Nutrition and Aging Biology: Hyperketonemia

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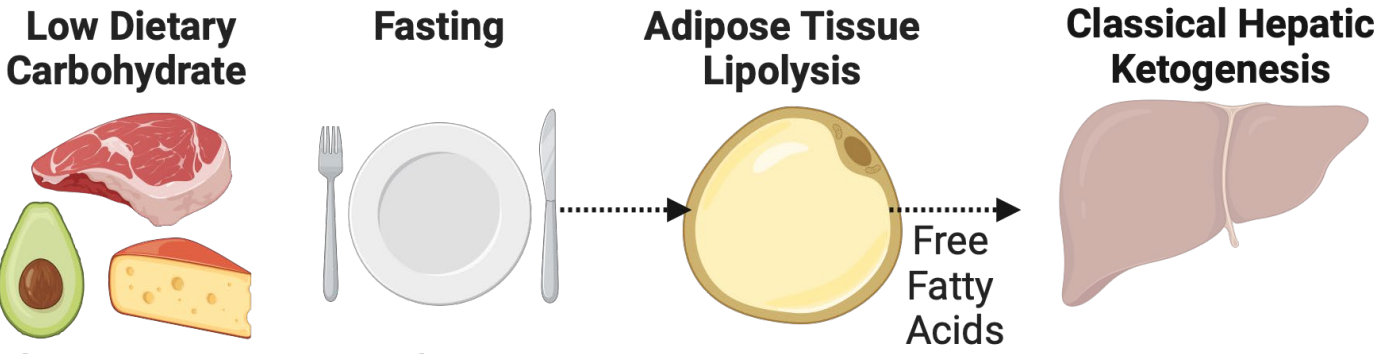
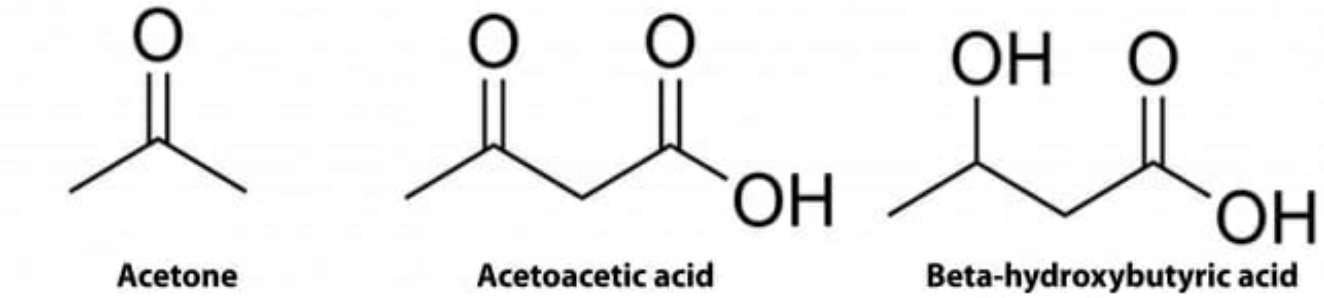
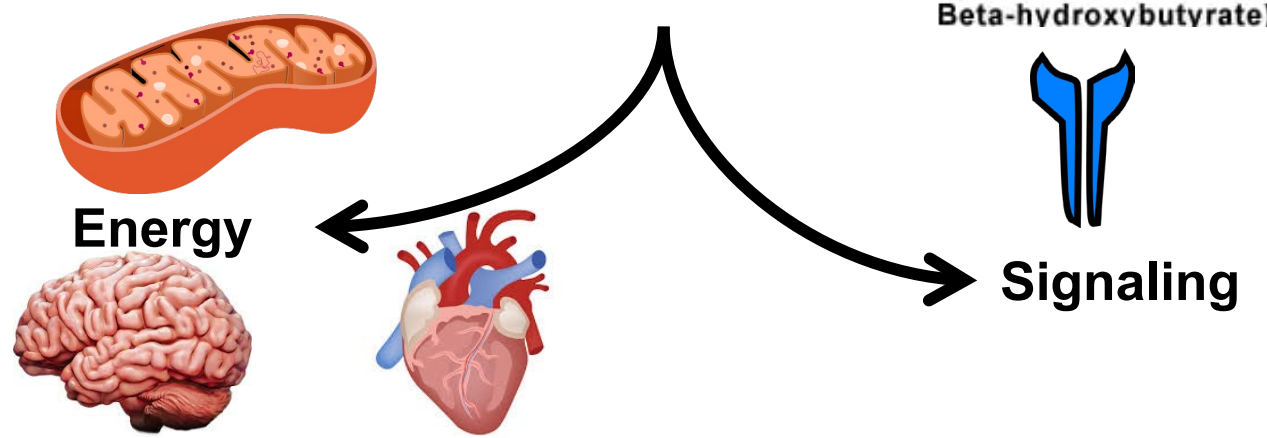
Disclosures
HVMN Inc: stock
BHB Therapeutics, Ltd: stock options
Selah Therapeutics, Ltd: Co-founder, stock options

Live better longer.

Ketone bodies are an energy and signal







BHB as a Signaling Metabolite

Feedstock for other metabolites
- e.g. GABA

Covalent protein modifications
- **BHBylation** → gene expression

Non-covalent enzyme regulation
- **HDACs, NLRP3, hnRNPA1**
- → gene exp., senescence, inflammation

Receptor agonism/antagonism
- **FFAR3, HCAR2** → metabolism, inflammation

Interacting with microbiome
- Abundance, metabolites, host immune

Key BHB intersections with hallmarks of aging

Epigenetic alterations
Loss of proteostasis
Deregulated nutrient sensing
Mitochondrial dysfunction
Cellular senescence
Stem cell exhaustion
Chronic inflammation
Dysbiosis

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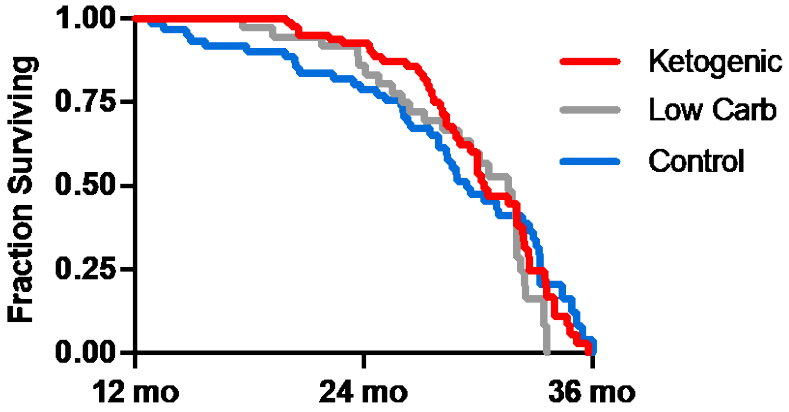
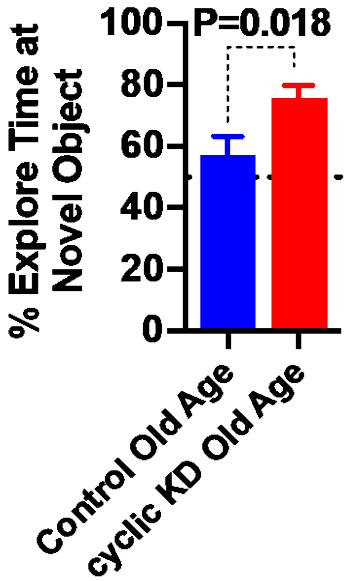
Ketogenic diet is linked to improved healthspan and lifespan





Newman and Verdin, Buck

Cell Metabolism

Ketogenic Diet Reduces Midlife Mortality and Improves Memory in Aging Mice

Short Article

Functional benefits of KD in multiple domains

Decreased insulin/IGF signaling

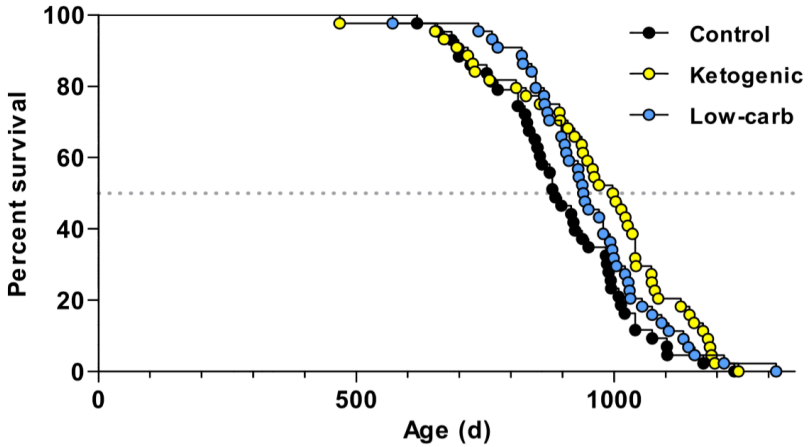
Mitochondrial biogenesis

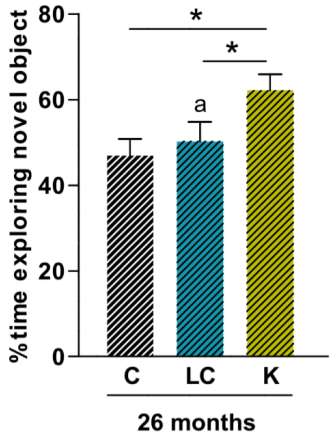
Preservation of skeletal muscle ***[Roberts 2017]***

Cognitive function (esp. AD) ***[Grammatikopoulou 2020]***

Synapse remodeling ***[Aucña-Catalán 2024]***

Decrease pro inflammatory gut microbiota ***[Ang 2020]***





Jon Ramsey, UC Davis

Cell Metabolism

A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice

Short Article

However – not all evidence is supportive…

KD may increase cellular senescence via p53 ***[Wei 2024]***

KD can be obesogenic in rodents and humans

Poorly formulated KD can adversely affect lipids

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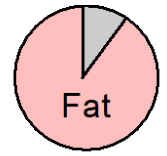
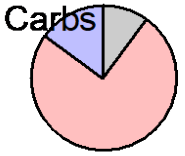
A mechanistic hierarchy for hyperketonemia ft. exogenous ketones



Ketogenic

Ketogenic diet

Carbohydrate Restriction



High fat

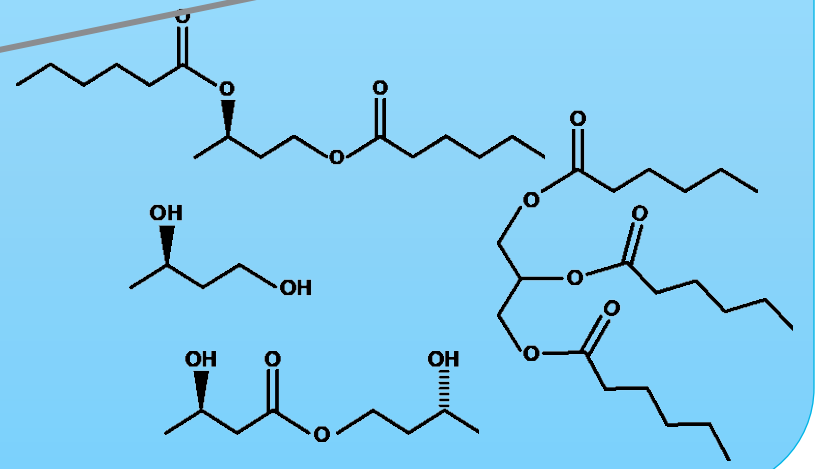
Ketogenesis

Hyperketonemia (BHB/AcAc)

Energetics

Signaling

Exogenous ketones



Key facts about exogenous ketones

- Increase blood [BHB] > 0.5 mM in minutes with no other diet changes
- Resulting ketosis lasts 1-5h
- Many types exist with different properties (not all created equal)
  - Ketone salts, medium chain triglycerides, BHB acid, ketogenic alcohol
  - We focus on **ketone esters**

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Cutting Edge: Translating Ketone Esters for Age Related Disease

Advantages
- No need for diet changes
- Isolate the effects of ketone bodies

Perceived Disadvantages
- Cost
- Compliance?
  - Large doses, short acting, poor taste
- Safety?

Key gaps in ketone ester literature…
- Longest study = 28 days
- No study in older adults >65y
- Some studies of age-related disease but no proof-of-concept study of aging biology

Case studies of two ARD indications

Heart Failure
- Reduction in cardiac output
- Shift in myocardial metabolism

Proposed mechanism of action - ketones
- Increase cardiac output
  - Increase heart rate (direct)
  - Decreased systemic vascular resistance (indirect)
  - Improved energetics? Substrate supply
- Reduced cardiac re-modelling

Frailty
- Dwindling' – weakness, slowness, decreased physiologic reserve, vulnerability
- Increases risk of disability

Proposed mechanism of action - ketones
- Address glucose hypometabolism
- Reduce NLRP3 mediated inflammation
- Anti-catabolic

Cognitive impairment is also a leading indication…

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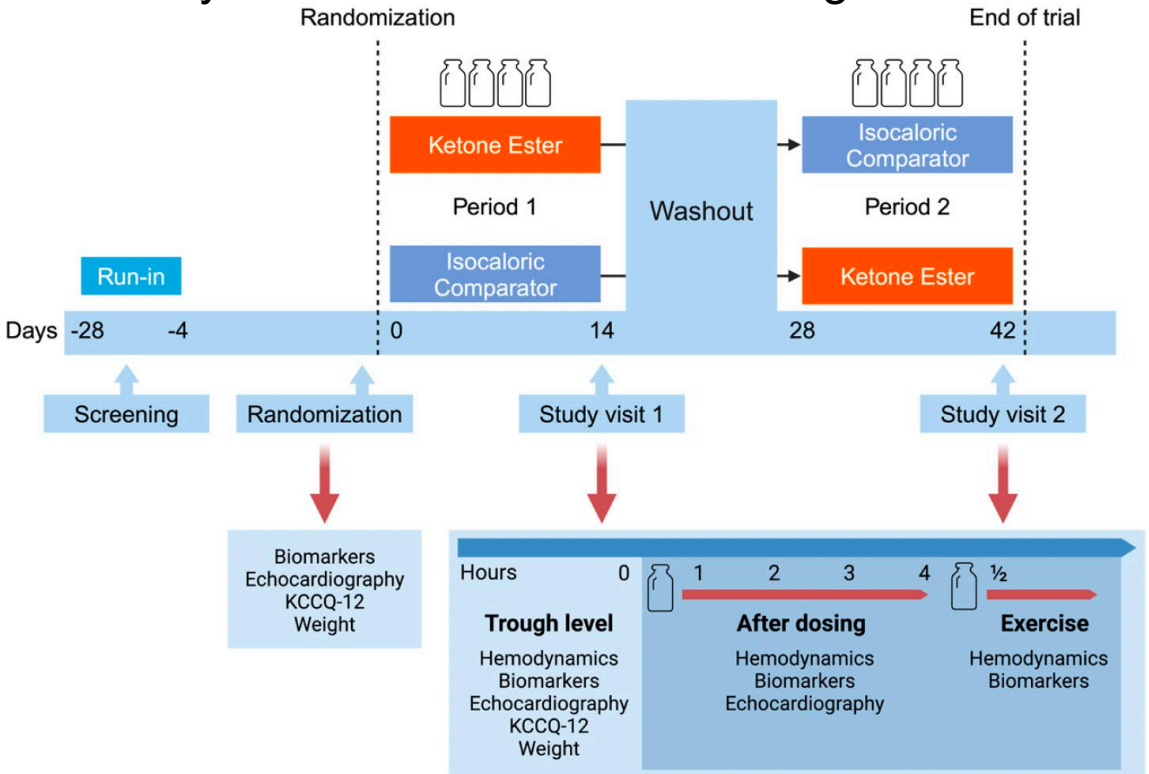
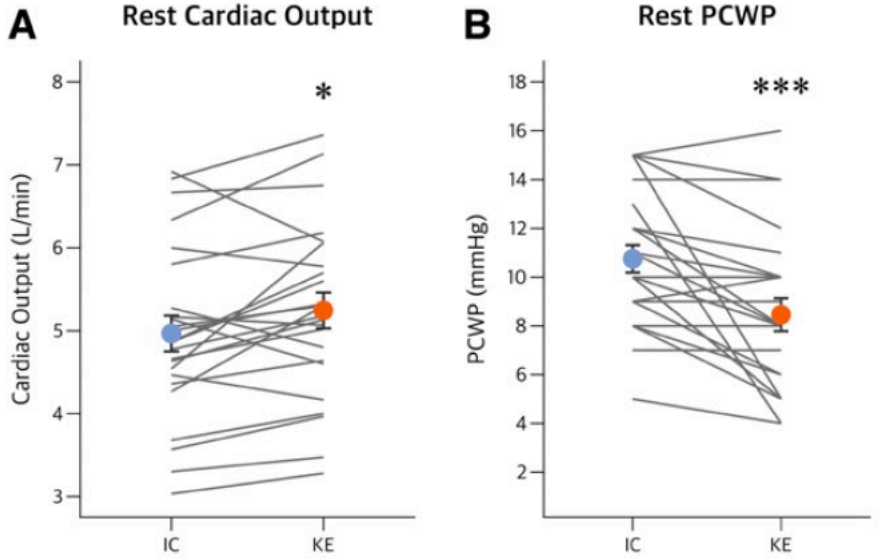
Age Related Disease: KE for Heart Failure

Berg-Hansen, K., et al., *Cardiovascular Effects of Oral Ketone Ester Treatment in Patients With Heart Failure With Reduced Ejection Fraction: A Randomized, Controlled, Double-Blind Trial.* Circulation, 2024. **149**(19): p. 1474-1489.

- **PREVIOUSLY:** Acute infusion of ketones increased cardiac output in healthy adults and patients with HFrEF
- **THIS STUDY:** Randomized, double-blind, comparator-controlled, crossover trial (NCT05161650)
- n = 24 HFrEF patients (mean age ~65 y)
- 14 days of ketone ester and PLA ingestion



- Improved hemodynamics at rest and during exercise
  - Increased cardiac output
  - Elevated left ventricular ejection fraction.
  - Reduced measures of congestion (pulmonary capillary wedge pressure, left atrial and ventricular volumes, and natriuretic peptides.)
- The CV effects persisted during incremental exercise.



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Age Related Disease: KE for Frailty – PILOT STUDY

NCT05585762

Screening & Consent

Kinetics
KE Beverage
n = 30

Week 0

Baseline:
Vitals, Labs, Physical, Cognitive, QoL, Biospecimen
n = 29

Week 1 (acclimation)

12.5g KE
0.5 bottle per day

Placebo
0.5 bottle per day

Week 2

25g KE
1 bottle per day

Placebo
1 bottle per day

Week 4

Safety:
Vitals, Labs

Week 12

Final:
Vitals, Labs, Physical, Cognitive, QoL, Biospecimen
n = 23

Kinetics
KE Powder
n = 21

TOLERANCE

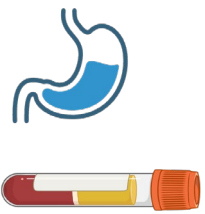
Confirm kinetics in the target (older) population

Specifically test safety and tolerability in the target population

Look for a signal in clinically meaningful, standardized outcomes

Mechanistic biomarker outcomes

N = 30 healthy older adults >65y (mean = ~75y)
Randomized, double blind, placebo-controlled pilot study
Primary outcome: Tolerability and safety



Clinical Outcomes

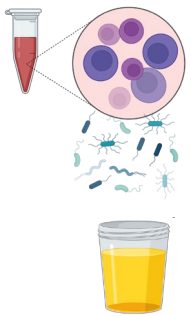
Tolerability
Tolerance questionnaire

Safety measures
Blood and urine lab tests
Vital signs

Physical function
1 rep max leg press, 6MWT, grip strength, SPBB

Cognitive function
MoCA, DSTT, Trails A and B

Quality of life / daily function
Sleep, mood, sexual function, fatigue



Biospecimens

Plasma
Proteomics, Metabolomics, Cytokines, Lipidomics

White Blood Cells (PBMCs)
Immunophenotyping
DNAm clocks

Stool
Microbiome

Urine
NMR Lipidomics

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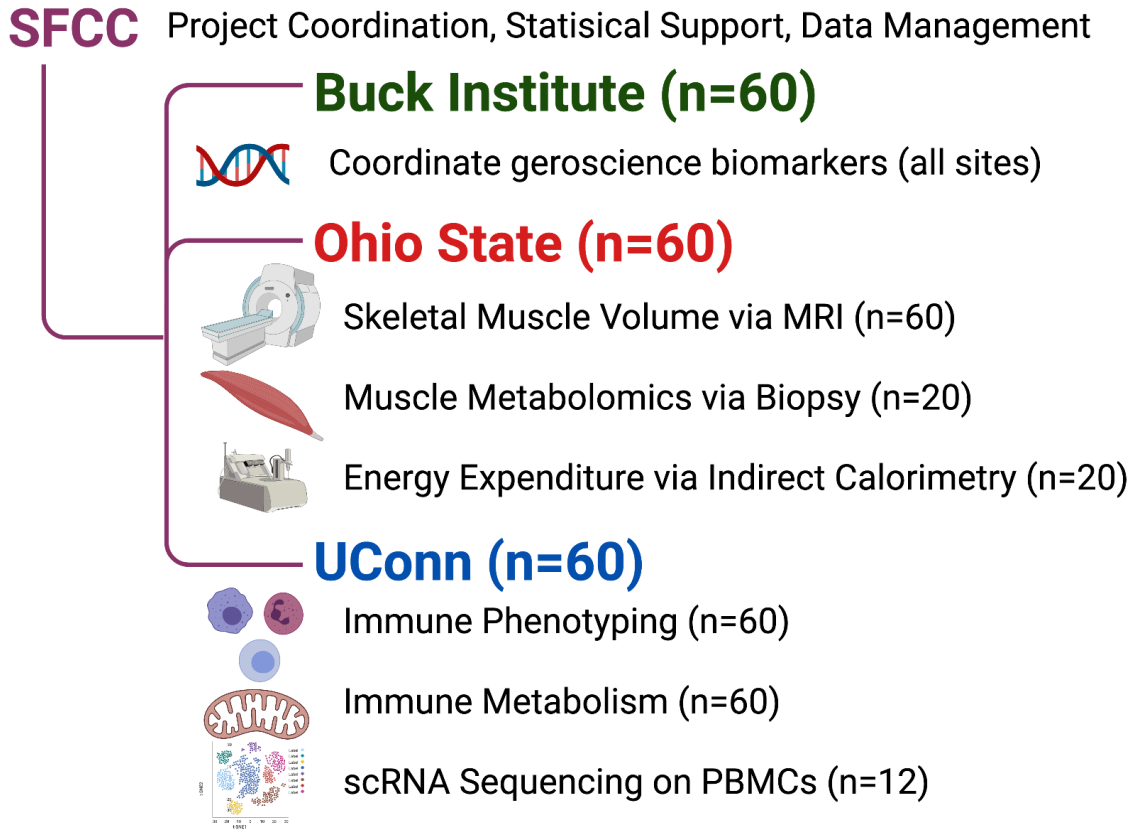
Future Directions – ready for TAKEOFF

- **TAKEOFF: T**argeting **A**ging with a **K**etone **E**ster for **F**unction in **F**railty (R01) – Enrollment Fall ‘24
- Increased sample size (n =180)
- Increased KE daily serving
- Pre-frail population
- Primary outcome = composite frailty score
- 20-week duration
- Additional immunophenotyping and muscle/metabolic outcome measures



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Summary and gaps

BHB and similar metabolites have diverse signaling activities in addition to energetic functions

Both energy and signaling functions are relevant to aging

---------- GAPS ----------

Dosing strategies / kinetics / duration / etc largely unknown

Human data on signaling functions are lacking

Optimal mix of energy/signaling unknown for specific conditions

High-quality large RCTs for diseases/conditions

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Thank you!

Collaborators:

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Buck Institute

Buck Institute Impact Circle

Dr. James Johnson

Protocol

Kinetic data

Tolerability/ safety data

https://clinicaltrials.gov/study/NCT05585762

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Live better longer.