Cellular Metabolism and Geroscience

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Live better longer.

Disclosures

Current Funding:
• National Institutes of Health: R01AG81226 (cMPI), R01AG067333 (PI), R01AG068025 (PI), R25AG073119 (MPI), R01AG074273 (Co-I), R01DK114034 (Co-I), P30AG044281 (OSC)
• Department of Defense: W81XWH2210867 (Co-I)
• Hevolution Foundation: HF-GRO-23-1199178 (PI), Buck Institute center grant (Co-I)
• Advanced Research Projects Agency for Health: 1AY2AX000072-01 (Co-I)
• Philanthropy: Dr. James Johnson, Buck Institute Impact Circle

Other Financial Relationships:
• San Francisco VA Medical Center part-time staff
• University of California San Francisco part-time staff

Conflicts of Interest:
- BHB Therapeutics, Ltd: Co-founder, stockholder
- Selah Therapeutics, Ltd: Co-founder, stockholder
- Junevity: Scientific Advisory Board
- Virta Health: former Scientific Advisory Board

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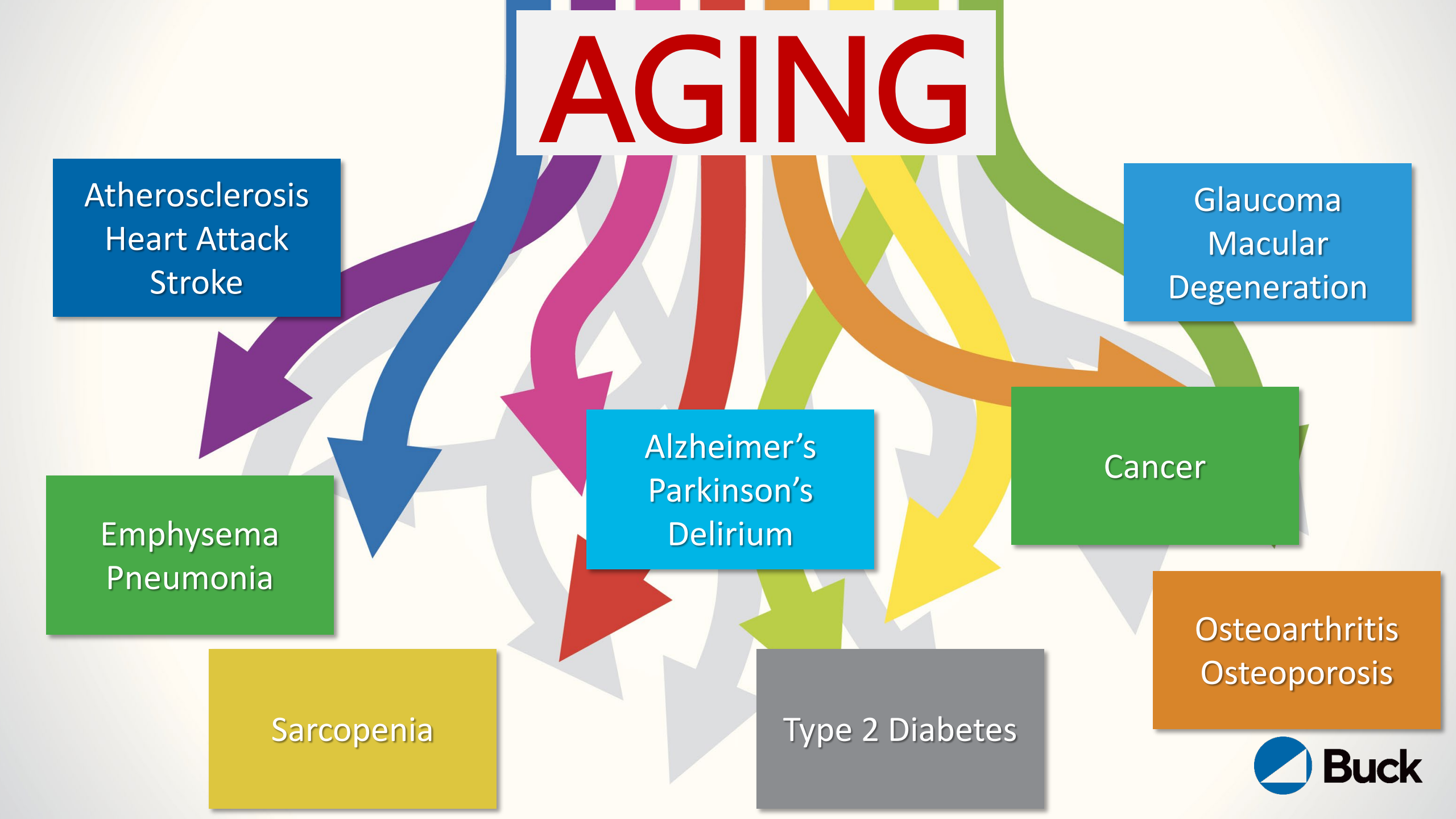
AGING
Atherosclerosis
Heart Attack
Stroke
Glaucoma
Macular
Degeneration
Emphysema
Pneumonia
Alzheimer's
Parkinson's
Delirium
Cancer
Osteoarthritis
Osteoporosis
Sarcopenia
Type 2 Diabetes
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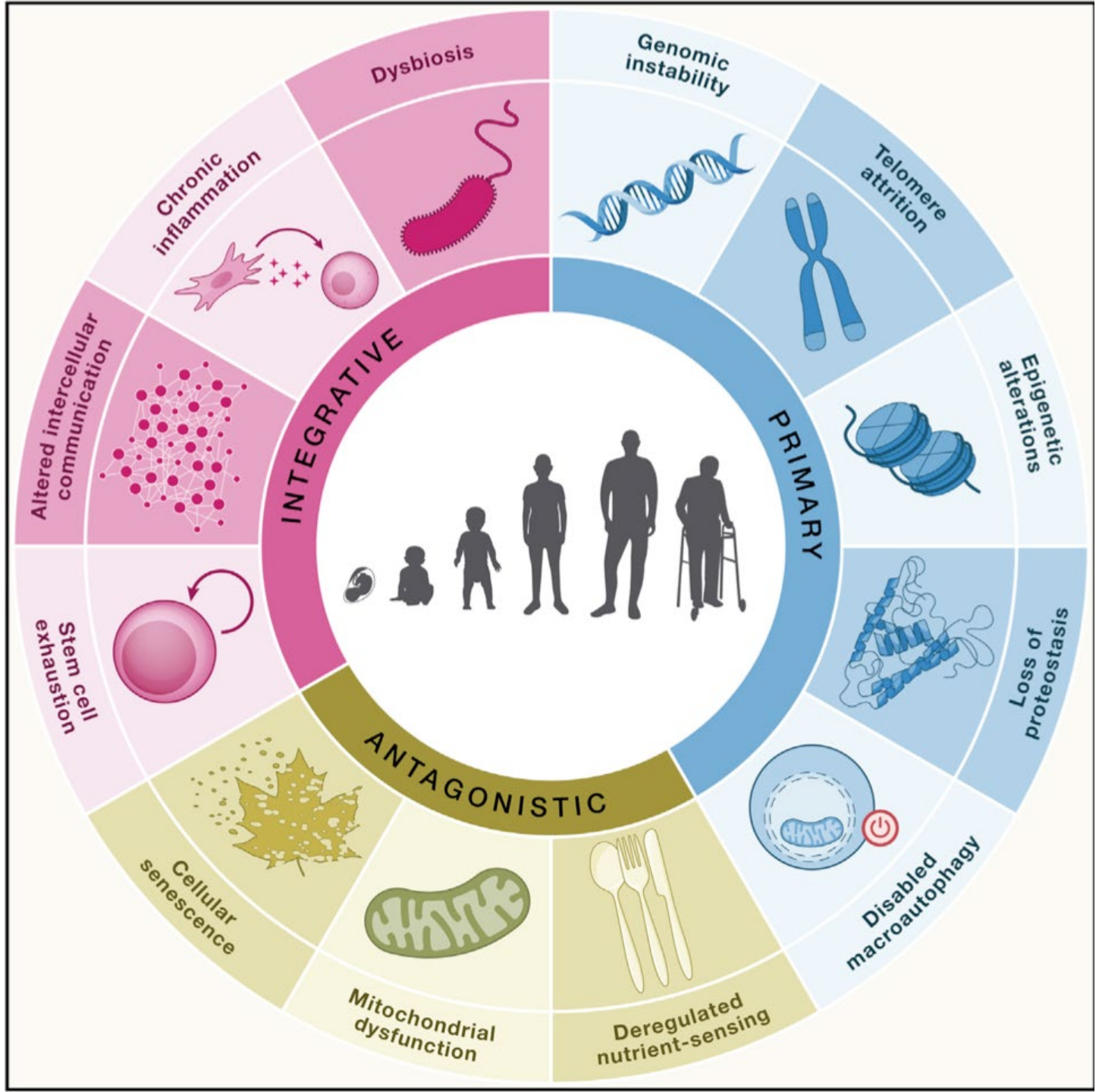
Aging phenotypes are driven by specific, modifiable molecular mechanisms…

The “Hallmarks of Aging”



López-Otín, PMID 36599349

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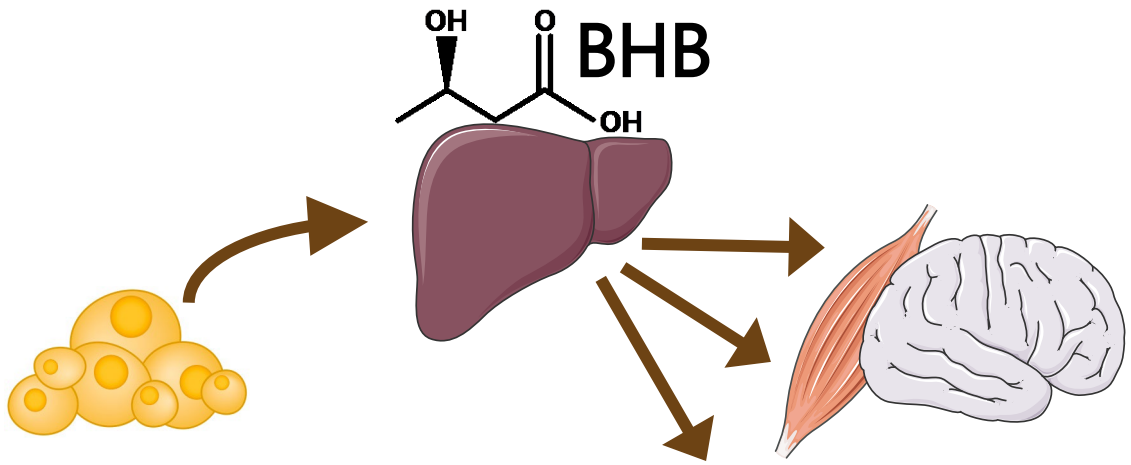
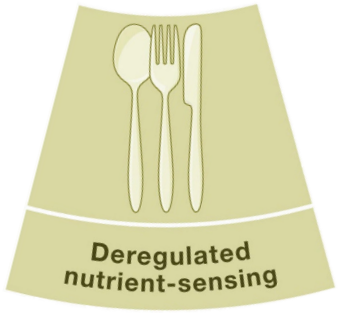
Ketone bodies are an example of metabolic signals

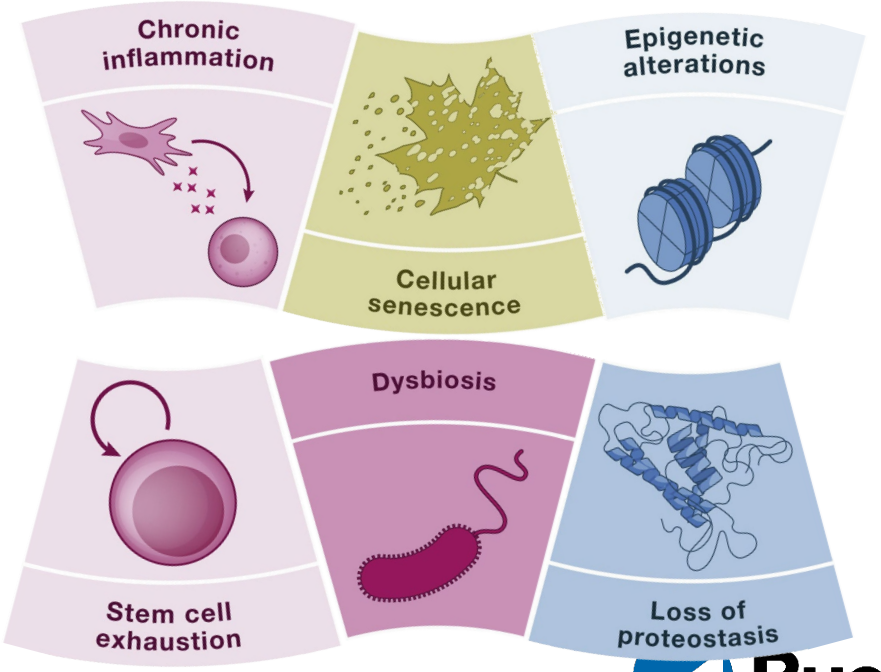


Constitutive: 10-50 µM
Fasting: 1-5 mM



Energetics/ATP

Direct or Indirect Signaling



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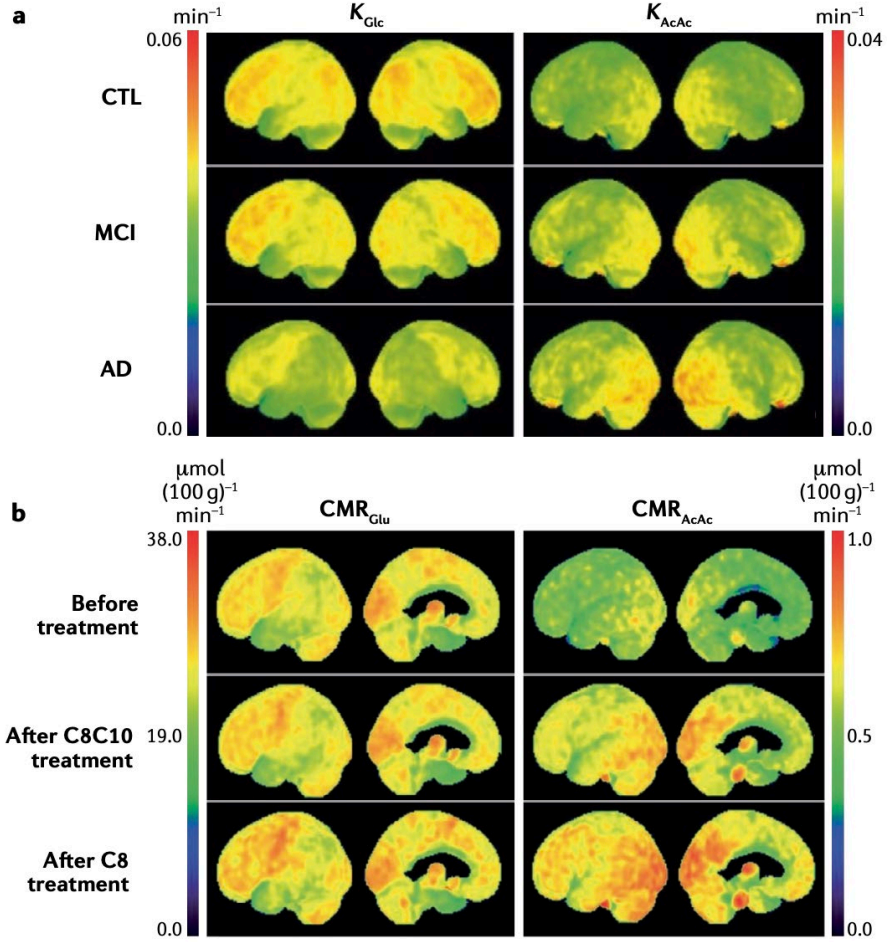
Ketone metabolism maintained in dementia



Croteau et al., Exp Gerontol 2018

Metabolism shifts to ketones in heart failure

Therapeutic Potential of Ketone Bodies for Patients With Cardiovascular Disease

JACC State-of-the-Art Review

Salva R. Yurista, MD, PhD,[a] Cher-Rin Chong, PhD,[b,c] Juan J. Badimon, PhD,[d] Daniel P. Kelly, MD,[e] Rudolf A. de Boer, MD, PhD,[a] B. Daan Westenbrink, MD, PhD[a]

The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense

Julie L. Horton,[1] Michael T. Davidson,[2] Clara Kurishima,[3] Rick B. Vega,[1] Jeffery C. Powers,[3] Timothy R. Matsuura,[4] Christopher Petucci,[1,4] E. Douglas Lewandowski,[1,5] Peter A. Crawford,[1,6] Deborah M. Muoio,[2] Fabio A. Recchia,[3,7] and Daniel P. Kelly[1,4]

The Failing Heart Relies on Ketone Bodies as a Fuel

Gregory Aubert, Ola J. Martin, Julie L. Horton, Ling Lai, Rick B. Vega, Teresa C. Leone, Timothy Koves, Stephen J. Gardell, Marcus Krüger, Charles L. Hoppel, E. Douglas Lewandowski, … See all authors

Originally published 27 Jan 2016 | https://doi.org/10.1161/CIRCULATIONAHA.115.017355 | Circulation. 2016;133:698–705

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> Cell Metab. 2017 Sep 5;26(3):547-557.e8. doi: 10.1016/j.cmet.2017.08.004.

Ketogenic Diet Reduces Midlife Mortality and Improves Memory in Aging Mice

John C Newman [1], Anthony J Covarrubias [2], Minghao Zhao [3], Xinxing Yu [4], Philipp Gut [5], Che-Ping Ng [2], Yu Huang [6], Saptarsi Haldar [6], Eric Verdin [7]

Affiliations + expand

PMID: 28877458 PMCID: PMC5605815 DOI: 10.1016/j.cmet.2017.08.004

> Cell Rep Med. 2024 Jun 18;5(6):101593. doi: 10.1016/j.xcrm.2024.101593. Epub 2024 Jun 5.

Ketogenic diet administration later in life improves memory by modifying the synaptic cortical proteome via the PKA signaling pathway in aging mice

Diego Acuña-Catalán [1], Samah Shah [2], Cameron Wehrfritz [2], Mitsunori Nomura [2], Alejandro Acevedo [3], Cristina Olmos [1], Gabriel Quiroz [1], Hernán Huerta [4], Joanna Bons [2], Estibaliz Ampuero [5], Ursula Wyneken [6], Magdalena Sanhueza [7], Felipe Arancibia [7], Darwin Contreras [8], Julio César Cárdenas [9], Bernardo Morales [8], Birgit Schilling [2], John C Newman [2], Christian González-Billault [10]

Affiliations + expand

PMID: 38843842 PMCID: PMC11228662 DOI: 10.1016/j.xcrm.2024.101593

> Aging Biol. 2024:2:20240038. doi: 10.59368/agingbio.20240038. Epub 2024 Dec 16.

Ketogenic Diet Reduces Age-Induced Chronic Neuroinflammation in Mice

Mitsunori Nomura [1], Natalia Faraj Murad [1], Sidharth S Madhavan [1 2], Wei-Chieh Mu [1], Brenda Eap [1 2], Thelma Y Garcia [1], Carlos Galicia Aguirre [1 2], Eric Verdin [1], Lisa Ellerby [1 2], David Furman [1 3 4], John C Newman [1 2 5]

Affiliations + expand

PMID: 39697898 PMCID: PMC11654834 DOI: 10.59368/agingbio.20240038

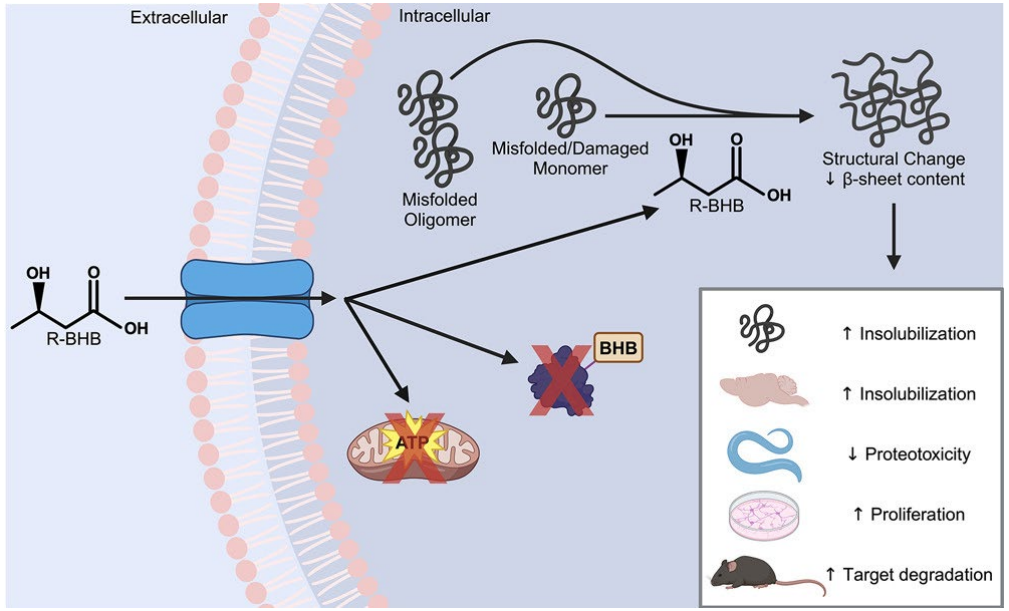
> Cell Chem Biol. 2025 Jan 16;32(1):174-191.e8. doi: 10.1016/j.chembiol.2024.11.001. Epub 2024 Dec 2.

β-hydroxybutyrate is a metabolic regulator of proteostasis in the aged and Alzheimer disease brain

Sidharth S Madhavan [1], Stephanie Roa Diaz [2], Sawyer Peralta [3], Mitsunori Nomura [3], Christina D King [3], Kaya E Ceyhan [3], Anwen Lin [3], Dipa Bhaumik [3], Anna C Foulger [3], Samah Shah [3], Thanh Blade [3], Wyatt Gray [3], Manish Chamoli [3], Brenda Eap [4], Oishika Panda [3], Diego Diaz [3], Thelma Y Garcia [2], Brianna J Stubbs [3], Scott M Ulrich [5], Gordon J Lithgow [4], Birgit Schilling [4], Eric Verdin [4], Asish R Chaudhuri [3], John C Newman [6]

Affiliations + expand

PMID: 39626664 PMCID: PMC11741930 (available on 2026-01-16)
DOI: 10.1016/j.chembiol.2024.11.001



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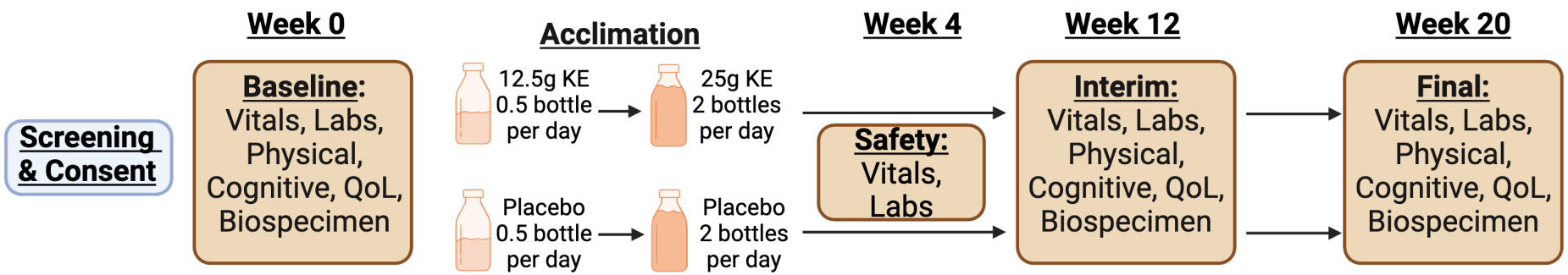
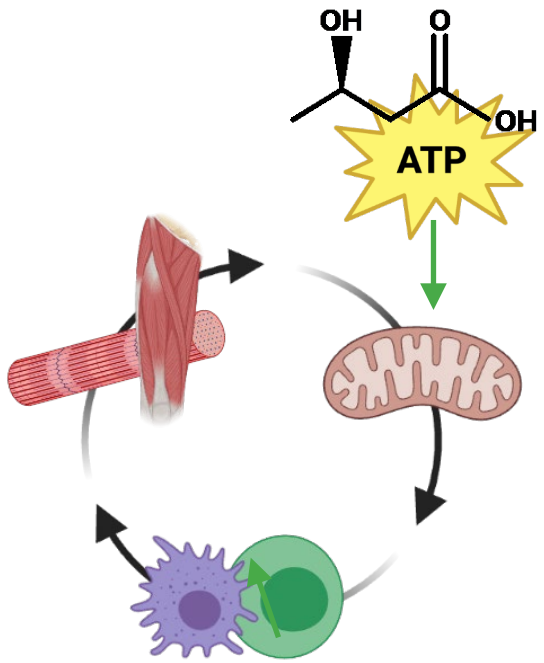
TAKEOFF: Targeting Aging with a Ketone Ester for Function in Frailty





SFCC Project Coordination, Statisical Support, Data Management

Buck Institute (n=60)

Coordinate geroscience biomarkers (all sites)

Ohio State (n=60)

Skeletal Muscle Volume via MRI (n=60)

Muscle Metabolomics via Biopsy (n=20)

Energy Expenditure via Indirect Calorimetry (n=20)

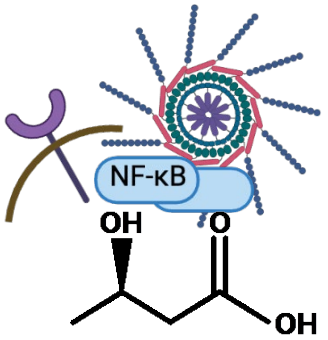
UConn (n=60)

Immune Phenotyping (n=60)

Immune Metabolism (n=60)

scRNA Sequencing on PBMCs (n=12)

R01AG081226
NCT06645847
N=180
Mechanism-focused
Pragmatic elements
Pre-frail older adults (via gait speed)
Composite functional primary outcome



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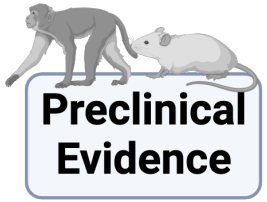
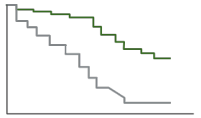
Identifying potential repurposed gerotherapeutics

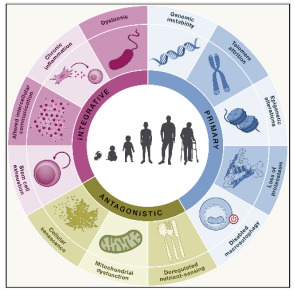


Preclinical Evidence

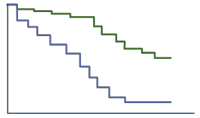


Lifespan
- ITP
- non-ITP

Health span
- function
- disease



Potential gerotherapeutic



Lifespan
- mortality from all causes
- mortality from off-target diseases

Clinical Evidence

Health span
- incident off-target disease
- function
- geriatric syndromes

From Sandra Aleksic, AECOM

Created with Biorender.com

Lopez-Otin et al. *Cell* 2023
Kulkarni, Aleksic et al. *Aging Cell* 2022

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Potential repurposed gerotherapeutics

Gerotherapeutic	Hallmarks of aging	Preclinical healhspan	Preclinical lifespan	Human healthspan	Human mortality	Score (out of 12)
SGLT-2 inhibitors	2	2	2	3	3	12
Metformin	2	2	1	3	3	11
Bisphosphonates	2	2	1	3	3	11
GLP-1 RAs	2	2	0	3	3	10
Acarbose	2	2	2	3	0	9
Rapamycin	2	2	2	3	0	9
Methylene blue	2	2	2	3	0	9
ACE inhibitors/ARBs	2			3	0	8
Dasatinib (+ quercetin)	2			3	0	8
Aspirin	2			1	0	7
Beta blockers	1	2	1	0	3	7
N-acetyl cysteine	2	2	1	0	0	5

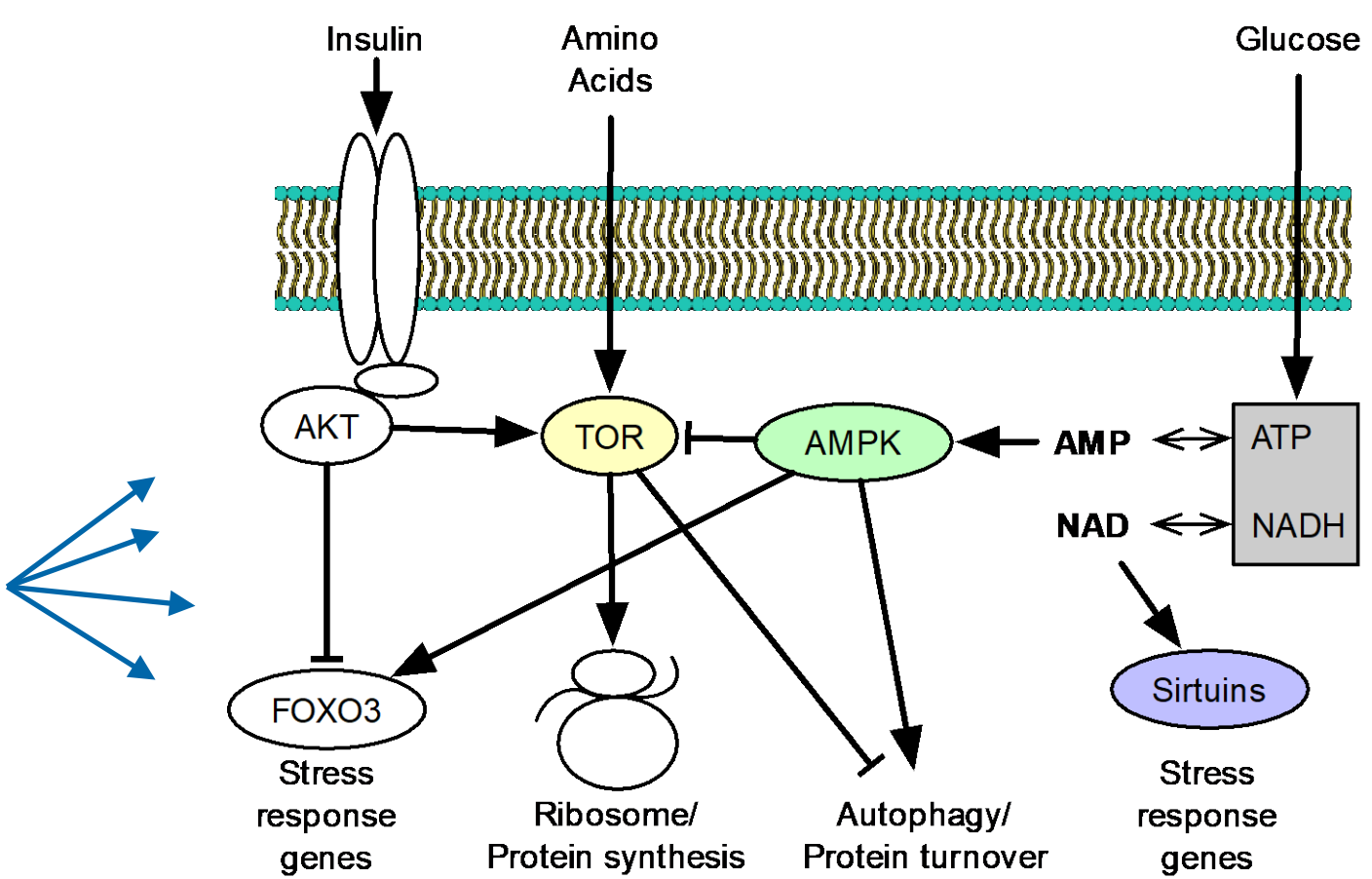
Drugs targeting cellular metabolism are top hits

Adapted from: Leone & Barzilai. *Medical Research Archives* 2024

Adapted from Sandra Aleksic, AECOM

Integrated geroscience mechanisms of cellular metabolism

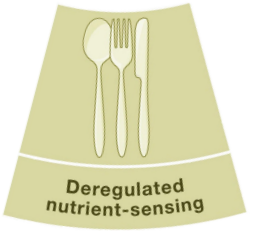
Metformin
GLP-1RA
SGLT2i
TOR inhibitors
…

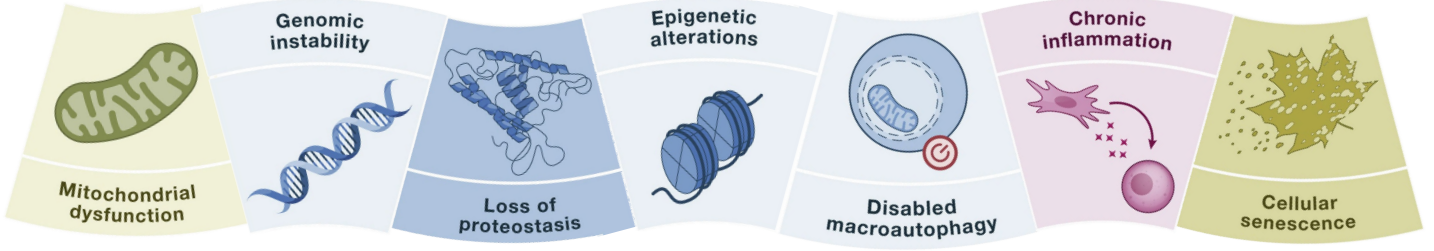


Energy Signals

Sensors

Stress Response





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Summary and Gaps

Cellular metabolites have diverse signaling activities in addition to energetic functions, all relevant to multiple age-related diseases

Both new metabolic therapies and repurposed metabolism-targeting drugs show promise as gerotherapeutics

GAPS

Human data on metabolite signaling functions are lacking

Preclinical data strongly point to sex differences

Early or late? Prevention vs treatment? SDoH as key risk factors?

Repurposed drugs require dedicated geroscience clinical trials

Thank you!

Collaborators:

Brianna Stubbs, DPhil

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Jenna Bartley, PhD

George Kuchel, MD

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Ester Hernandez

Jessica Johl, PhD

Sid Madhavan

Nikki Moreno

Mitsunori Nomura, PhD

Alejandra Perez

Chatura Senadheera

Wendie Silverman-Martin, RN

Elizabeth Stephens

Current Funding:

Buck Institute

NIA R01 AG 081226

NIA R01 AG 067333

NIA R01 AG 068025

NIA R25 AG 073119

NIA Diversity Supplements

Dr. James Johnson

Longevity Impetus Grants

UCSF Pepper Center

US Dept of Defense

Lab alumni contributing to the work presented:

Gabriela Alvarez

Thanh Blade

Asish Chaudhuri, PhD

Diego Diaz

Brenda Eap, PhD

Wyatt Gray

Stephanie Roa

Sawyer Peralta

Oishika Panda, PhD

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