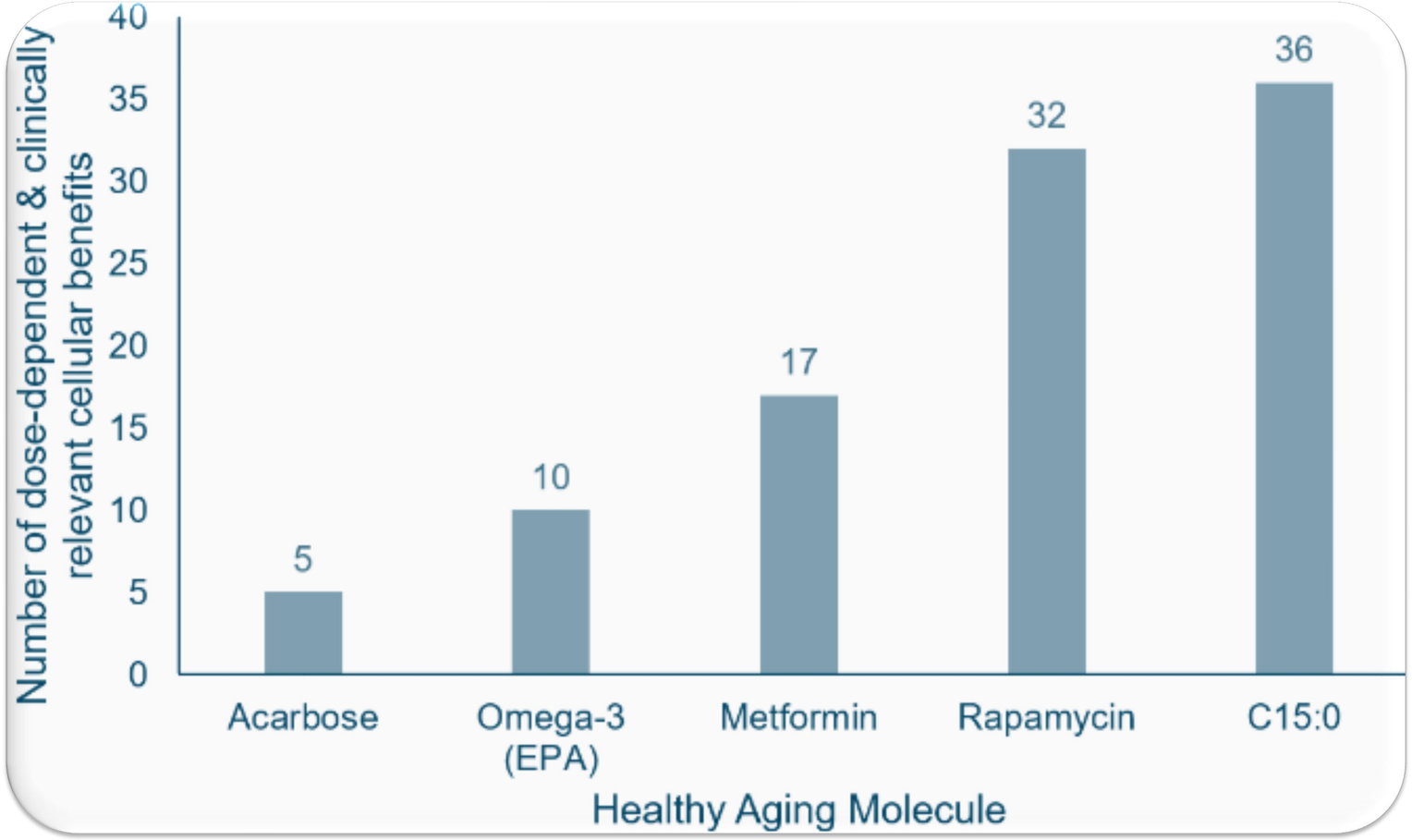
BioMAP System	Health Systems	Omega-3 (EPA)	C15:0 (FA15)
Total clinically relevant benefits		10	36
4H	Immune, gut	✓	✓
LPS	Heart, joint, metabolism	✓	✓
SAg	Immune, joint, skin, gut, RBCs	✓	✓
BT	Immune, lung	✓	✓
3C	Heart, immune		✓
HDF3CGF	Liver, joints		✓
MyoF	Liver, lung		✓
BE3C	Lung		✓
CASM3C	Immune, heart		✓
MPHG	Heart, joint, immune		✓

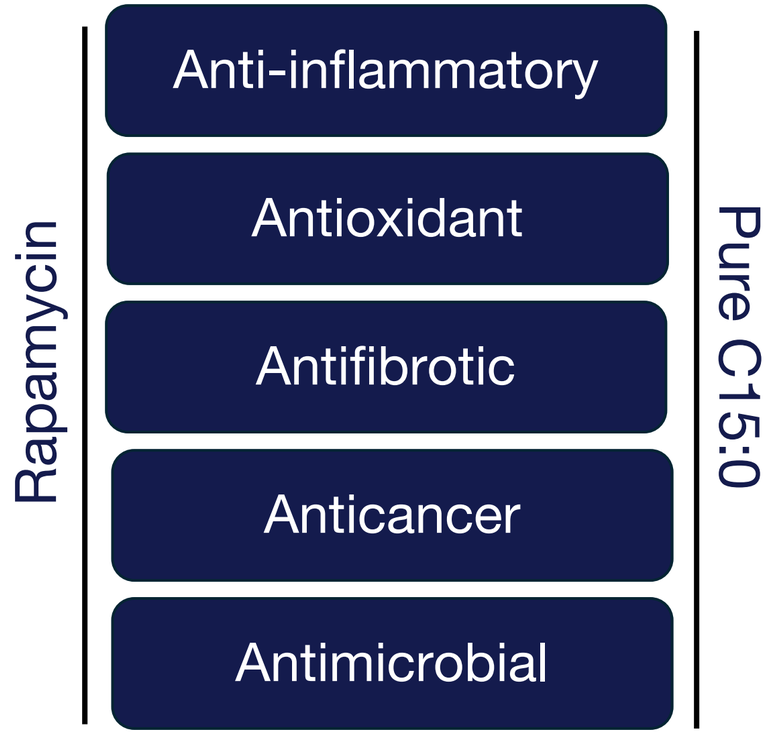
36+ cellular benefits

Venn-Watson et al. 2022

Better than leading longevity enhancing molecules.

Dose-dependent activities that surpassed rapamycin, metformin & acarbose





Venn-Watson & Schork 2023

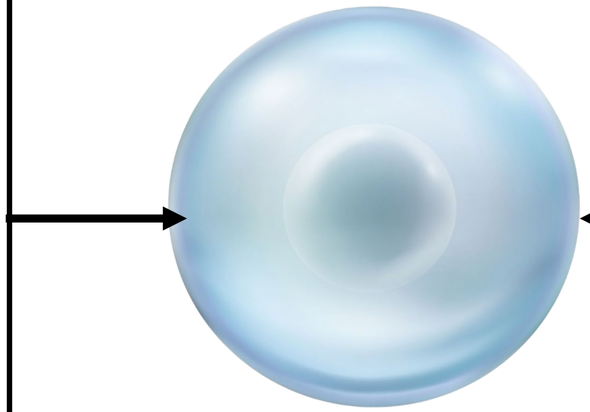
C15:0 targets six hallmarks of aging.

Slows aging at the cellular level

Slows cellular senescence
Inhibits mTOR
Strengthens cells by 80%

Repairs mitochondria
Lowers ROS by45%

Stops inflammaging
Lowers 18+ proinflammatory cytokines



Restores cellular signaling
Activates AMPK, AKT, and PPARα/δ

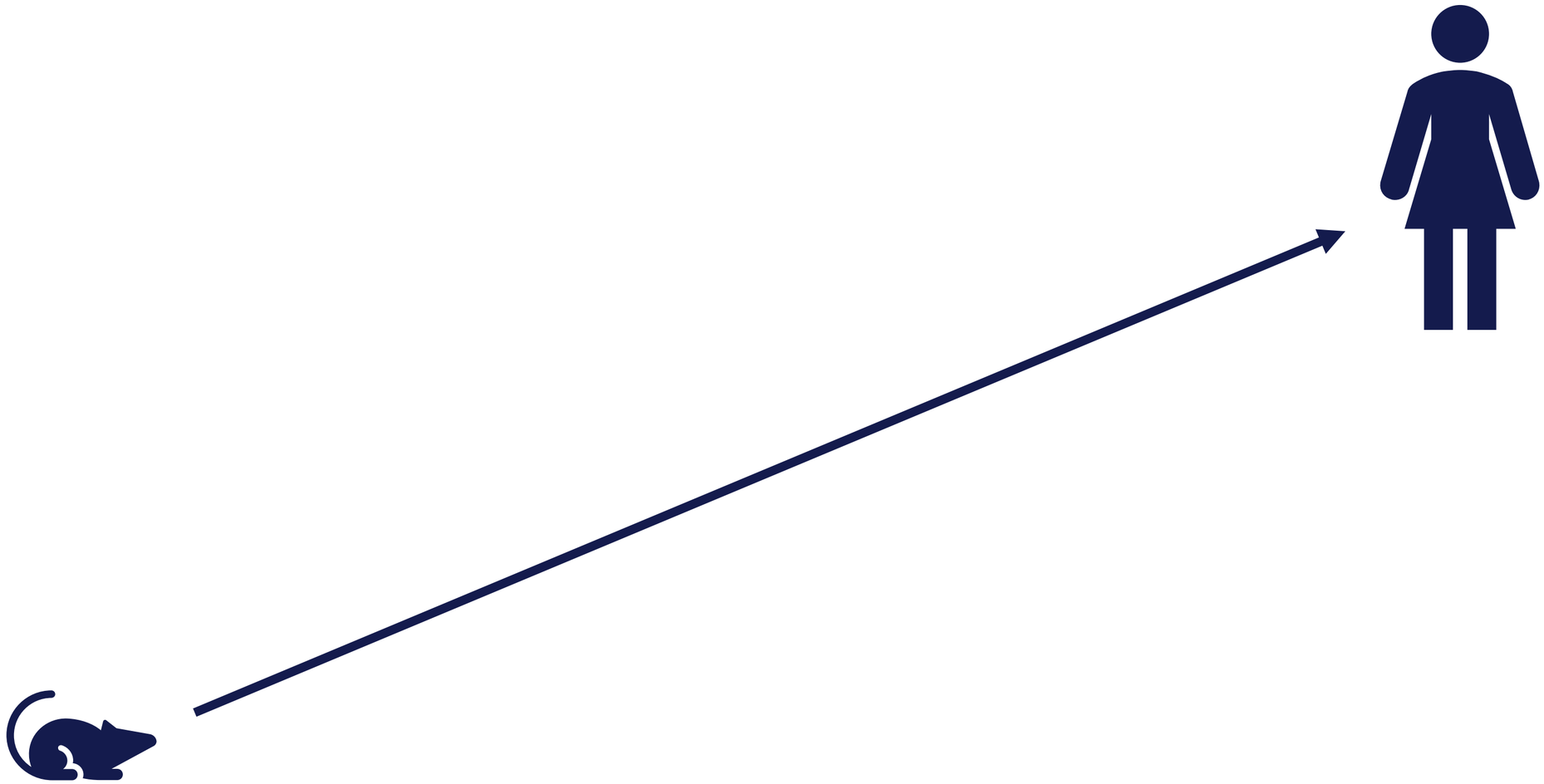
Slows epigenetic alterations
Slows DNA methylation & biological aging

Replenishes gut microbiome
Increases growth of core *Bifidobacterium adolescentis*

Venn-Watson et al. 2020,2023; To et al. 2022, Fu et al 2021, Bishop et al. 2023, Liu et al. 2023, Chooi et al. 2024

The Cell Membrane Pacemaker Theory of Aging.

The greater the cell membrane stability, the longer a species' longevity

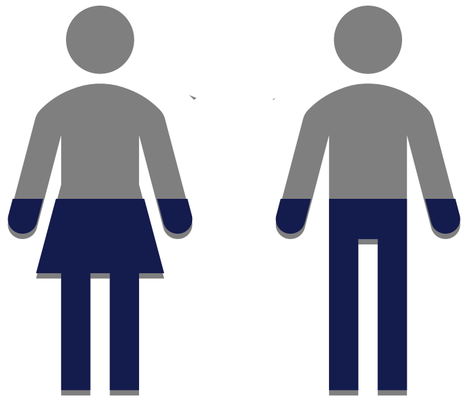


Hulbert 2005

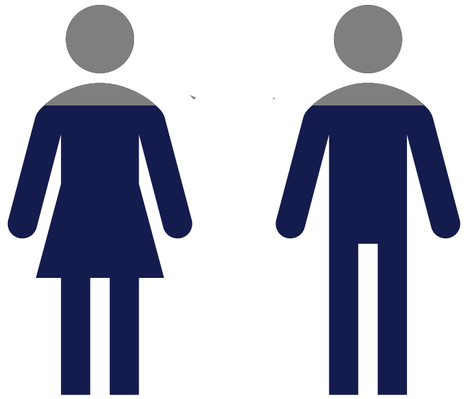
The Cellular Stability Hypothesis.

The greater the cell membrane stability, the longer an individual's longevity

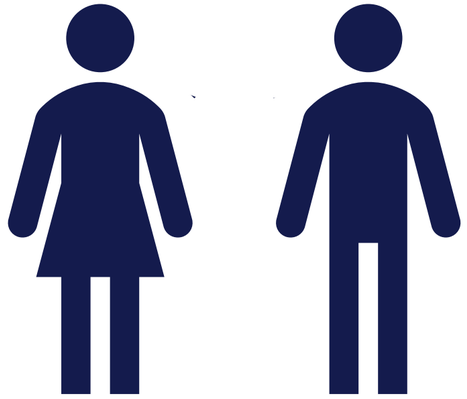
≤ 0.2% C15:0
Nutritional deficiency
Accelerated aging



> 0.2%-0.4% C15:0
Nutritionally replete
Normal aging



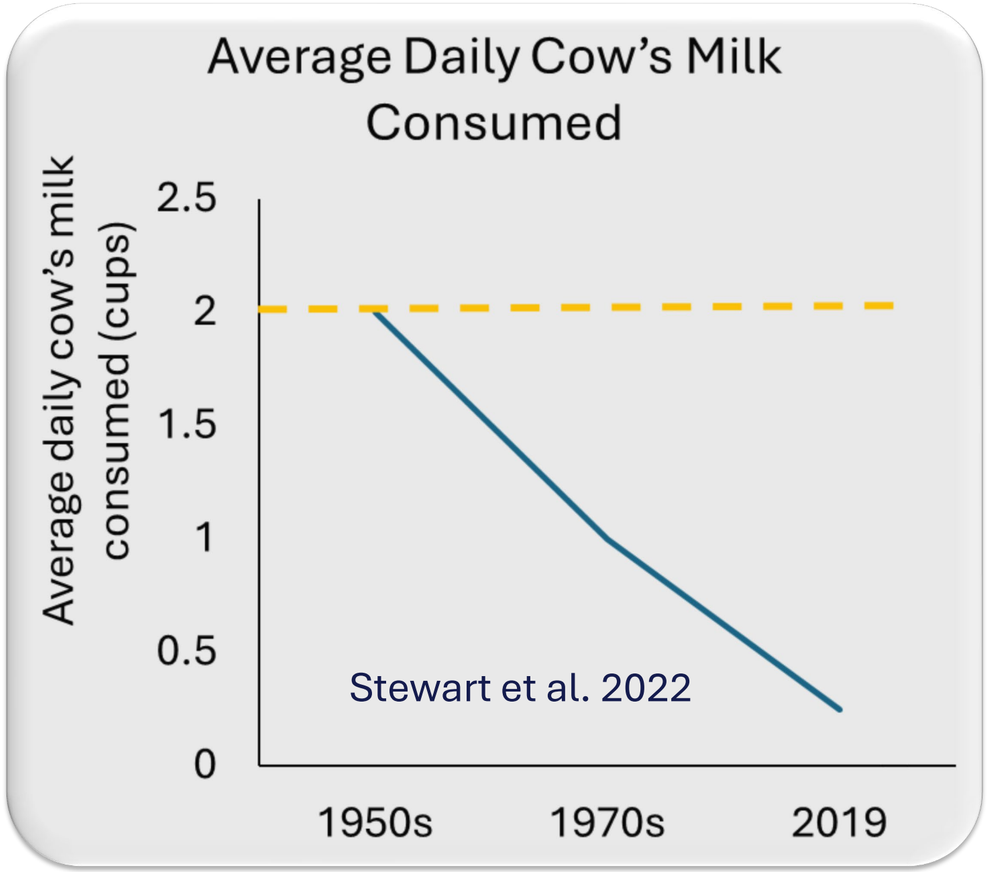
> 0.4%-0.64% C15:0
Optimal
Slower aging

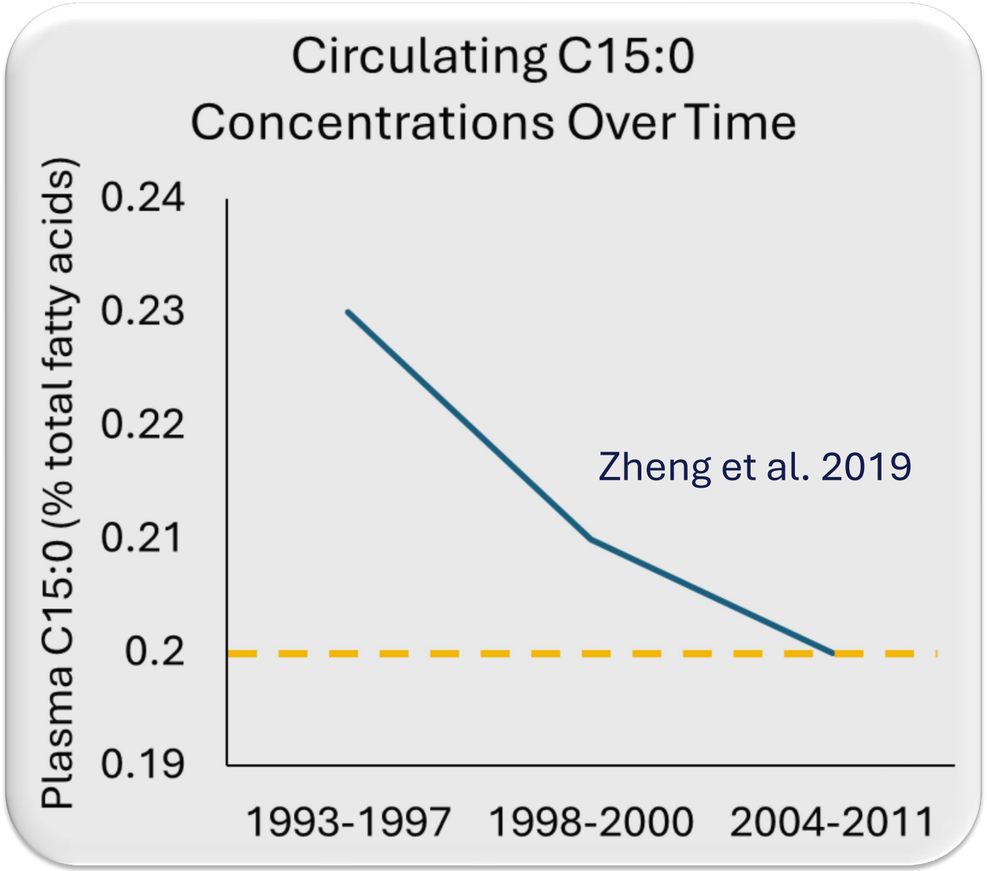


Venn-Watson 2024

Our C15:0 levels have been declining.

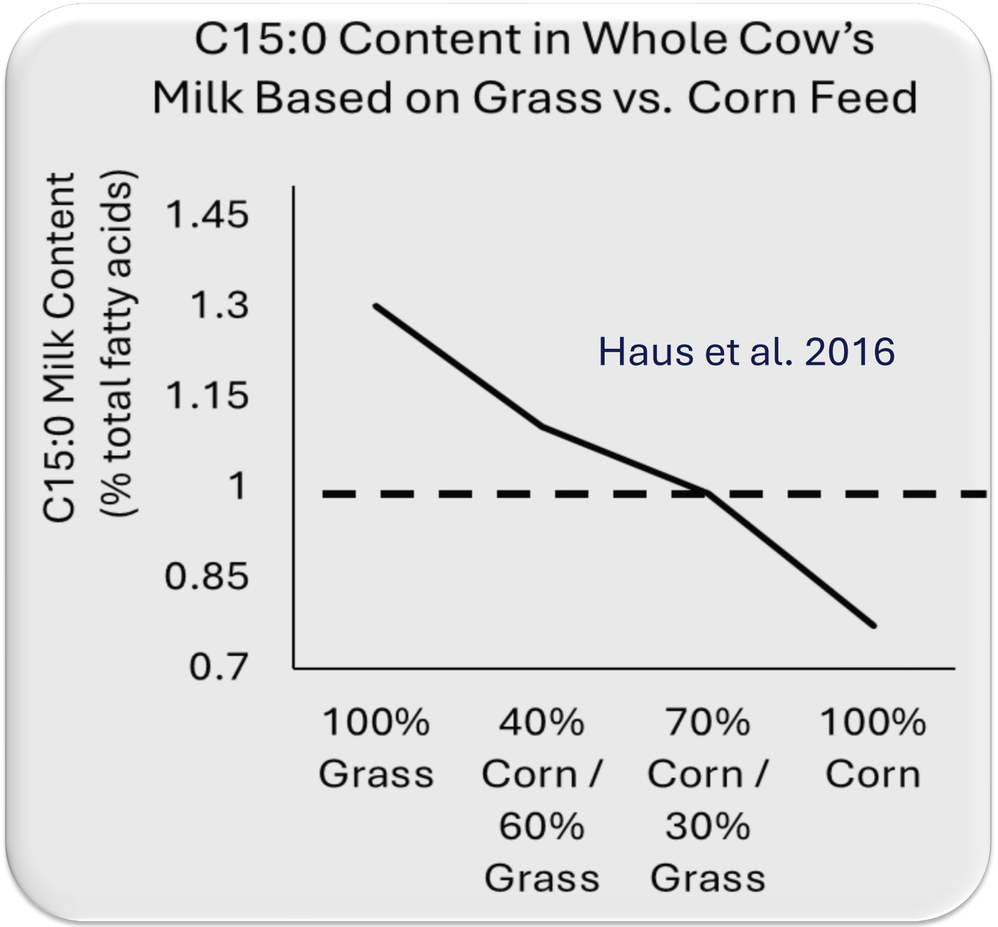
Decreased intake of whole fat dairy products has resulted in declining C15:0 levels

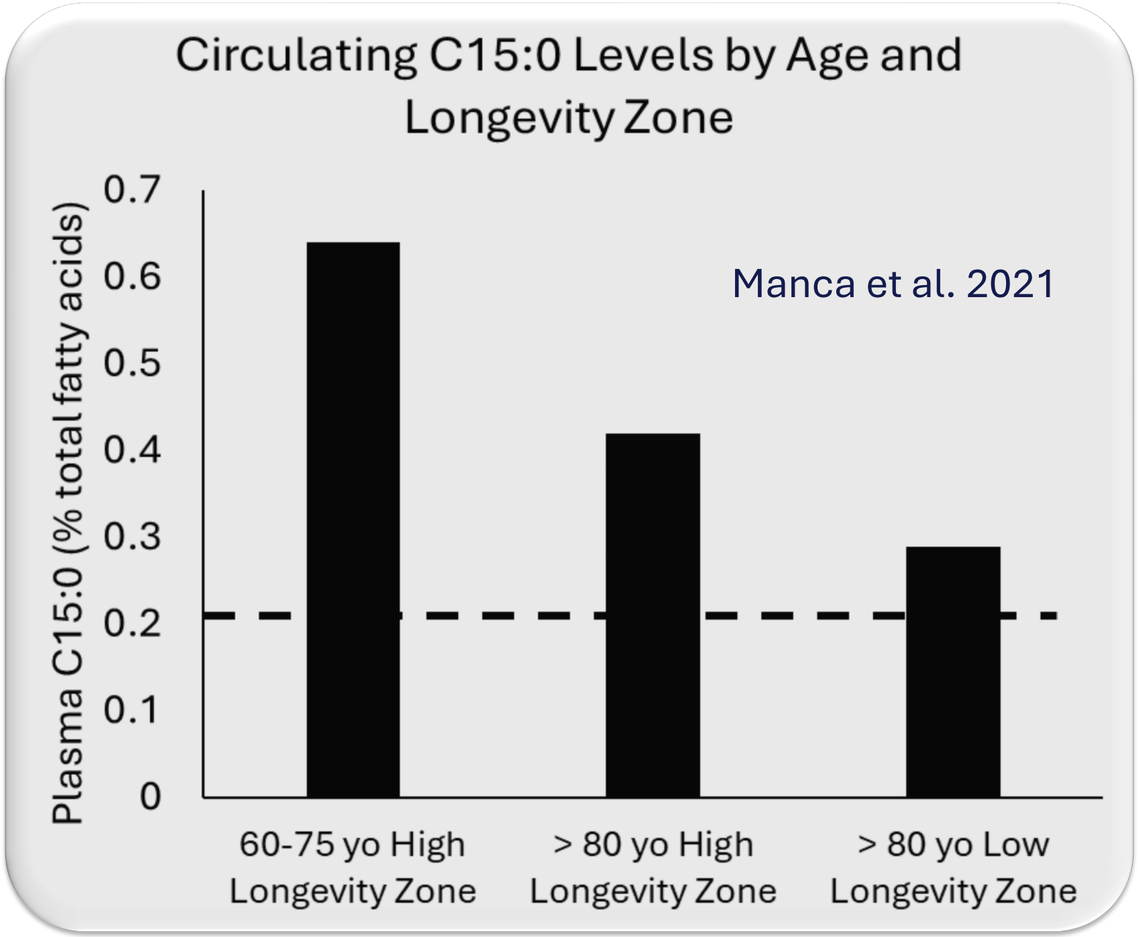




Our C15:0 levels have been declining.

Industry changes and aging are contributing to declining C15:0 levels, too





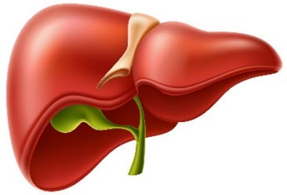
C15:0 Deficiency = Cellular Fragility Syndrome.

The first nutritional deficiency syndrome to be discovered in 75 years

≤ 0.2% circulating C15:0

Cellular Fragility Syndrome

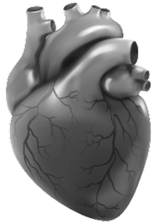
RBC membranes become fragile, resulting in lipid peroxidation



RBCs engulfed by liver macrophages, resulting in **dysmetabolic iron overload syndrome (DIOS)**

Ferroptosis

Insulin resistance
Hyperglycemia
Dyslipidemia
NAFLD➡ NASH
Chronic inflammation



Heart disease

Neurodegenerative disease

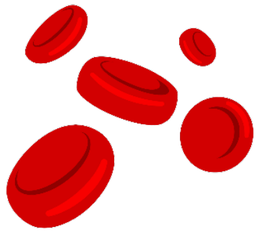
Venn-Watson et al. 2024

Cellular Fragility Syndrome.

Nutritional C15:0 deficiency diagnostic tests

≤ 0.2% C15:0

Low C15:0 RBC levels



Fragile RBCs

Elevated RDW

Elevated Reticulocytes

Elevated osmotic fragility

+/- Low hemoglobin

Iron overload

Hyperferritinemia

Diagnostic Tests

Ferroptosis

High lipid peroxidation products (TBARS) + high ferritin

General indices of NAFLD/NASH, insulin resistance, T2D & CVD

Elevated glucose

Elevated cholesterol, TGs

Elevated liver enzymes

High IL-6, TNFα, MCP-1

Venn-Watson et al. 2024

This is fixable.

Most people need 100 to 200 mg C15:0 per day to not be deficient.

Venn-Watson et al. 2020, 2024

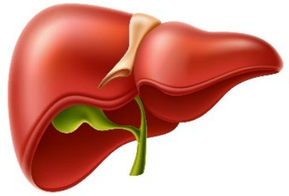
C15:0 Reverses Cellular Fragility Syndrome.

Replenishing healthy C15:0 levels restores long-term health

> 0.2% circulating C15:0

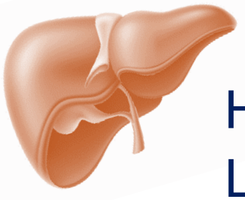
Cellular Stability

RBC membranes restored, resulting normalized hemoglobin & RDW

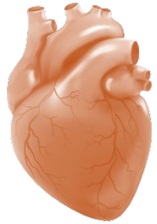


Iron deposition stopped, **resulting in lower liver enzymes +/- lower ferritin**

Ferroptosis stopped



Healthy liver
Lower glucose
Lower TG
Lower liver enzymes



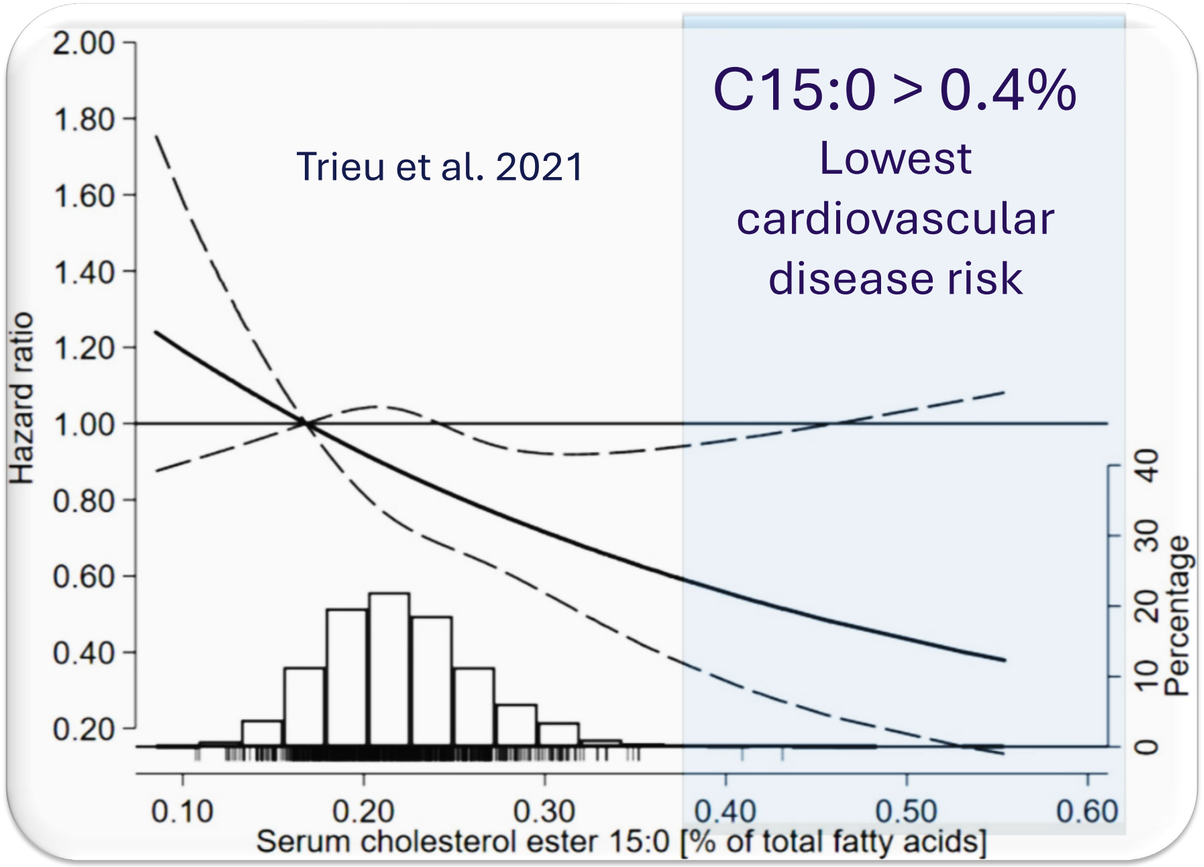
Healthy hearts
Lower LDL-C, IL-6, TNFα, and MCP-1

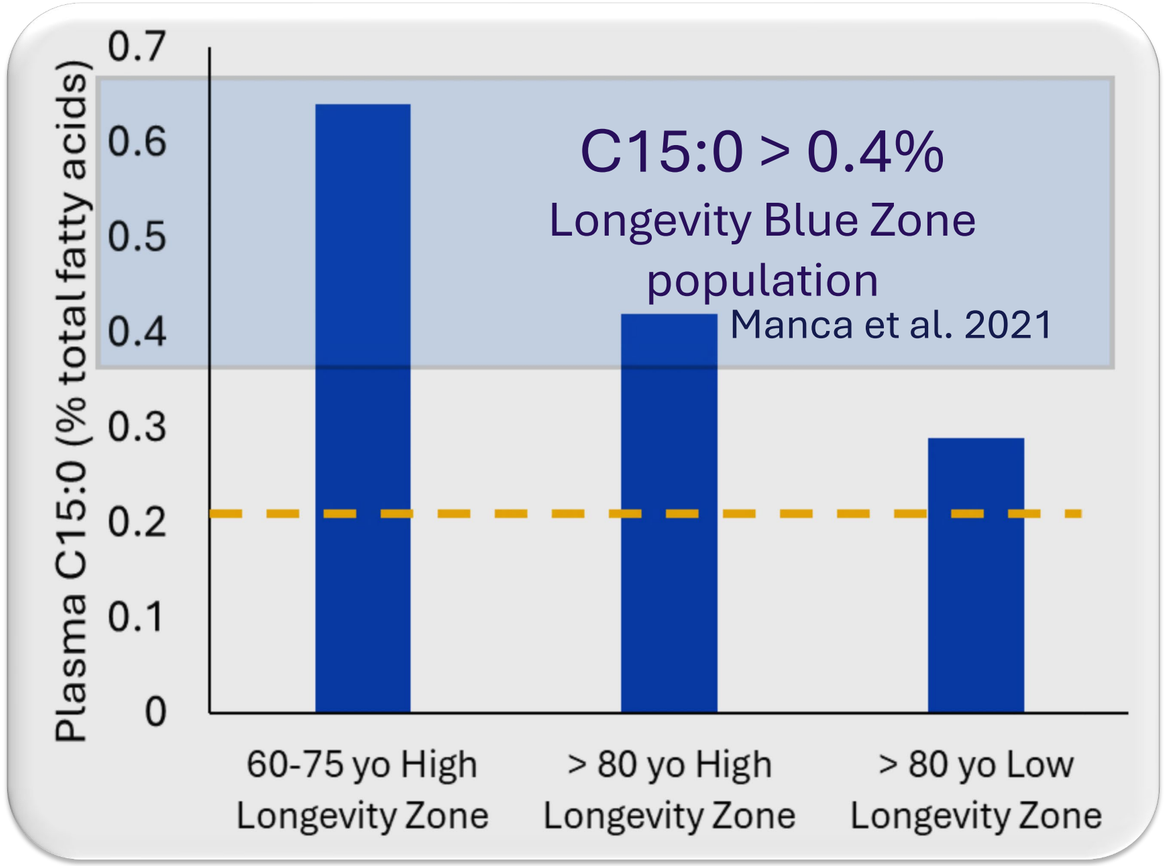
Improved cognition

Venn-Watson et al. 2024

Optimizing C15:0 for longevity.

0.4% to 0.64% proposed as optimal for heart health & longevity





Why not just eat more dairy fat?

Dairy fat does not consistently show benefits & individual active ingredients can ***lose efficacy*** when mixed in dairy fat.

Less bioavailable triacylglyceride form

Only 1% C15:0

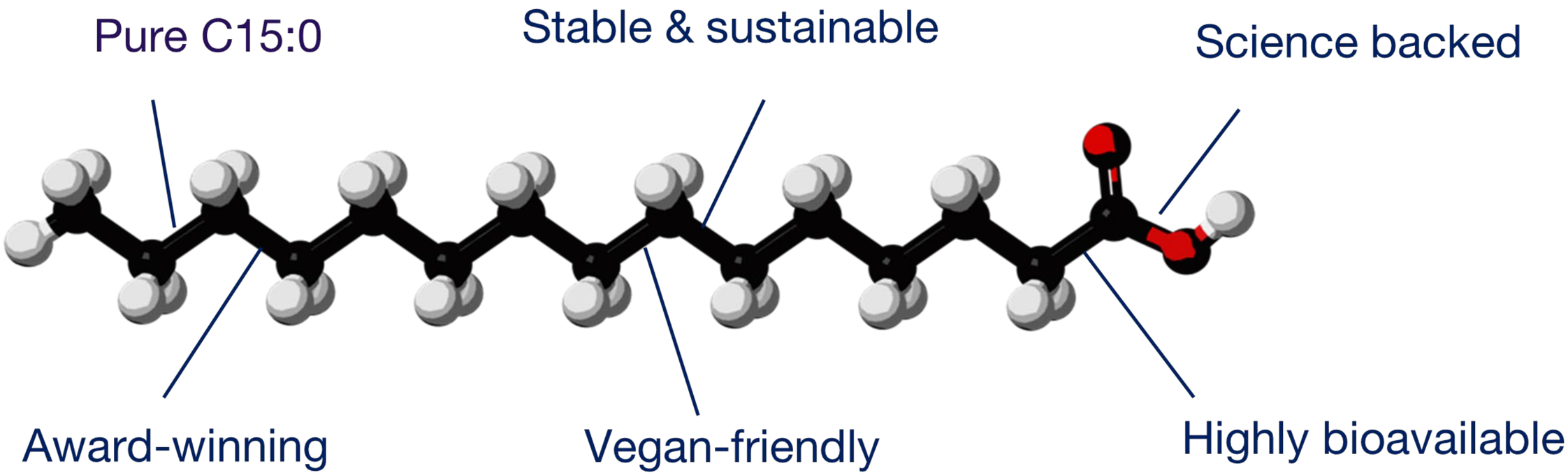
> 40% proinflammatory fats

Highly variable C15:0 content based on breed, season, feed & dairy food

Mansson 2008, Haus et al. 2016, Thorning et al. 2017

Optimizing nature to extend healthy aging & longevity.

Restoring global health and advancing longevity with pure C15:0



Venn-Watson et al. 2020, 2022, 2023; Chooi et al. 2024

NUTRITIONAL OUTLOOK ***BEST OF THE INDUSTRY***: BEST INGREDIENT SUPPLIER 2021

NUTRAINGREDIENTS ***INGREDIENT OF THE YEAR***: ***HEALTHY AGING*** 2024 FINALIST

FAST COMPANY ***WORLD CHANGING IDEA***: WELLNESS 2022, 2024

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