REAGAN-UDALL FOUNDATION FOR THE FDA

Affecting the Aging Trajectory:

Regulatory Constructs for Gerotherapeutic Drug, Biologic & Device Development

Hybrid Public Meeting

May 27, 2026 | 10am-4pm *(eastern)*

ARPA-H and XPRIZE Foundation provided funding for this meeting

REAGAN-UDALL FOUNDATION FOR THE FDA

Welcome

Susan C. Winckler, RPh, Esq.

Chief Executive Officer
Reagan-Udall Foundation for the FDA

Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

For virtual participants: Your microphone and video will remain off during the meeting

Questions may be submitted at any time:
Virtual participants may use the Zoom Q&A function
In-person participants may use the question cards available in the room

This public meeting is being recorded

The slides, transcript, and recording will be available at www.ReaganUdall.org

Agenda

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10am	Welcome & Opening Remarks
10:20am	The Healthspan Imperative: Geroscience, Federal and Private Sector Investment, and the Evidence Base
10:45am	Landmark Evidence: What Aging Trials Have Taught Us About Endpoints, Populations, and Feasibility
11:30am	Toward Regulatory Constructs: Intrinsic Capacity, Adult Health Curves, & Multi-Domain Endpoints
12:15pm	Lunch

1:05pm	XPRIZE Healthspan and PROSPR Awardees: Evidence Being Built at Scale
2:05pm	Regulatory Landscape: What Pathways Exist, Where They Break Down, and What Constructs Are Needed
2:25pm	Industry Perspectives: What Product Sponsors Need from FDA to Bring Gerotherapeutics to Market
3:05pm	Next Steps to Designing Workable Regulatory Constructs for Gerotherapeutics
3:55pm	Closing Remarks
4pm	Adjourn

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Opening Remarks

Steven Kozlowski, MD

Chief Scientist - Office of the Chief Scientist
Office of the Commissioner
U.S. Food and Drug Administration

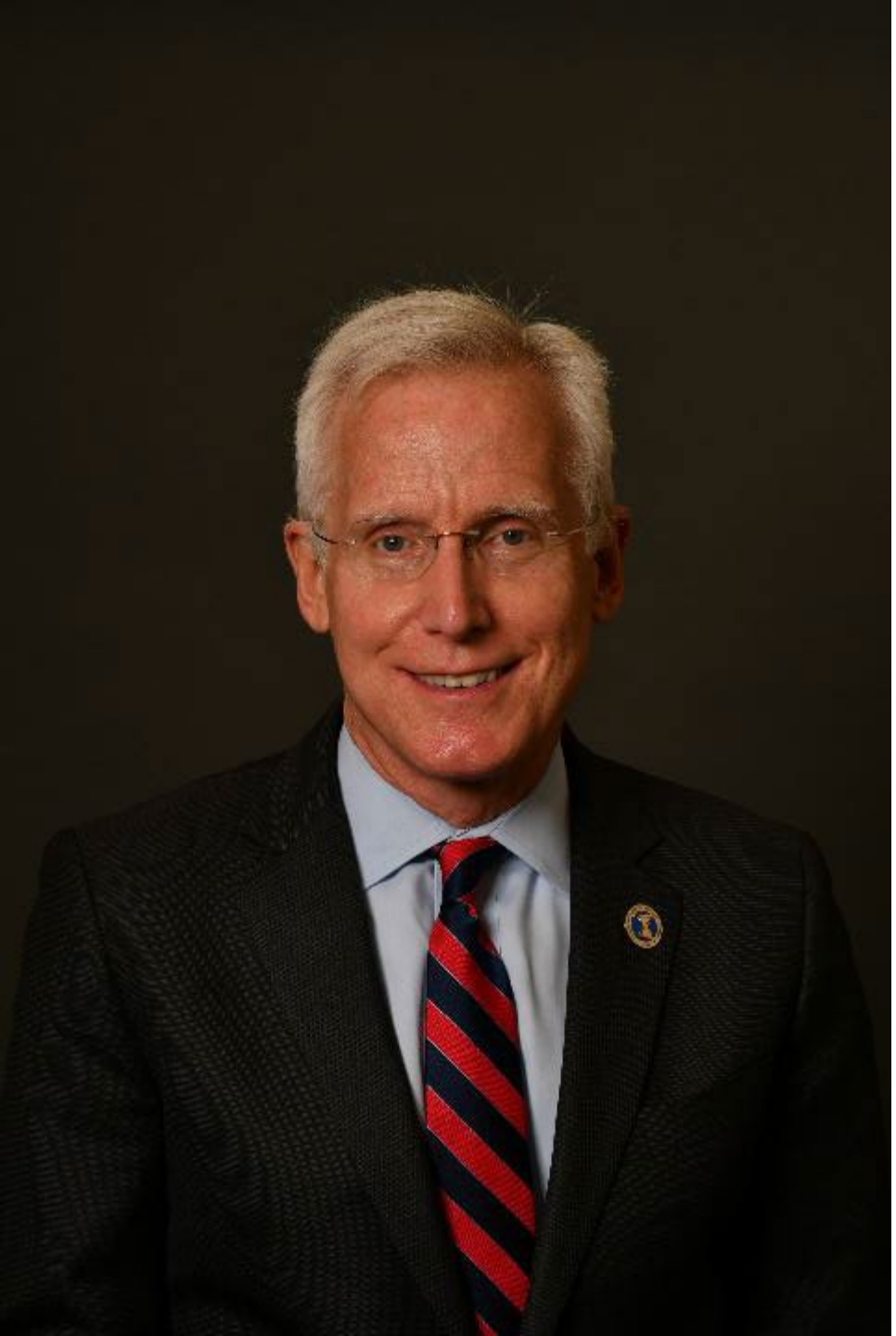
The Healthspan Imperative

Geroscience, Federal and Private Sector Investment, and the Evidence Base

REAGAN-UDALL FOUNDATION FOR THE FDA

<u>Presenters</u>

- **James Appleby, BSPharm**, MPH, CEO, Gerontological Society of America
- **William Greene, MD**, Chief Investment Officer, Hevolution Foundation
- **Jamie Justice, PhD**, Executive Director, XPRIZE Healthspan, XPRIZE Foundation
- **Andrew Brack, PhD**, Program Manager, PROactive Health Office, ARPA-H



REAGAN-UDALL FOUNDATION FOR THE FDA

James Appleby, BSPharm, MPH

CEO

Gerontological Society of America

GERONTOLOGICAL SOCIETY OF AMERICA®

Applying Geroscience to Improve Healthspan

James C. Appleby, CEO

Gerontological Society of America

Vision: Meaningful Lives As We Age

Mission: Foster excellence, innovation, and collaboration to advance aging research, education, practice, and policy.

- 6,500 experts in aging
- Researchers, clinicians, and educators
- Scholars from 26 academic disciplines
- Study all facets of aging
- Life course orientation

Geroscience defined

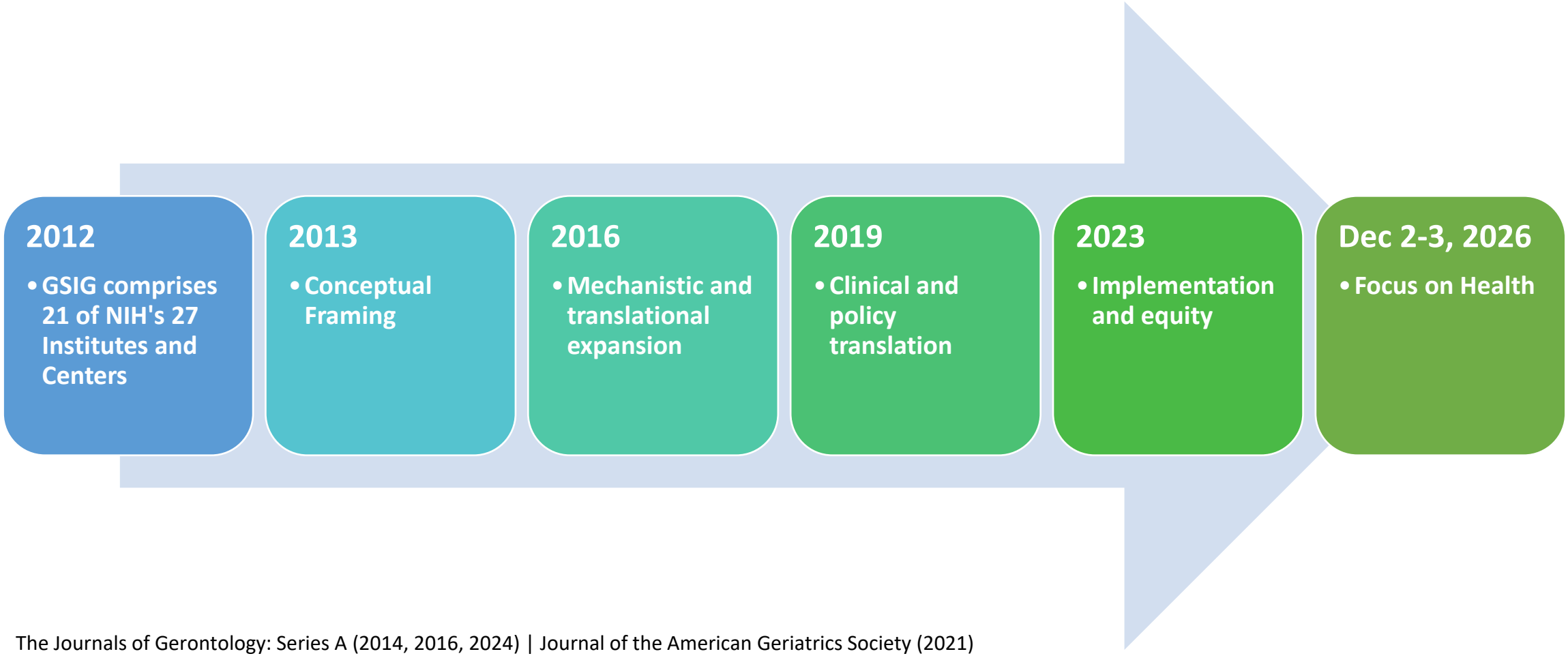
Geroscience is the interdisciplinary field that studies the biological mechanisms of aging to understand how they drive the onset and progression of chronic diseases and age-related conditions.

Key concepts:

- The fundamental biology of aging is the greatest risk factor for almost all chronic diseases.
- By slowing or manipulating the aging process, we can delay the onset of multiple age-related illnesses.
- The goal is to extend healthspan—the period of life spent in good health, free from chronic disease and disability—rather than just total lifespan.
- https://www.afar.org/what-is-geroscience-2

Development of the Field

NIH Geroscience Interest Group (GSIG) & Summit Milestones



The Journals of Gerontology: Series A (2014, 2016, 2024) | Journal of the American Geriatrics Society (2021)

Key Considerations

- Communications - Slowing vs reversing aging?
- Geroscience is not the same as geriatric medicine.
- When in the life-course will interventions be applied?
- Geroscience is a multidisciplinary endeavor.
- Interventions need to be widely available to all.
- Essential to support development of new geroscientists.
  (GSA is hosting Geroscience Education & Training Network-2)
- Essential to listen to both scientists AND patients/consumers.

GSA 2026
November 4–7
National Harbor, MD

Reinforcing Resilience in Aging Science, Research and Education.

See you at the Harbor!

Discover cutting-edge research, fresh perspectives, and opportunities to connect with leaders in aging and gerontology at the GSA 2026 Annual Scientific Meeting.

- 4,500 + Attendees
- Attendees from 44+ Countries
- 1,316+ Symposia
- 701+ Papers
- 2,049+ Posters

REAGAN-UDALL FOUNDATION FOR THE FDA

William Greene, MD

Chief Investment Officer
Hevolution Foundation

HEVOLUTION

Bridging the Gap Between Lifespan and Healthspan

Today, 1 billion people are over 60 — and every region is aging

Aging across the world | A universal trend

Per WHO: populations will continue to age even as totals plateau

Today
Nearly 1 in 7 people on earth is **over sixty**.

By 2050
2.1 billion — one in five people on earth.

The shift
Rising life expectancy. Falling birth rates. Aging is **compounding**.

Japan
Median age **48 today**, projected to hit **54 by 2050**, and dependency ratio inverts

Emerging markets
China, Cuba, Italy, Spain, S. Korea all projected to exceed a median age of **50 by 2050**.

WHO, Ageing and Health Fact Sheet (2025); UN World Population Prospects (2024 Revision).

10 YEARS

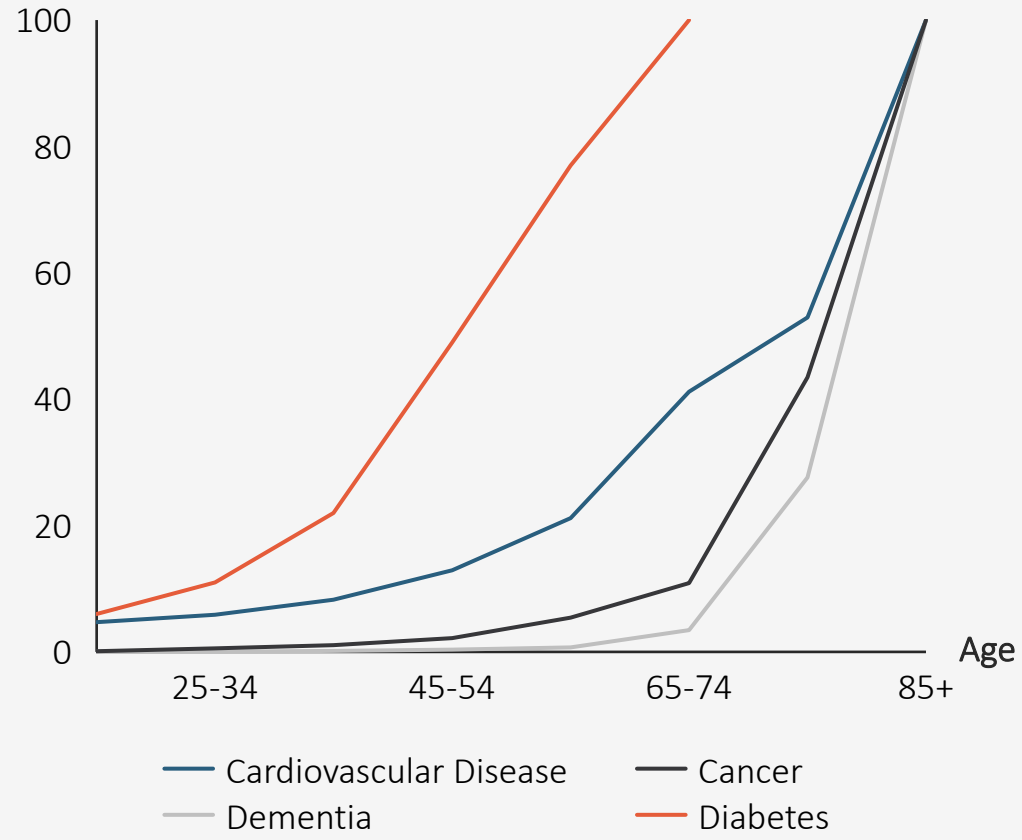
The decade we lose - everyone, everywhere

Years of Life Lost to Poor Health: By WHO Region

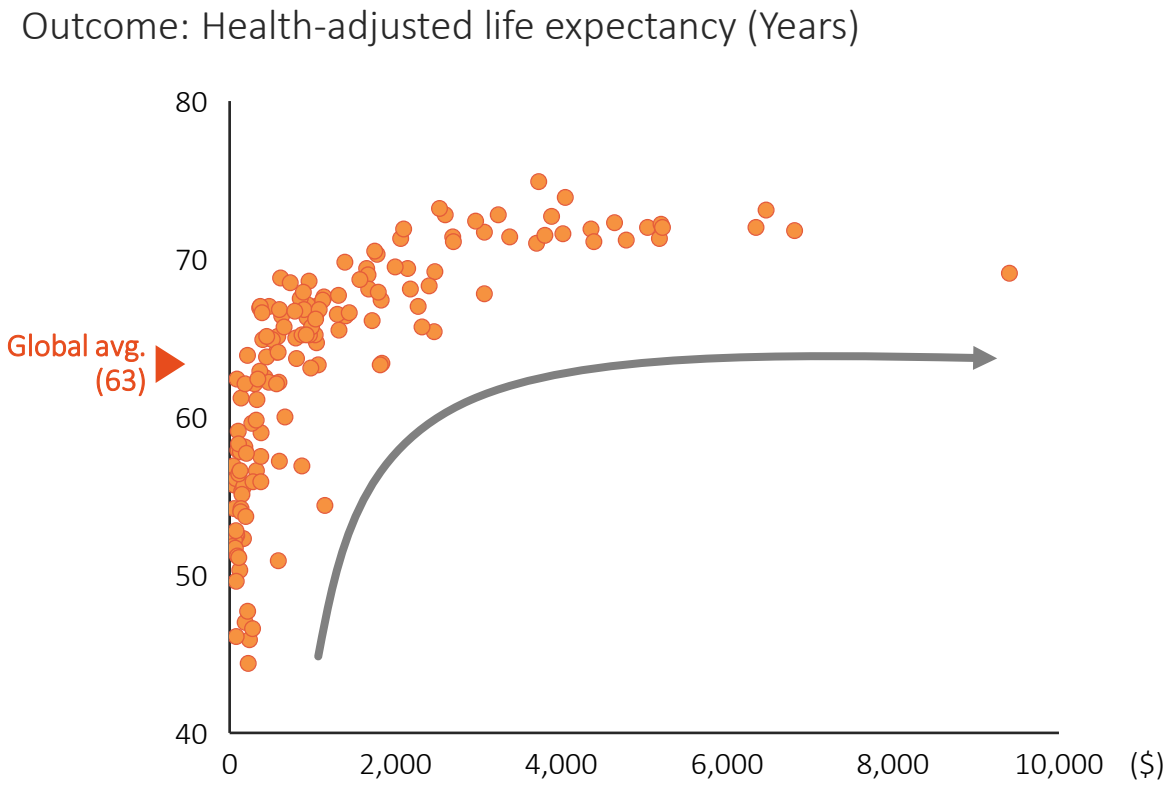
Region	Lifespan	HALE	Gap (Years)
Global	73.4	63.7	9.7
Americas	77.2	66.2	11.0
Europe	78.2	68.3	9.9
Western Pacific	77.7	68.6	9.1
South-East Asia	71.4	61.5	9.9
Eastern Mediterranean	69.7	60.4	9.3
Saudi Arabia	74.3	64.0	10+
Africa	64.5	56.0	8.5

Source: WHO Global Health Estimates (2021); Hevolution Foundation.

Age is the No. 1 risk factor for most major diseases today



…. And the current approach is NOT creating additional gains

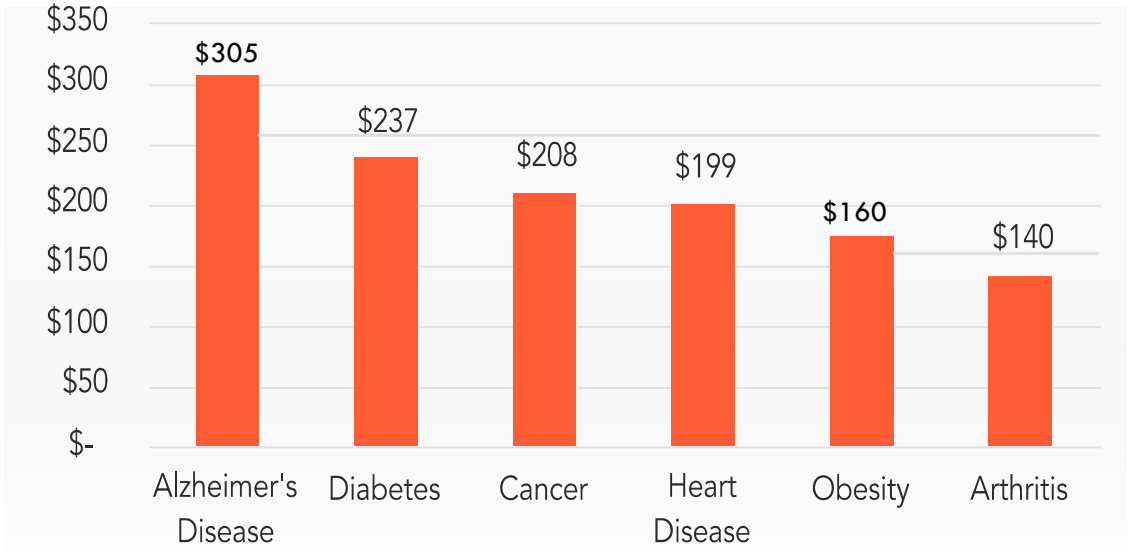


Spend: Health expenditure per capita ($ PPP)

Sources: WHO, The World Bank, American Heart Association, Kaiser Family Foundation

Economic Imperative | Age-related diseases carry massive health and economic costs

Annual direct costs of age-related diseases in the US ($Billions)



Source: US Centers for Disease Control and Prevention (CDC)

- In the U.S. alone, we spend over $1 trillion per year treating major age-related diseases; growing rapidly
- Indirect costs such as those incurred due to loss of economic productivity drastically increase this number
- Pension systems designed for 65-year life span are funding lives to 85. The math does not add up
- Costs in the U.S. for Alzheimer's alone are projected to reach $1.1 trillion by 2050

If we could intervene in aging, society would reap **substantial benefits**:

- **Reduce age-related diseases via a shift from reactive amelioration to proactive treatment and prevention**
- **Diminished vulnerability to future disability, increased individual productivity, and decreased healthcare costs globally**
- **Compress morbidity by just 12 months → trillions of dollars per year in healthcare savings and productivity gains**

Hevolution Foundation | *Global Non-profit aiming to expand healthy lifespan for the benefit of all humanity*

- Hevolution is dedicated to understanding the processes of aging and translating innovation in the emerging field of healthspan
- We provide grants and early-stage investments to support independent research and entrepreneurship aiming to extend healthy years of life for people everywhere

Our Vision

To extend healthy lifespan for the benefit of all humanity.

Our Mission

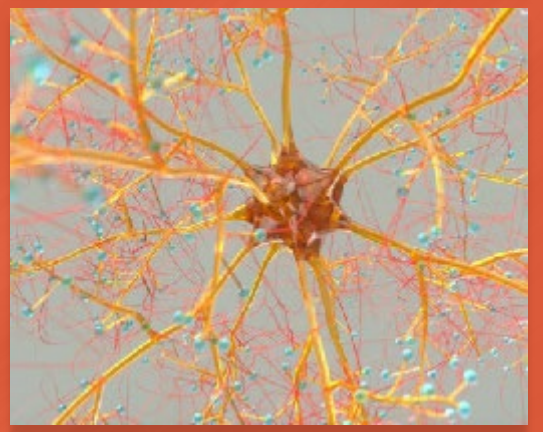
Drive efforts to extend healthy human lifespan and understand the processes of aging, leveraging a broad set of tools through diverse approaches

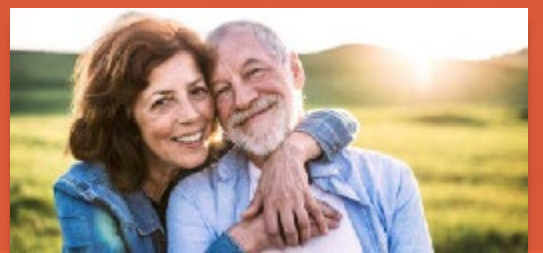
Our Progress

Established under Royal Order in the Kingdom of Saudi Arabia, Hevolution brings together the best experts from around the world to solve humanity's most pressing challenge: *Unhealthy aging*.

Since publicly launching in 2022, Hevolution has allocated over $400 million through grants and investments to advance progress in this field.

HEVOLUTION




What we've done so far

HEVOLUTION

$400 Million

Deployed in under three years. ~200 grants. 25+ partnerships. The largest philanthropic funder in the field.

HEVOLUTION

Global Healthspan Summit 2025

World's Largest

Convening that brought together the UN, the WHO, and the field's leaders.

XPRIZE HEALTHSPAN

$101 Million

A ten-year global prize to restore a decade of healthy function. Hevolution is the lead funder.

HEVOLUTION

Investments

Leading healthspan investing voice globally driving innovation and catalyzing clinical translation.

Hevolution Investments

Strategic venture-capital arm of the Hevolution Foundation *— backing therapies, platforms, and technologies to extend human healthspan*

800+	60+	Global	Convener
pipeline opportunities evaluated to date	years combined team experience in aging & VC	leading voice in healthspan investing	Catalyst uniting Pharma, VCs, CROs, and academia

Where we invest | *Focus areas across the healthspan stack*

01 Biotherapeutics

Novel therapeutics targeting the biology of aging –small molecules, biologics, advanced therapies to treat chronic disease.

02 Systems Biology

Multi-omic platforms, pathway mapping, and combination strategies that address aging as a root cause.

03 Data Platforms

Data-enabled discovery — AI / ML, longitudinal biomarker datasets, and software tools that accelerate target discovery and clinical validation.

Big Pharma | US Venture Capital | European Venture Capital | International CROs | Aging Biologists

Only together can we overcome one of the greatest challenges facing humanity: Unhealthy aging

HEVOLUTION


HEVOLUTION
Thank You

REAGAN-UDALL FOUNDATION FOR THE FDA

Jamie Justice, PhD

Executive Director, XPRIZE Healthspan

XPRIZE Foundation


Can a drug, biologic, or device affect how we age?

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD | GSK

PRIZE PURSE

$101 MILLION PRIZE

$10 MILLION BONUS

BREAKTHROUGH

Seven year global competition to advance proactive, accessible therapeutics that can improve function and increase human healthspan.


If a medicine could improve how we age…
… how would we know?

TESTING & JUDGING

10+ Finalist Teams will begin 1-year randomized controlled clinical trials in 2026.

The **WINNING TEAM** must demonstrate that their therapeutic treatment restores muscle, cognitive, and immune function in older persons. The therapeutic treatment must take 1-year or less..

TESTING & JUDGING

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The **WINNING TEAM** must demonstrate that their therapeutic treatment restores muscle, cognitive, and immune function in older persons. The therapeutic treatment must take 1-year or less.

Awarding of the best team is indexed to **response thresholds** that surpass age-related declines expected over 10 years, 15 years, or 20 years in referent populations.

XPRIZE HEALTHSPAN FINALS

10+ TEAMS TO RUN 1-YEAR RCTs | AUG 2026 - DEC 2029

COMMON PROTOCOLS

Primary Judging:

- Muscle Function
- Cognitive Function
- Immune Aging

Additional Measures:

- Clinical Characteristics
- Adverse Events & Safety
- Intrinsic Capacity
- Biomarkers

CENTRAL RESOURCES

Data Coordinating Center

HEALTH
UNIVERSITY OF UTAH

Central Labs & Biobank

UC San Diego
SAM AND ROSE STEIN INSTITUTE FOR RESEARCH ON AGING

FUTURE DEVELOPMENT

- Biomarker Discovery
- Meta-Analyses
- Patient Selection
- Surrogate Endpoint Evaluation

https://www.xprize.org/competitions/healthspan#guidelines

REAGAN-UDALL FOUNDATION FOR THE FDA

Andrew Brack, PhD

Program Manager, PROactive Health Office
ARPA-H

ARPA-H

WHY IT EXISTS	To change the course of human health
WHAT IT BUILDS	Breakthrough capabilities that open new areas of health innovation
TIMELINE	Health breakthroughs in years, not decades
WHY NOW	Designed for opportunities ready for acceleration

PROSPR

Up to $144M over 5 years

Geroscience is ready for clinical action and regulatory engagement

PROSPR will identify predictive and intervenable surrogates of hard endpoints to rapidly test therapeutics targeting aging in clinical trials

Multiple PROSPR performers will soon seek input from FDA

Conducting trials for aging is prohibitively slow and expensive

Aging trials will take too long because we don't have **short-term healthspan surrogates**

A typical drug takes 15 years and $2B. But clinical endpoints like disease onset or mortality can **take decades to manifest**

PROSPR will accelerate the translation of heathspan-extending therapeutics:

Conducting Healthspan Clinical Trials
Testing first-gen therapies using repurposed pharmacologics

Developing an Intrinsic Capacity (IC) Score
A composite measure of physiological and biochemical change intended to predict long-term health outcomes

Validating Second-Gen Longevity Interventions
Identifying novel interventions to extend human healthspan

- WHO concept
- Feel and function
- Multi-domain functional health
- ICD-11 (MG2A)

Healthspan-extending therapeutic trials are **no longer conceptual**. Cross-disciplinary teams have formed. Therapeutic assets, clinical trials, and regulatory touchpoints are on **a near-term horizon**.

Kick off: February 2026

ARPA H

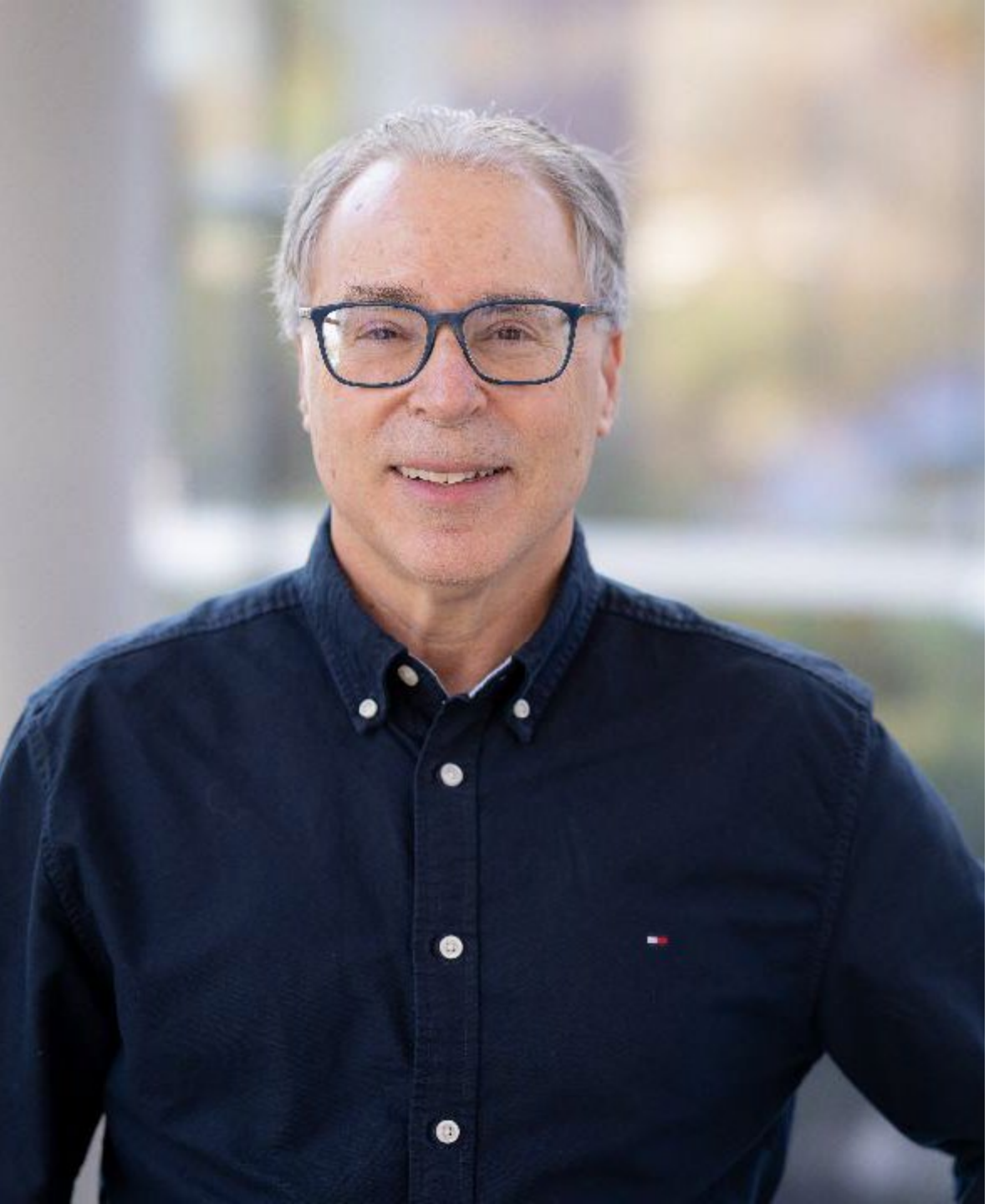
Landmark Evidence

What Aging Trials Have Taught Us About Endpoints, Populations, and Feasibility

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters

- **Nir Barzilai, MD**, Director, Institute for Aging Research, Albert Einstein College of Medicine, President of the Academy of Geroscience
- **Stephen Kritchevsky, PhD**, Professor, Gerontology and Geriatrics Internal Medicine, Wake Forest University School of Medicine
- **Joan Mannick, MD**, Chief Medical Officer, Altos Labs
- **Eric Morgen, MD, MPH, FRCPC**, Chief Operating Officer, BioAge Labs



REAGAN-UDALL FOUNDATION FOR THE FDA

Nir Barzilai, MD

Director, Einstein Institute for Geroscience

President, Academy for Geroscience

Nir Barzilai, M.D.

Professor of Medicine and Genetics
Director: Einstein Institute for Geroscience

President:

Executive-: Longevity Biotech Association
Council: The Healthy Longevity Medicine Society

(from cells to countries)

- Affecting the Aging Trajectory

What does it take to show that a drug is gerotherapeutic?

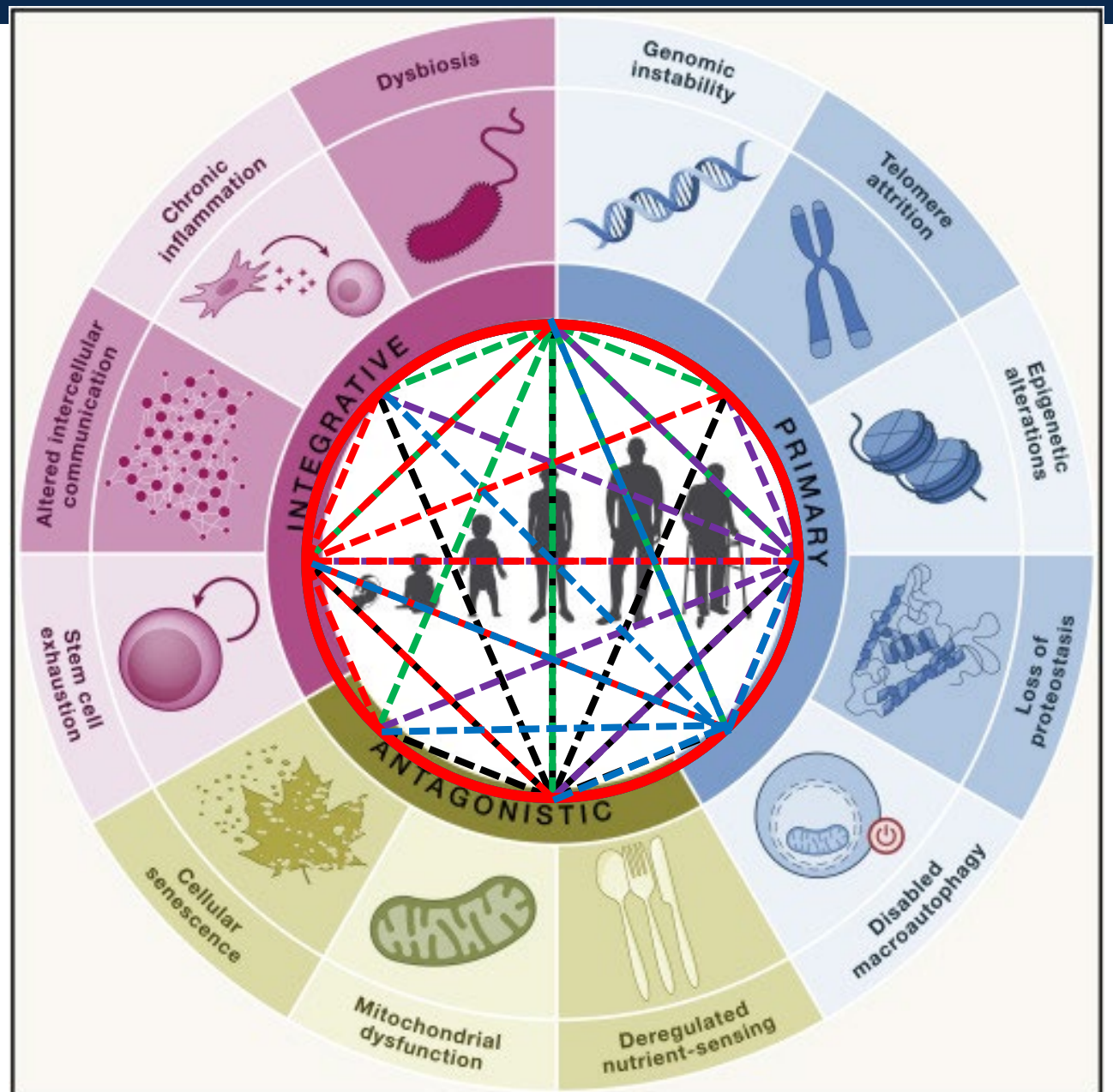
Aging has biology:

This biology drives age-related diseases (Alzheimer's, cancer, heart, diabetes...)

Aging can be targeted so that it can be delayed and some cases stopped and reversed.

Spend time optimizing your health rather than treating diseases!

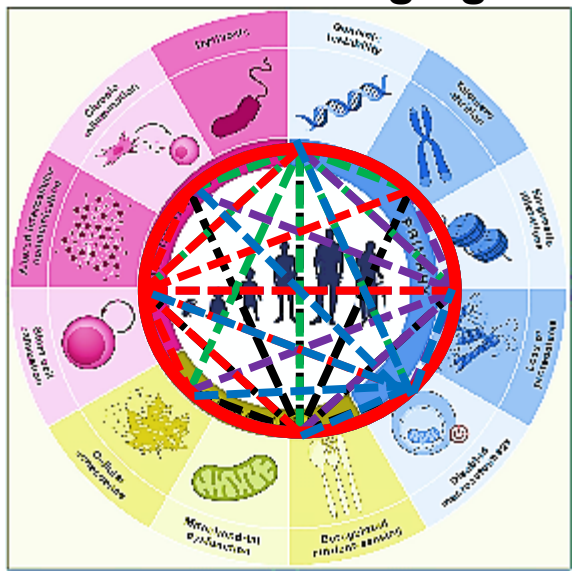
Hallmarks of Aging (mechanisms)



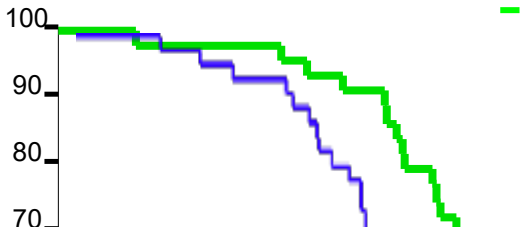
How can we assess if a drug is a gerotherapeutic?

Preclinical

Hallmarks of aging

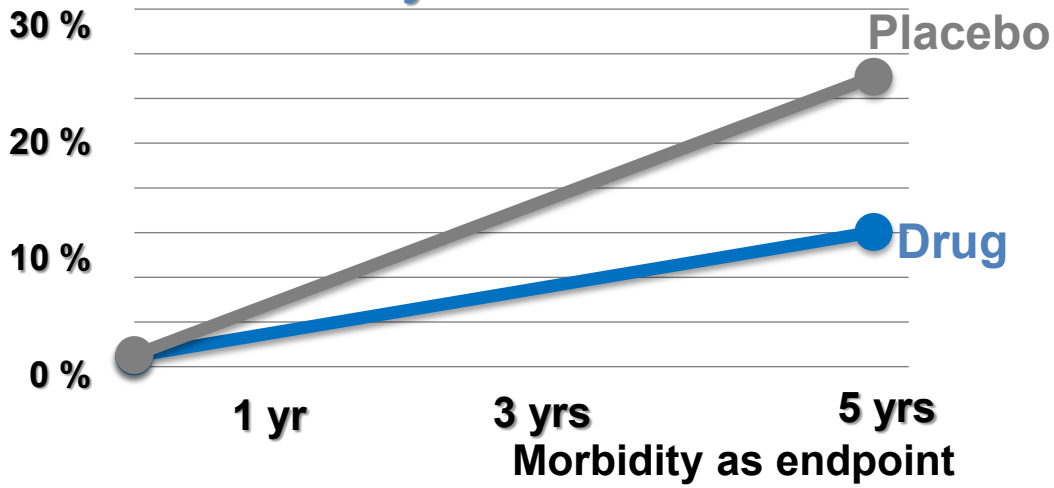


Health and life span (CR)



Clinical

Cumulative Multi-morbidity



Cumulative Overall Mortality

Repurposing (FDA approved) Gerotherapeutics

Geroscience-guided repurposing of FDA-approved drugs for aging

COVID-19 mortality

6 geroscience point | 6 clinical point | 12 total

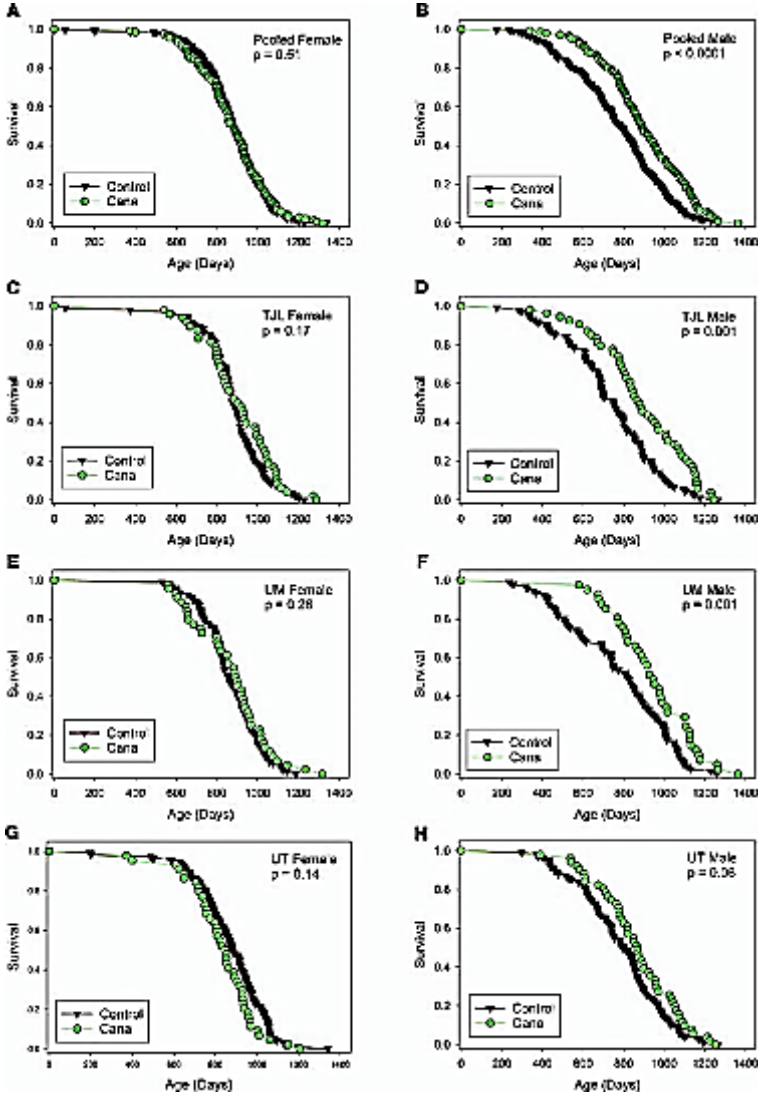
Gerotherapeutic	Hallmarks of aging	Preclinical healthspan	Preclinical lifespan	Human healthspan	Human mortality	Score (out of 12)
SGLT-2 inhibitors	2	2	2	3	3	12
Metformin	2	2	1	3	3	12
Bisphosphonates	2	2	1	3	3	11
GLP1 receptor agonists	2	2	1	3	3	12
Rapamycin/rapalogues	2	2	2	3	0	9
Acarbose	2	2	2	3	0	9
Methylene blue	2	2	2	3	0	9
ACEi/ARB	2	2	1	3	0	8
Dasatinib + (quercetin)	2	2	1	3	0	8
Aspirin	2	2	2	1	0	7
Beta blockers	1	2	1	0	3	7
N-acetyl cysteine	0	2	2	0	0	5

Aging Cell. 2022 PMID: 35343051

Medical Research Archives 2024

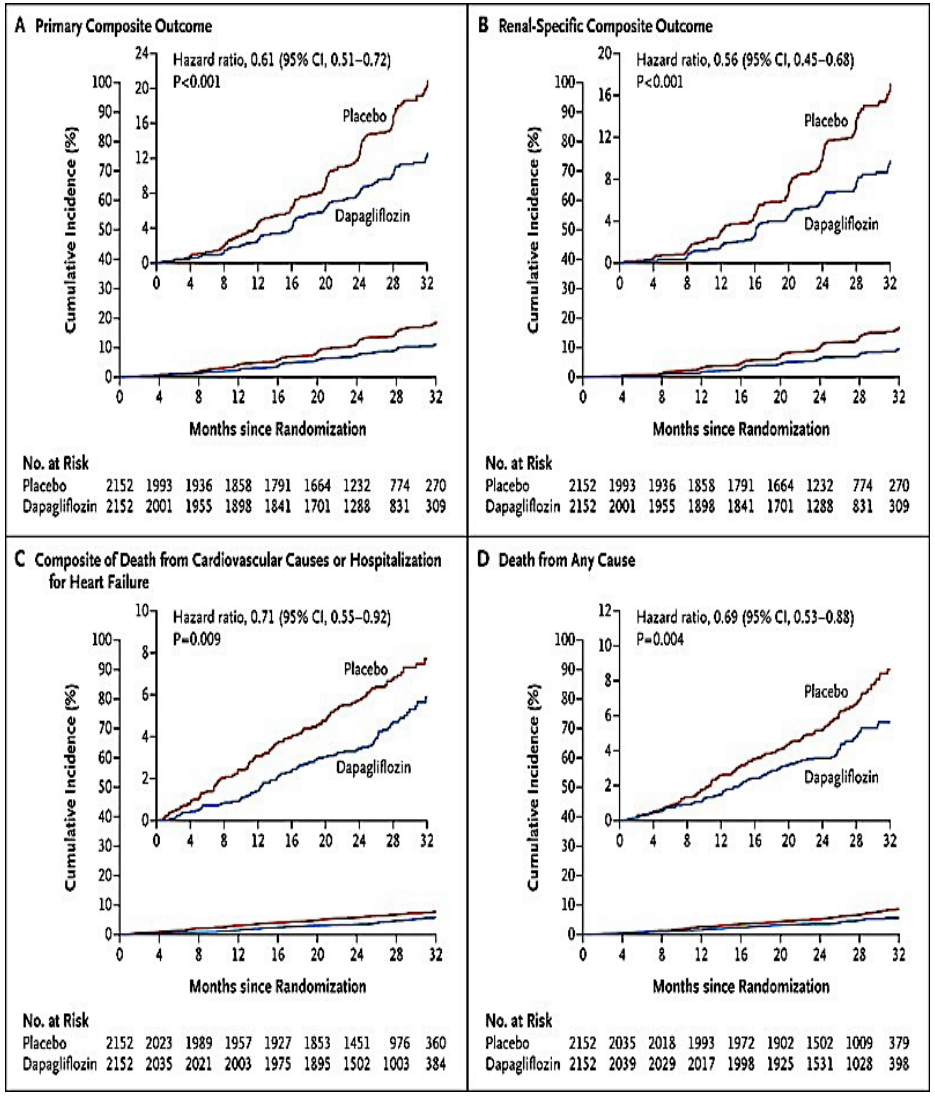
Canagliflozin extends lifespan in genetically heterogeneous male but not female mice

(Miller RA, JCI insight 10-20)



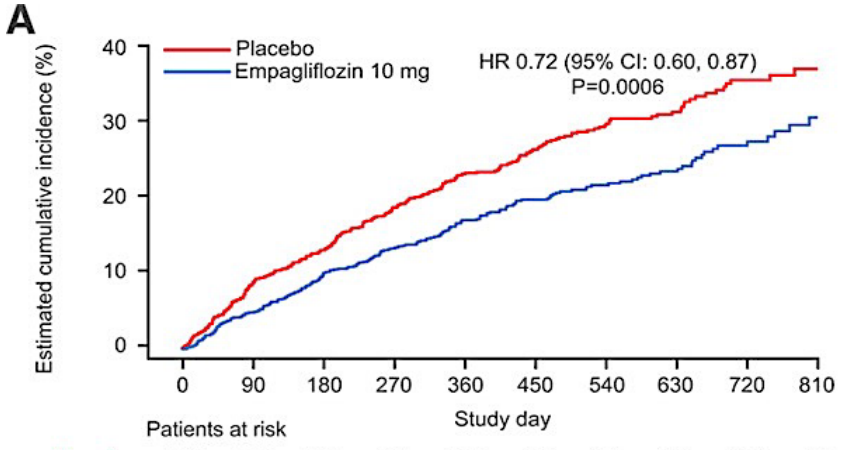
Dapagliflozin in patients with CKD

(Heerspink et at, NEJM October 8 2020)



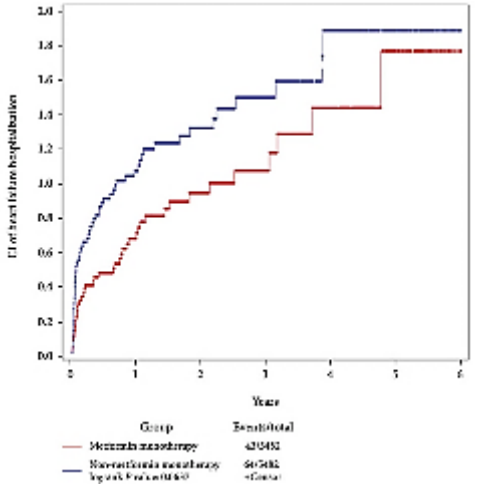
Healthspan Outcomes

SGLT2: -28% CVD and Renal



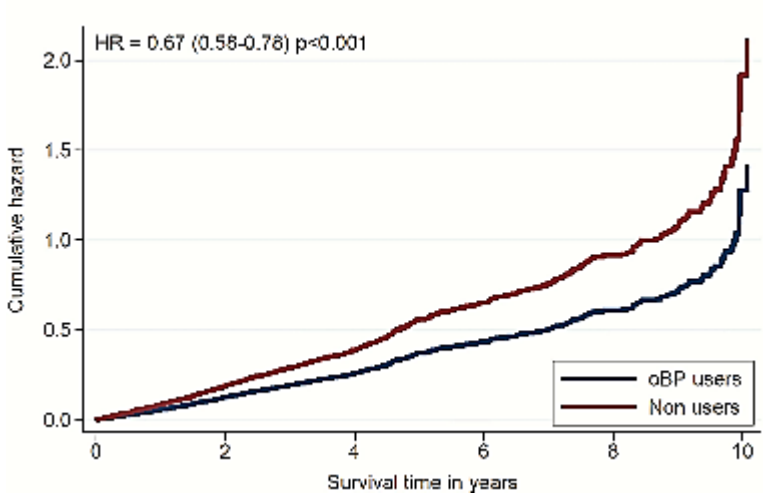
Anker et al. *Circulation*, 2021.

Metformin: - 30% HFH



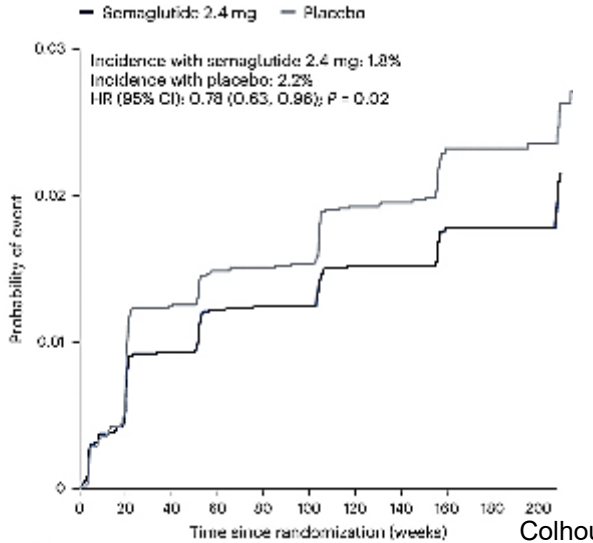
He et al. *J Diabetes Res*, 2021.

Bisphosphonates: - 33% CVD



Rodriguez et al. *J Clin Endocrinol Metab*, 2020.

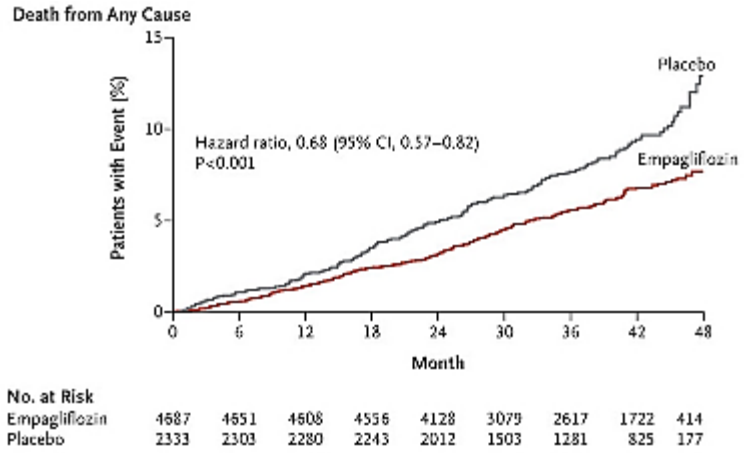
Semaglutide: - 22% Renal Outcomes



Colhoun et al. *Nat Med*, 2024.

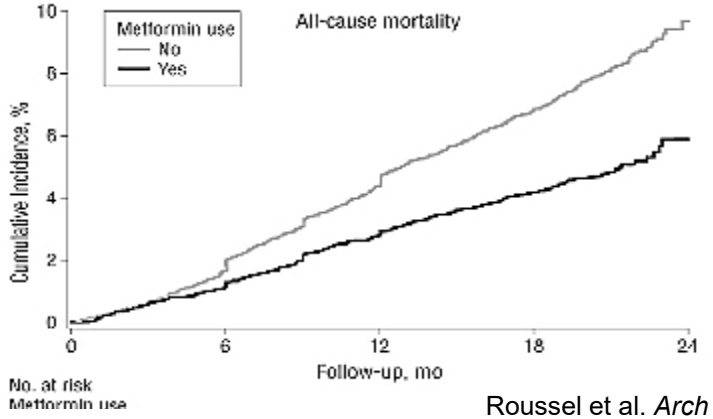
Mortality Outcomes

SGLT2: -32% any cause mortality



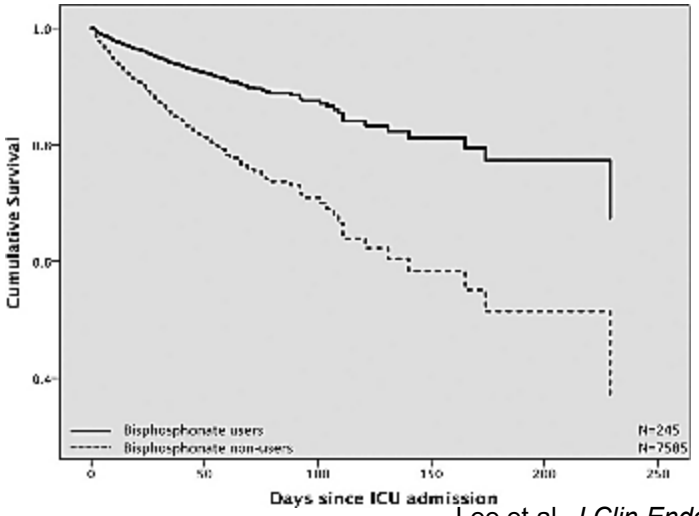
Zinman et al. *N Engl J Med*, 2015.

Metformin: - 24% mortality in Diabetics with atherothrombosis



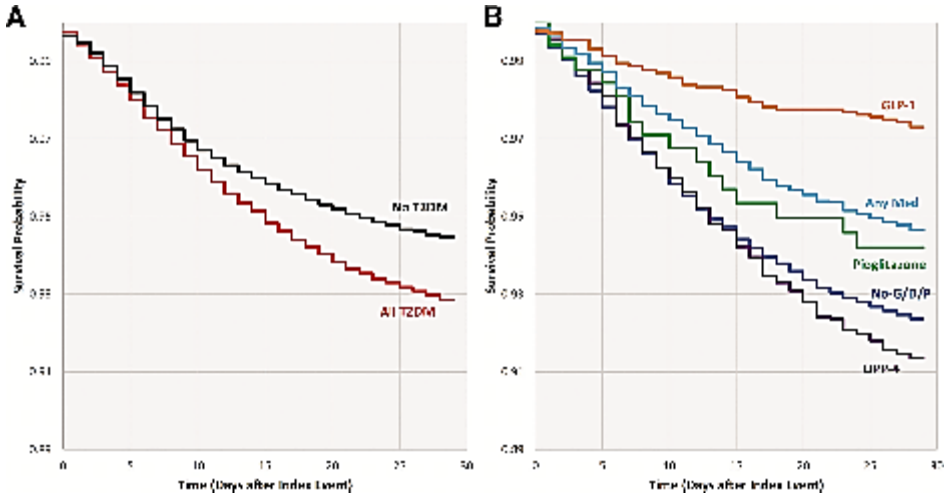
Roussel et al. *Arch Intern Med*, 2010.

Bisphosphonates: - 59% ICU mortality



Lee et al. *J Clin Endocrinol Metab*, 2016.

GLP-1: - 43% mortality



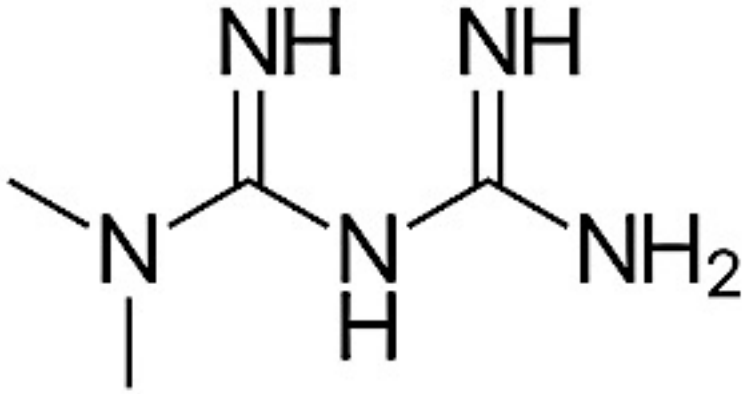
Nyland et al. *Diabetes*, 2021.

Examples of repurposed drugs (Legal, but with NO FDA approval)

Metformin repurpose:

- **Obesity**
- **PCOS**
- **Prediabetic**
- **COVID-19**

Macular Degeneration

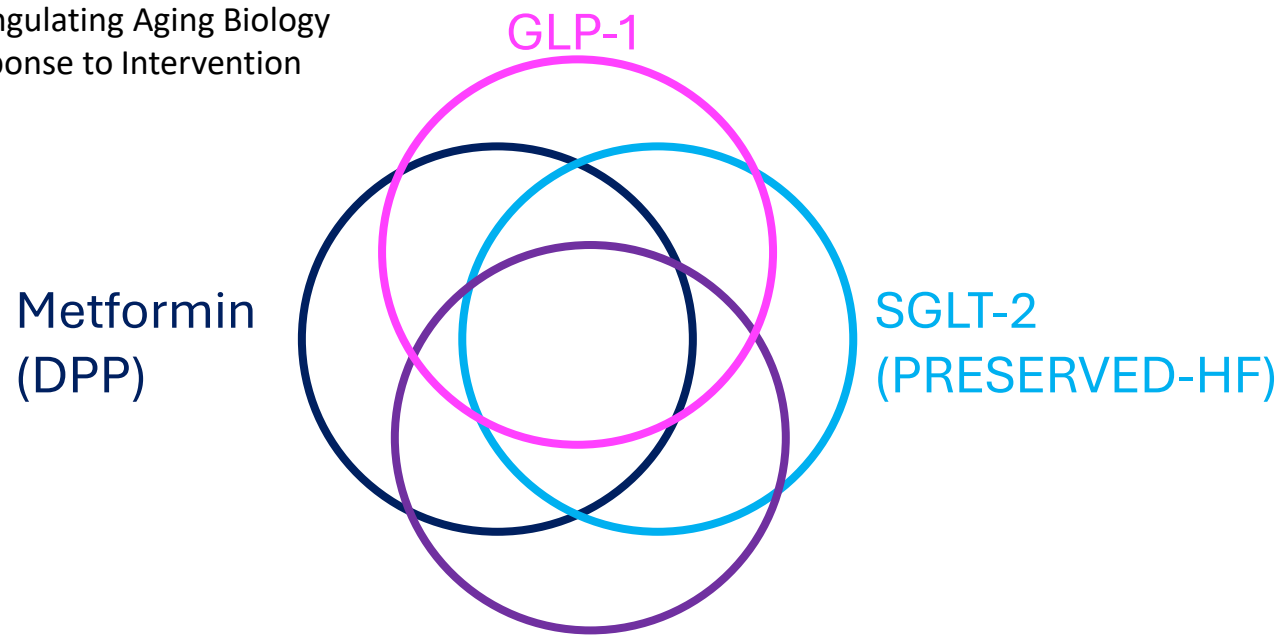


AGING?

Biomarkers for biological age that change with gerotherpaeutics

FAST Initiative Vision
(Now PROSPR)

Triangulating Aging Biology
Response to Intervention



REAGAN-UDALL FOUNDATION FOR THE FDA

Stephen B. Kritchevsky, PhD

Professor, Gerontology and Geriatrics Internal Medicine
Wake Forest University School of Medicine

The Challenge of Multi-Domain / Composite Endpoints

STEPHEN B. KRITCHEVSKY, PhD

TOBY R. ALLIGOOD, MD ENDOWED PROFESSOR IN GEROSCIENCE

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE

Affecting the Aging Trajectory: Regulatory Constructs for Gerotherapeutic Drug, Biologic, and Device Development

May 27, 2026

Complementary Strategies for an Aging Society

Current Biomedical Paradigm

The Geroscience Paradigm

What's the Endpoint?

If you had an intervention that slowed aging – how would you know it?

We asked this question in focus groups with 28 experts including geriatricians, subspecialists, statisticians, pharma-based scientists, and regulatory specialists.

Most agreed that the outcome should :

include **several dimensions of health**

reflect **participant goals** and desired outcomes

include **patient reported outcomes**

be **recognized by the FDA** or other regulatory authority

be **tailored** to the specific patient population

result in changes **noticeable to the participant**

Biomarkers are insufficient

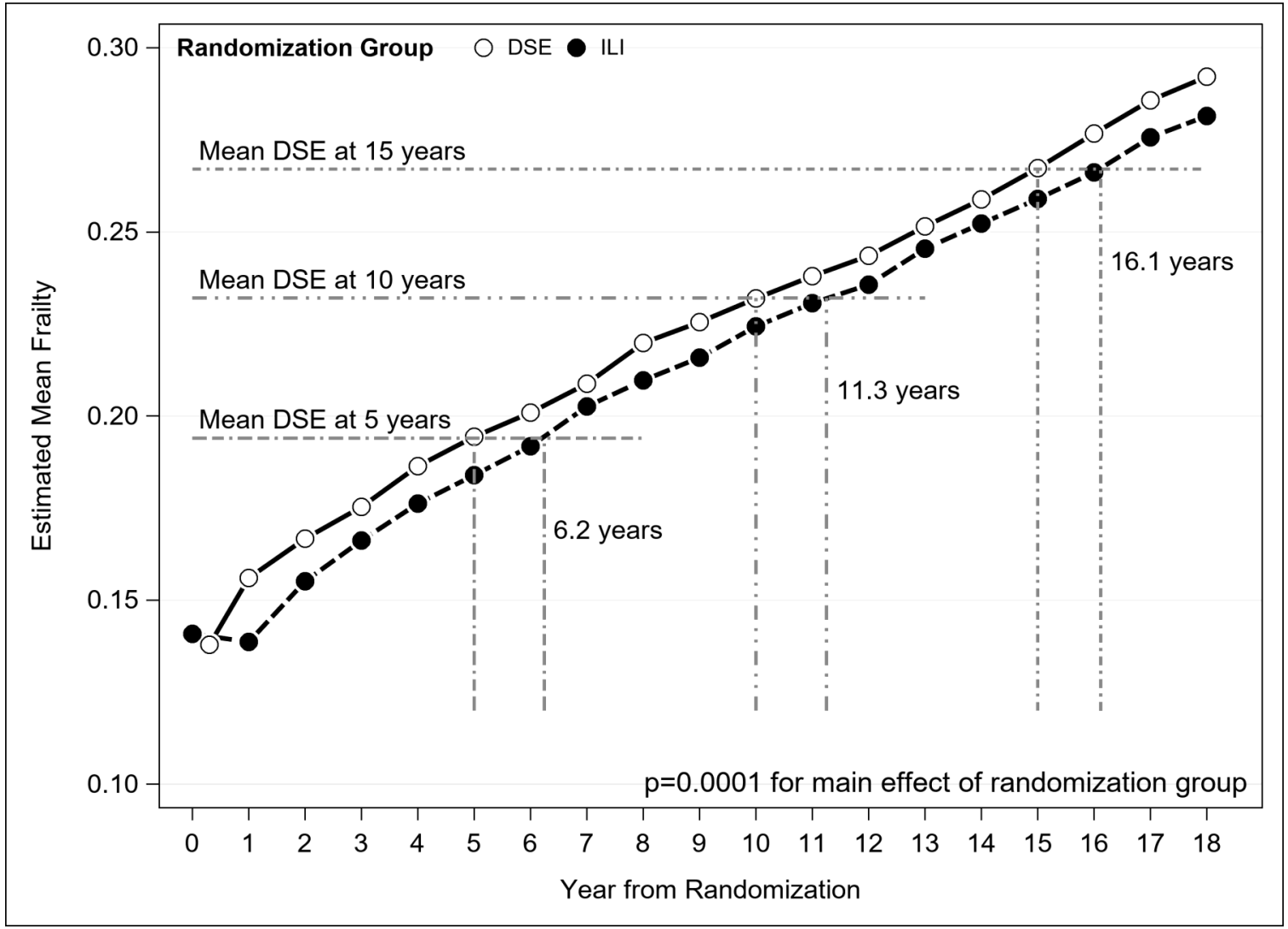
Kritchevsky S, et al Res Sq [Preprint]. 2025 Feb 12:rs.3.rs-5920485. doi: 10.21203/rs.3.rs-5920485/v1. PMID: 39989956; PMCID: PMC11844647.

Deficit Accumulation (Frailty) in the Look AHEAD Study

○ Diabetes Support and Education (DSE)

● Intensive Lifestyle Intervention (ILI)

Frailty – Proportion of Health or Functional Deficits from a List of 38



Espeland MA, et al. Diabetes Care. 2026 doi: 10.2337/dci25-0126.

Outcomes for Geroscience-Inspired Prevention Trials

Model Organism Perspective

- All-Cause Mortality

Geriatrics Perspective (Disability Free Survival)

- ASPREE & PREVENTABLE Trials[1]
- Frailty Phenotype[2] ; Intrinsic Capacity[3]; Resilience

Multimorbidity Perspective (↓Rate of New Disease Accrual)

- Targeting Aging With Metformin (TAME) [4]
- Look AHEAD: Rate of Accrual of 9 diseases over 8 years[5]

Deficit Perspective (↓ Accrual of Important Health Conditions and Impairments)

- SPRINT/Look AHEAD Frailty Indices (~38 diseases, clinical findings, and self-reported functions)[6]

Patient's Perspective

1. aspree.org/usa/wp-content/uploads/sites/3/2014/04/ASPREE-Protocol-Version-9_-Nov2014_FINAL.pdf
2. Espinoza SE et al. J Gerontol A Biol Sci Med Sci. 2020 75(1):102-109.
3. Beard JR et al. BMJ Open 2019 9(11):e026119
4. Justice JN, et al. Cardiovasc Endocrinol Metab. 2018 Dec;7(4):80-83.
5. Espeland, M.A.,et al. J Am Geriatr Soc, 68: 2249-2256. doi:10.1111/jgs.16672
6. Simpson FR,. J Gerontol A Biol Sci Med Sci. 2020 Sep 25;75(10):1921-1927.

TAME Aging Outcomes Trial Design

Age 65-80 years AND
Slow gait speed OR Age-related disease

Metformin (1500 mg 1×/day)
vs. Placebo (0 mg 1×/day)

n = 3000, 6-year, 14 Clinical Sites;
double-blind randomized placebo
controlled trial

(**Clinical**) Time to incidence of any age-related disease:
MI, stroke, CHF, cancer*, MCI/dementia, or death.

(**Functional**) Decline in mobility or cognitive function.

(**Biological**) Change in biomarkers of aging.

Reactions to the TAME Primary Endpoint

1. Will metformin have the same effect on each component?
2. The most common end-point will drive the result.
3. You need to do a separate trial for each component.
4. Even if you got a positive result, you wouldn't know if it was through an aging-related mechanism.

Composite Outcomes – Statistical Considerations

Potential Advantages –

Increasing the number of components increases the event rate leading to shorter trials or smaller samples sizes.

The outcome of interest might be multi-dimensional, and a composite allows for more than one kind of outcome to be included while preserving the Type I error (α) rate.

Potential Disadvantages -

Intervention benefits are assumed to relate to all components. If this isn't true then the intervention effect is diluted resulting in a lower effect size and lower statistical power.

May be challenging to express the benefits in readily understandable terms.

Tailoring Endpoints for an Intervention

HALLO-P (U01AG073240) – a 3-year planning grant to design a 5-year randomized trial of caloric restriction in older adults.

Selecting Index Components

1. Related to Obesity / Overweight
2. Age-Related
3. Risk or severity is ameliorated by intentional weight loss
4. Onset or severity associated with aging-related biomarkers
5. The occurrence leads to changes in clinical care or decreased quality of life

Index Elements

A. Chronic Disease (Acute Coronary Syndromes; DVT; Stroke; CHF; CKD; Weight Related Cancers)

B. Reversible Diseases / Conditions (Hypertension; Type 2 Diabetes; OSA; Knee / Hip Pain ; Depressive Symptoms)

C. Quality of Life / Function (Slowness; Lower Extremity Weakness; Exercise Intolerance; Tiredness / Fatigue)

Advantages of an Index

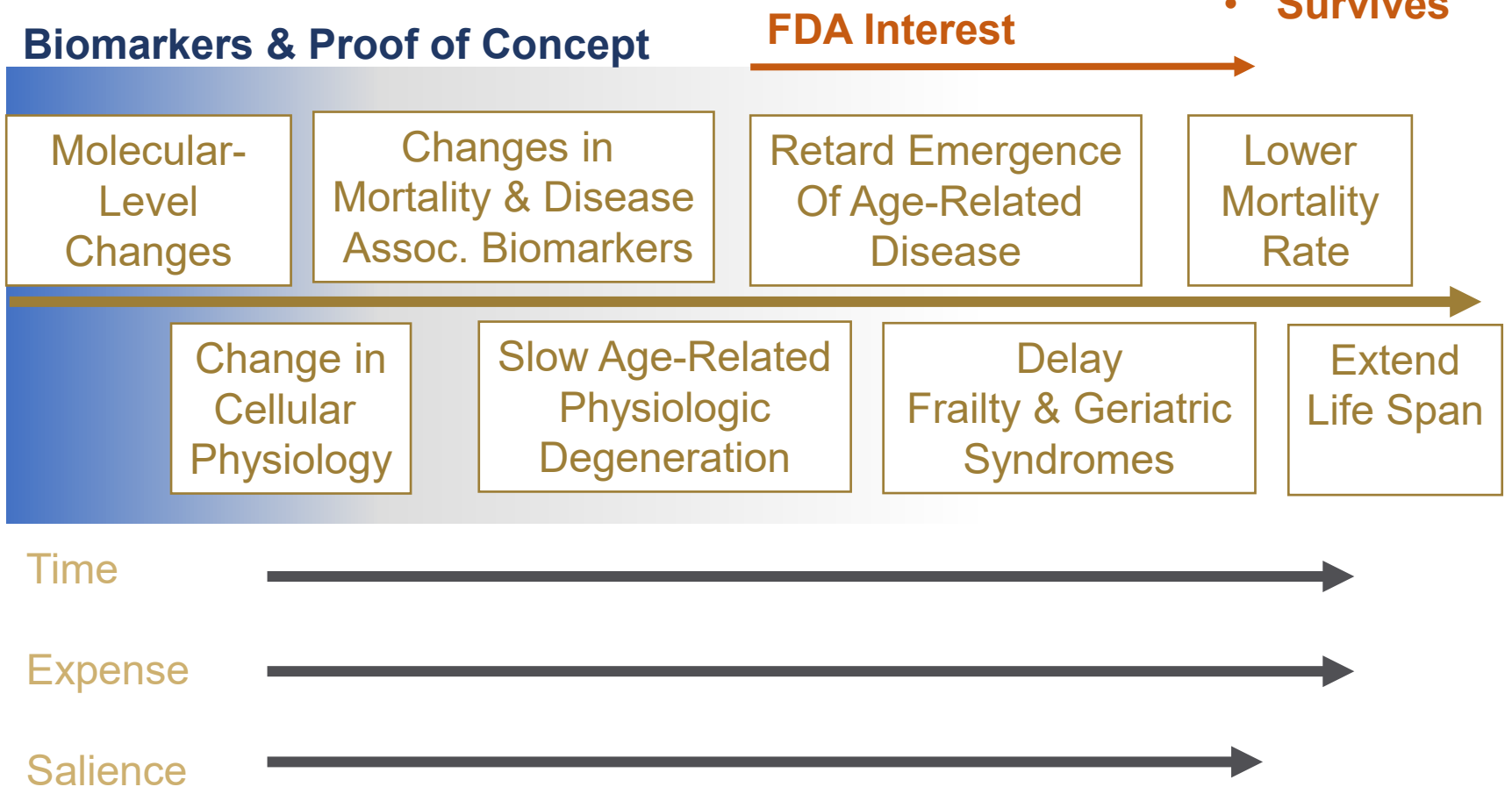
1. Captures a wide-range of benefits
2. Clinical Communication
3. Easier Recruiting compared to a single disease / disease class
4. Smaller sample size compared to single disease studies
5. Congruent with obesity as a major driver of multi-morbidity
6. Congruent with the idea that CR slows aging – per focus groups

Miller ME, et al . Geroscience. 2025 May 31. doi: 10.1007/s11357-025-01708-4.

Clinical Trials in Geroscience

Evaluation Continuum for Aging Outcome Trials

FDA Indication:
- **Function**
- **Feels**
- **Survives**



Kritchevsky, Justice. *JGMS* (2020) 75(1): 99–101.

REAGAN-UDALL FOUNDATION FOR THE FDA

Joan Mannick, MD

Chief Medical Officer

Altos Labs

ALTOS

Improving immune function in the elderly as a regulatory construct for gerotherapeutic drugs

Lessons learned from clinical trials of mTOR inhibitors

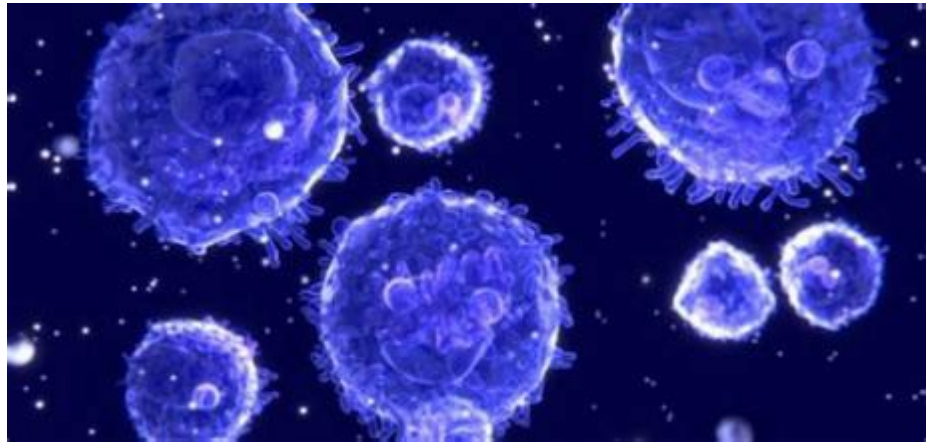
Joan Mannick, MD
CMO, Altos Labs

Disclosure Slide

- Joan Mannick was a shareholder in Novartis and resTORbio who conducted the mTOR inhibitor clinical trials and is currently an employee at Altos Labs. Altos Labs has no connection to and is not responsible for the trials and data being presented.

ALTOS™

Improving immune function in older adults may have pleiotropic health benefits



Decreased Incidence or Severity of Infections

Improved Vaccination Response

Decreased Cancer Incidence

Decreased Aging Of Other Organ Systems

(Yousefzadeh MJ et al., Nature 2021)

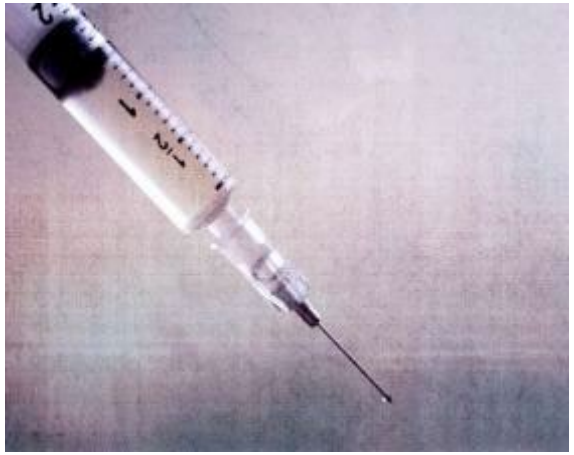
Increased Clearance Of Senescent Cells

ALTOS

Inhibiting a protein called mTOR has been shown to improve immune function in older animals

Old Mice

6 weeks
mTOR inhibitor



Improved Influenza
Vaccination Response

Chen C et al., Sci Signal, 2009

Clinical Development of mTOR inhibitors to improve immune function in older adults

Phase 2a
6 weeks of mTOR
Inhibitor treatment

2014

Phase 2a
6 weeks of mTOR inhibitor treatment

2018

+

Phase 2b
16 weeks of mTOR inhibitor treatment

2019

ALTOS™

The FDA requested a change in primary endpoint from the Phase 2b to Phase 3 trial

Trial	Subject Number	Endpoint	
Phase 2b	652	Percent of subjects with a **laboratory-confirmed** respiratory tract infection	✓
Phase 3	1052	Percent of subjects with **symptoms** consistent with a respiratory tract infection	X

(Mannick JB et al., Lancet Healthy Longevity, 2021)

ALTOS™

Lessons Learned from the Phase 2 and 3 mTOR Inhibitor Program

1. Low doses or intermittent doses of mTOR inhibitors was well-tolerated in older adults

2. Low doses of mTOR inhibitors consistently and significantly upregulated antiviral immune responses in older adults

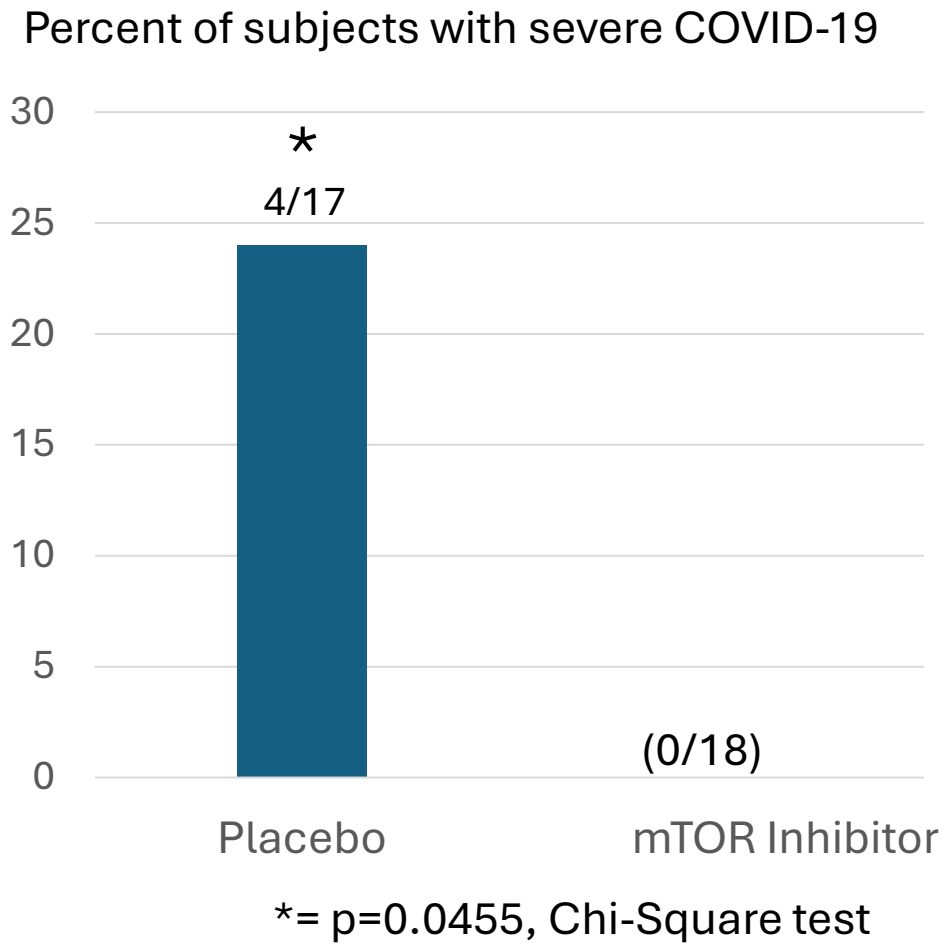
3. mTOR inhibitors may have a greater impact on severity than incidence of laboratory-confirmed respiratory tract infections

4. mTOR inhibitors may have the greatest benefit in the oldest adult populations (≥ 75 years)

ALTOS™

mTOR inhibition decreased the severity of COVID-19 in nursing home residents

Can low dose mTOR inhibitor therapy decrease the severity of RTIs in a very elderly population?



unpublished data

ALTOS™

Conclusions

- Enhancing immune function in the elderly may be a viable regulatory path for gerotherapeutic drugs
- Establishing regulatory endpoints for this new area of drug development will be important
  - The incidence or severity of RTIs is a feasible endpoint due to the high incidence of RTIs in older adults
  - It will be critical to use lab-confirmed RTIs not respiratory symptoms as an endpoint for this indication
- Biomarkers that guide selection of older adult populations with deficient immune responses will be important for future clinical trials

REAGAN-UDALL FOUNDATION FOR THE FDA

Eric Morgen, MD, MPH, FRCPC

Chief Operating Officer

BioAge Labs

BIOAGE

Drug Discovery for Healthy Aging

Gerotherapeutic Drug Development
May 27, 2026

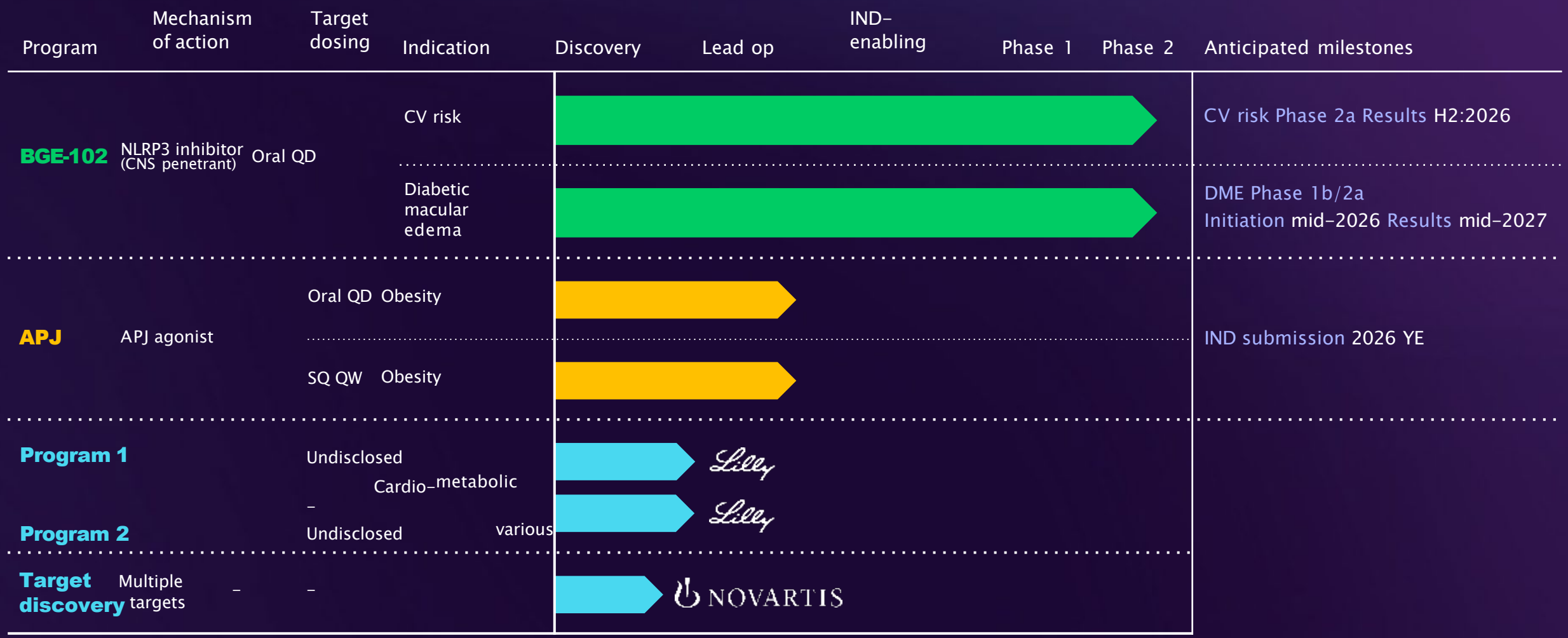
Eric Morgen, MD
COO
BioAge Labs

We are harnessing the biology of human aging to develop new therapies for metabolic diseases

BIOAGE

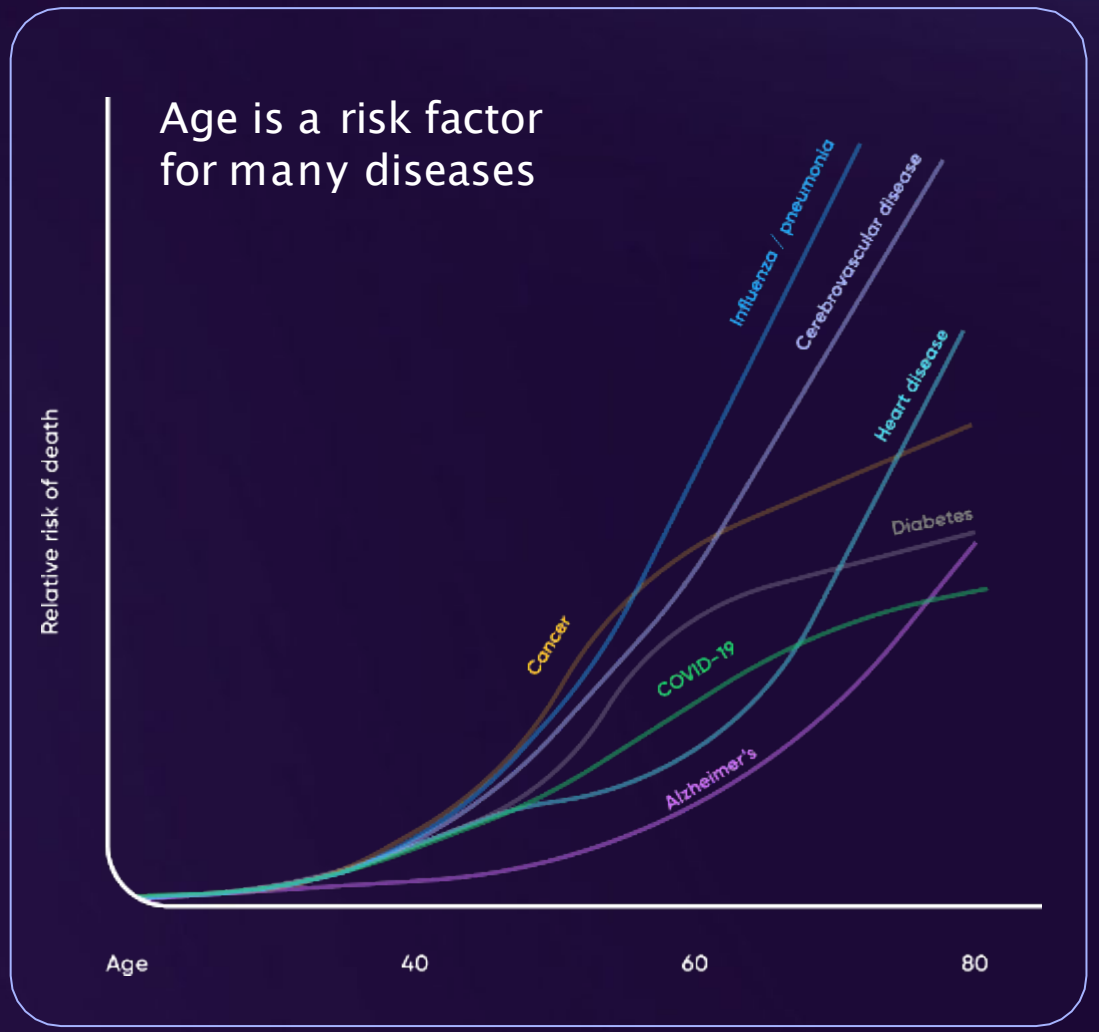
Pipeline overview

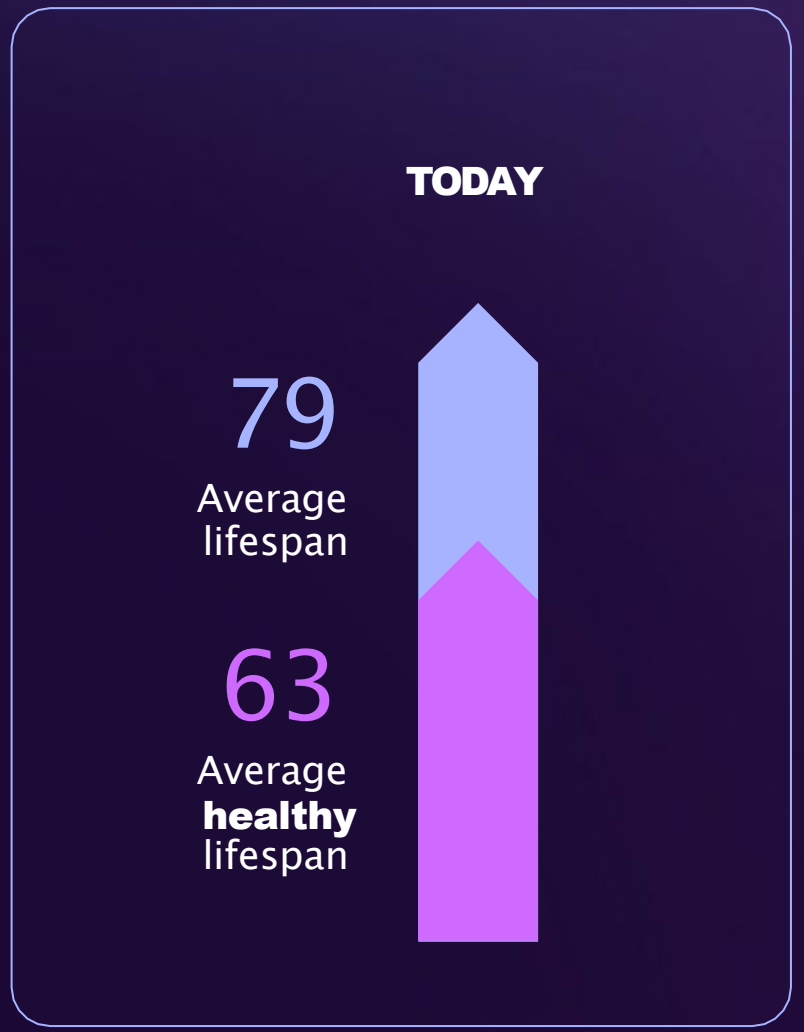
Leveraging the BioAge platform to address key unmet needs in metabolic aging



BIOAGE

Aging is one of the greatest challenges for human health





80%
of adults 65+ have at least one chronic condition[1]

>$500B
Annual health care costs for chronic disease among 65+ in US[2]

Sources:
1. "The Top 10 Most Common Chronic Conditions in Older Adults." The National Council on Aging. April 2021. https://www.ncoa.org/article/the-top-10-most-common-chronic-conditions-in-older-adults
2. Centers for Disease Control and Prevention, https://www.cdc.gov/chronicdisease/about/costs/index.htm#:~:text=More%20than%20877%2C500%20Americans%20die,lost%20productivity%20on%20the%20job. 4. Van Houtven G, Honeycutt AA, Gilman B, et al. Costs of Illness Among Older Adults: An Analysis of Six Major Health Conditions with Significant Environmental Risk Factors [Internet]. Research Triangle Park (NC): RTI Press; 2008 Sep. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532461/ doi: 10.3768/rtipress.2008.rr.0002.0809.

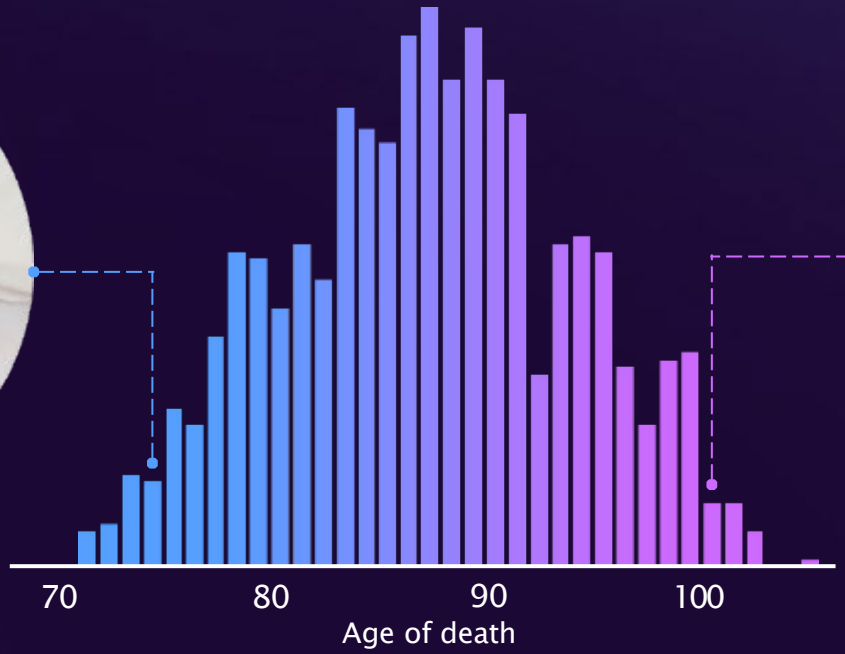
BIOAGE

Disease-first focus: We advance programs for specific diseases

BIOAGE

The BioAge Platform

Human data is unlocking R&D for aging, helping us uncover aging pathways and novel drug targets that impact healthspan



A 50+ year natural human experiment

50M+	10K+	50+
Molecular data points	Profiles generated	Years of follow-up

Detailed healthspan trajectories

Physical function
- Grip strength
- Walking speed
- Mobility

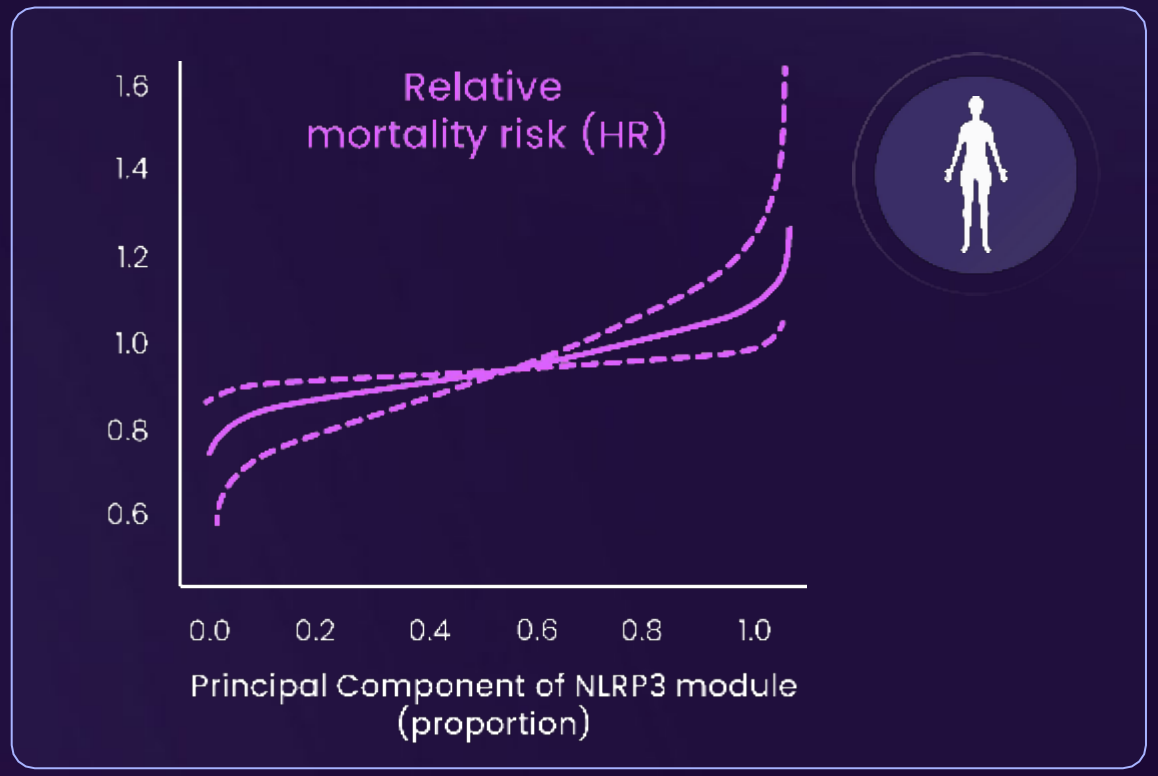
Metabolism
- BMI
- Skinfold thickness
- Waist / hip circumference

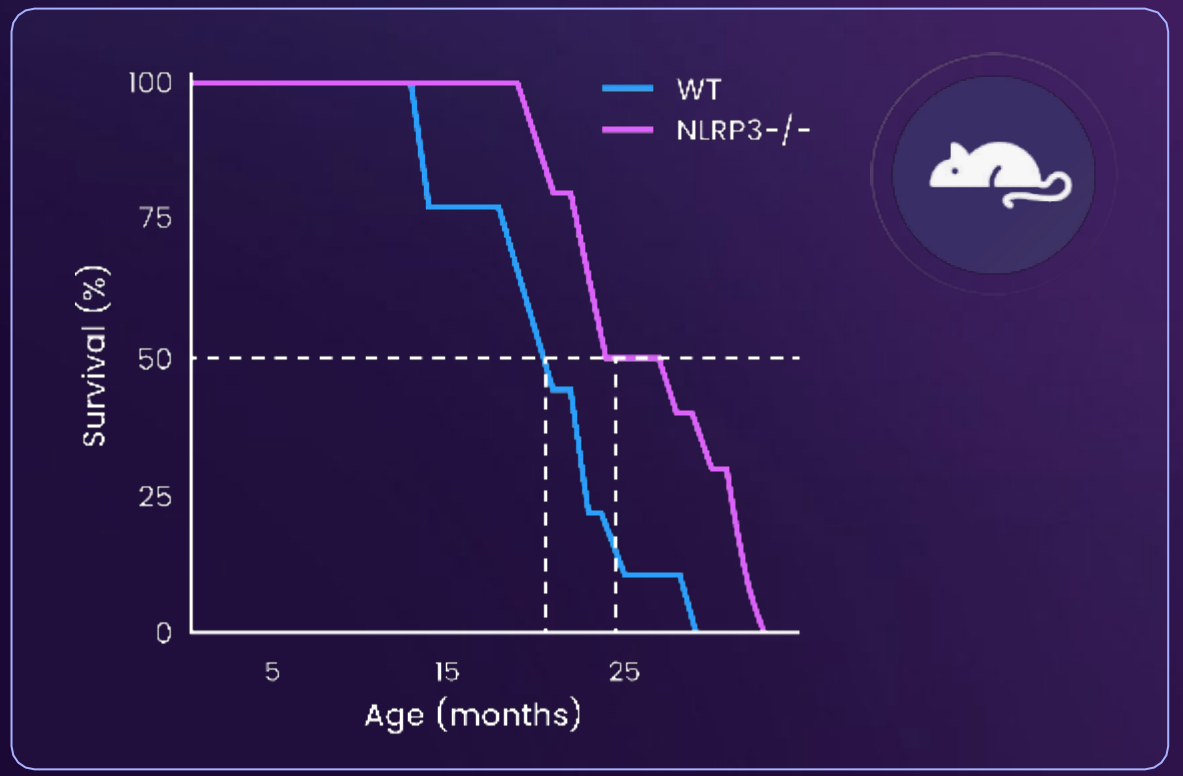
BIOAGE

NLRP3

Reduced NLRP3 activity is associated with longevity

Reduced NLRP3 activity is associated with longevity





Strong human genetic evidence for NLRP3 in cardiometabolic disease

Mendelian randomization: NLRP3 levels strongly predictive of heart failure (↑ 1SD expression = up to ↑ 70% risk)

GoF mutations ↓ lean mass & body composition ↑ atherosclerosis

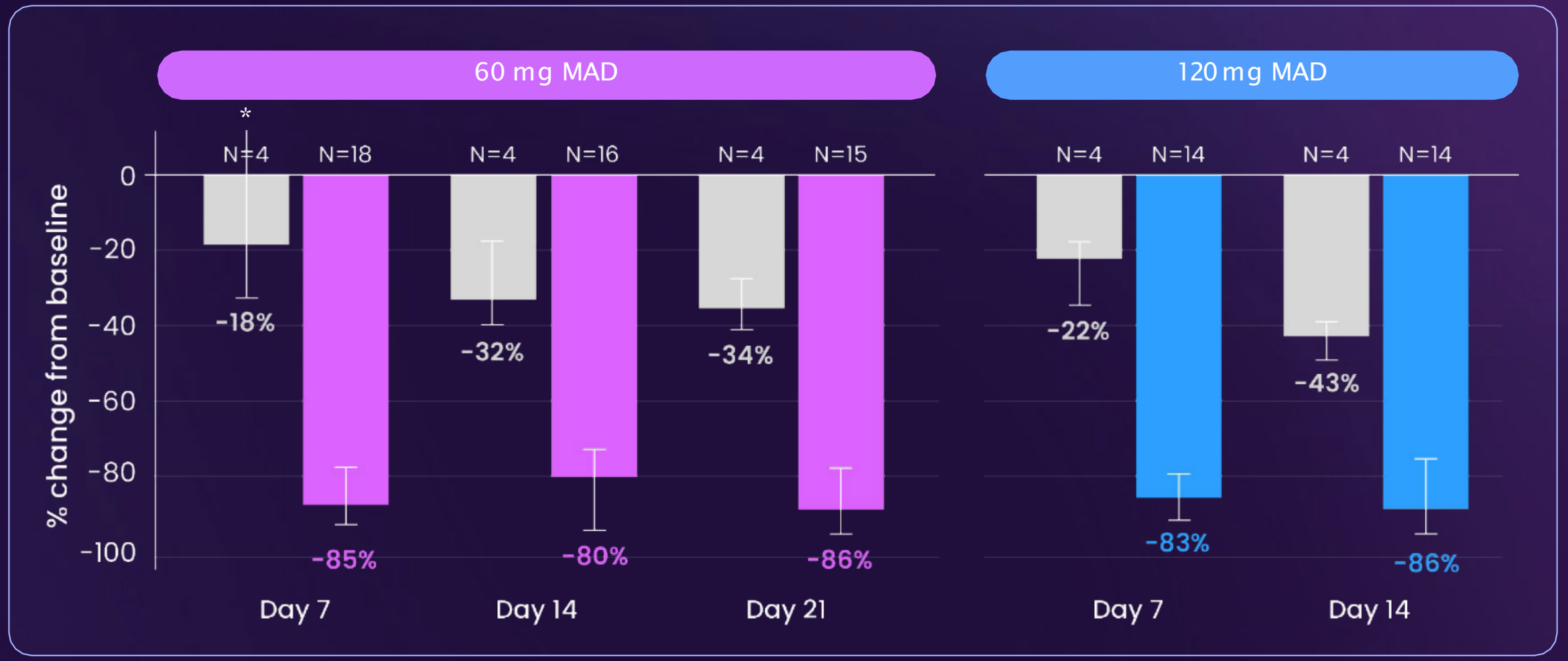
Source: Marín-Aguilar et al. 2020; BioAge human genetic analysis

BIOAGE

NLRP3

OBESE MAD

60 mg & 120 mg doses of BGE-102 resulted in 86% reductions in hsCRP, consistent with best-in-class efficacy



*Note: median values, error bars show IQR (Q1-Q3); * Day 7 placebo IQR upper limit is 115% median baseline hsCRP 60 mg cohort 6.30 mg/L for both active treatment and placebo, 120 mg cohort 4.85 mg/L for active treatment and 4.25 mg/L for placebo*

BIOAGE

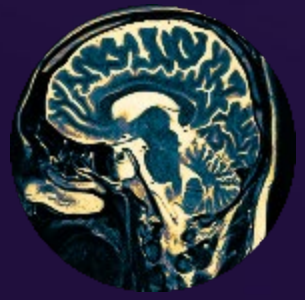
BGE-102 has the potential to address a range of cardiometabolic and neuroinflammatory disorders

Neuro-inflammation

Peripheral inflammation

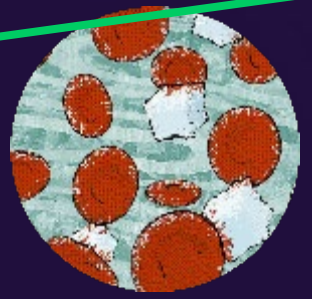
BGE-102 addressable diseases

Neurodegeneration

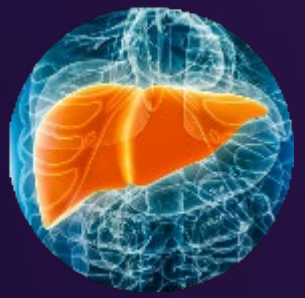


Ophthalmology

CVD (ASCVD, HF)



Insulin resistance



MASLD / MASH

BioAge clinical trials starting this year

BIOAGE

The THRIVE act: a potential new pathway for healthspan drugs

"Healthspan Product": Any FDA-regulated drug (or other product) that increases healthspan

"Increases Healthspan": Prevents or reverses **two or more** age-related diseases

Creates a new FDA indication that doesn't exist today.

No existing pathway is changed.

Healthspan endpoints are inherently harder to demonstrate

Potential societal benefit warrants strong incentives — just as with rare diseases and regenerative medicine

This is an exciting time with emerging efforts to push the field forward

LBA LONGEVITY BIOTECHNOLOGY ASSOCIATION

BIOMARKERS OF AGING CONSORTIUM

THE ALLIANCE FOR LONGEVITY INITIATIVES

nature biotechnology

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nature > nature biotechnology > correspondence > article

Correspondence | Published: 26 June 2023

Defining a longevity biotechnology company

Nicola Boekstein, Nir Barzilai, André Bertram, Joe Betts-LaCroix, Kristen Fortney, Stephen B. Helliwell, Michael Hufford, Joan Mannick, Jerry McLaughlin, Jim Mellon, Eric Morgen, Nils Regge, Daisy A. Robinton, David A. Sinclair, Sergey Young, Risa Starr, Alex Zhavoronkov & James Peyer

Nature Biotechnology (2023) | Cite this article

Kitalys Institute

XPRIZE HEALTHSPAN

BIOAGE

Toward Regulatory Constructs

Intrinsic Capacity, Adult Health Curves, and Multi-Domain Endpoints

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters

- **David B. Allison, PhD**, Chief of Nutrition and Director, USDA Children's Nutrition Research Center, Baylor College of Medicine
- **John Beard, MBBS, PhD**, Irene Diamond Professor, Columbia University Mailman School of Public Health
- **Kelly Anderson, PhD**, Scientific Engineering and Technical Advisor, ARPA-H
- **Nicholas Schork, PhD**, Director, Quantitative Medicine & Systems Biology, HonorHealth Research Institute

REAGAN-UDALL FOUNDATION FOR THE FDA

David B. Allison, PhD

Chief of Nutrition and Director
USDA Children's Nutrition Research Center
Baylor College of Medicine

Baylor College of Medicine

DEPARTMENT OF PEDIATRICS

USDA

Texas Children's Hospital

What Would Convince Us? Evidence, Endpoints, and Longevity in Aging Trials

David B. Allison, Ph.D.

David.Allison@bcm.edu

Baylor College of Medicine

May 27, 2026

Outline

I. Endpoints in Trials Targeting Aging

II. Biomarkers and Composite Measures Are Not Convincing

III. Mortality Function as a Substitute for Longevity

IV. Assumptions and Heterogeneity

V. Conclusion

Endpoints in Trials Targeting Aging

GeroScience (2022) 44:2925–2931
https://doi.org/10.1007/s11357-022-00671-8

COMMENTARY

Endpoints for geroscience clinical trials: health outcomes, biomarkers, and biologic age

Steven R. Cummings · Stephen B. Kritchevsky

Endpoint	Strength	Limitation
Total mortality	Directly measures survival Clinically meaningful	Rare → requires large, long trials Mixes different causes of death
Disability-free survival	Patient-relevant (function + quality of life)	Hard to define consistently Can change over time
Specific diseases	Measurable; regulatory relevance	Does not reflect overall aging One disease ≠ whole system
Multimorbidity	Reflects multiple age-related conditions	Depends on which conditions are included
Frailty (Indices/ Phenotype)	Captures overall aging/vulnerability	No standard measure May be insensitive to change

Improving a Marker Does Not Guarantee Slowing Biological Age and Improving Survival

A correlate is not a surrogate. Validation requires that the intervention's effect on the marker reliably predicts its effect on the clinical outcome (Fleming & DeMets, 1996).

Surrogates have repeatedly misled in cardiology, osteoporosis, and HIV — including cases where the marker improved while mortality worsened (e.g., Cardiac Arrhythmia Suppression Trial, fluoride for osteoporosis, CD4 in Concorde).

Multi-domain composites carry a weighting problem: domain weights are analyst choices, not data-driven facts, and different specifications yield different conclusions from the same trial.

Fleming, T. R., & DeMets, D. L. (1996). Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine, 125*(7), 605–613.

What Does It Take to Be Convincing?

- Statistical significance
  - Evidence against chance (*p*-values, confidence intervals) ≠ real-world importance
- Clinical relevance
  - Does it meaningfully affect how patients feel, function, or survive
- Trust and credibility
  - Study design quality
  - Transparency
  - Reproducibility

Convincingness is audience-dependent – **FDA, Physicians, Patients/Public, and Scientists.**

Esterhuizen et al. (2025) *BMJ Open*

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What Ultimately Matters: Feel, Function, and Survive (FDA Perspective)

- Clinical benefit is defined as a positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.

- A biomarker, measured as an indicator of biological responses to an exposure or intervention, is not a measure of how an individual feels, functions, or survives.

- Only a clinical outcome assessment (COA) can directly capture the clinical benefit.

Feel	Function	Survive
• Symptoms or other unobservable concepts known only to the patient. • Assessed using PRO (Patient Reported Outcomes) instruments such as questionnaires, numeric rating scales, or diaries.	• Observable signs, behaviors, or other manifestations related to a disease or condition. • Physical, cognitive, daily activities • Measured using the Clinician-reported outcomes (ClinROs).	• Overall survival • Surrogate endpoint can be used to measure clinical benefit, but it doesn't directly measure it.

BEST Qualification Glossary in https://www.ncbi.nlm.nih.gov/books/NBK338448/
Patient Focused Drug Development Glossary in https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary
Medical Device COA in https://www.fda.gov/about-fda/division-patient-centered-development/clinical-outcome-assessments-coas-medical-device-decision-making

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Why Longevity Should be the Central Focus?

- It is an objective, clinically meaningful endpoint that can be measured easily and precisely, getting the balance correct here will be critical going forward.

- Prolongation of life in the setting of a life-threatening disease is of clear inherent value, and therefore, overall survival should be prioritized as a primary endpoint when feasible.

- "*Overall survival is both an efficacy and a safety endpoint; it can be favorably impacted by the therapeutic benefits of a specific drug and negatively impacted by the drug's toxicity.*“ - FDA, 2025

FDA (2025). *Approaches to Assessment of Overall Survival in Oncology Clinical Trials: Draft Guidance for Industry*

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Short-term Mortality Can Approximate Lifespan Effects

Can Rodent Longevity Studies be Both Short and Powerful? Get access ›

Henry T. Robertson, Daniel L. Smith, Nicholas M. Pajewski, Richard H. Weindruch, Theodore Garland, Jr, George Argyropoulos, Alex Bokov, David B. Allison

The Journals of Gerontology: Series A, Volume 66A, Issue 3, March 2011, Pages 279–286, https://doi.org/10.1093/gerona/glq190

Published: 04 November 2010 **Article history** ▾

- We may not need full lifespan follow-up to infer effects on longevity.
- Mortality effects are stable over time.
- Shorter follow-up gives similar conclusions.
- Potential issue: Power → can be offset by larger sample.

Lifespan Differences Are Explained by Changes in Mortality Trajectories

JOURNAL ARTICLE

Why Do Life Spans Differ? Partitioning Mean Longevity Differences in Terms of Age-Specific Mortality Parameters

Scott D. Pletcher ✉, Aziz A. Khazaeli, James W. Curtsinger Author Notes

The Journals of Gerontology: Series A, Volume 55, Issue 8, 1 August 2000, Pages B381–B389, https://doi.org/10.1093/gerona/55.8.B381

Published: 01 August 2000 **Article history** ▾

"… longevity differences mediated by temperature [in Drosophila] and dietary restriction [in rats] result predominantly from differences in the rate of increase in mortality with age."

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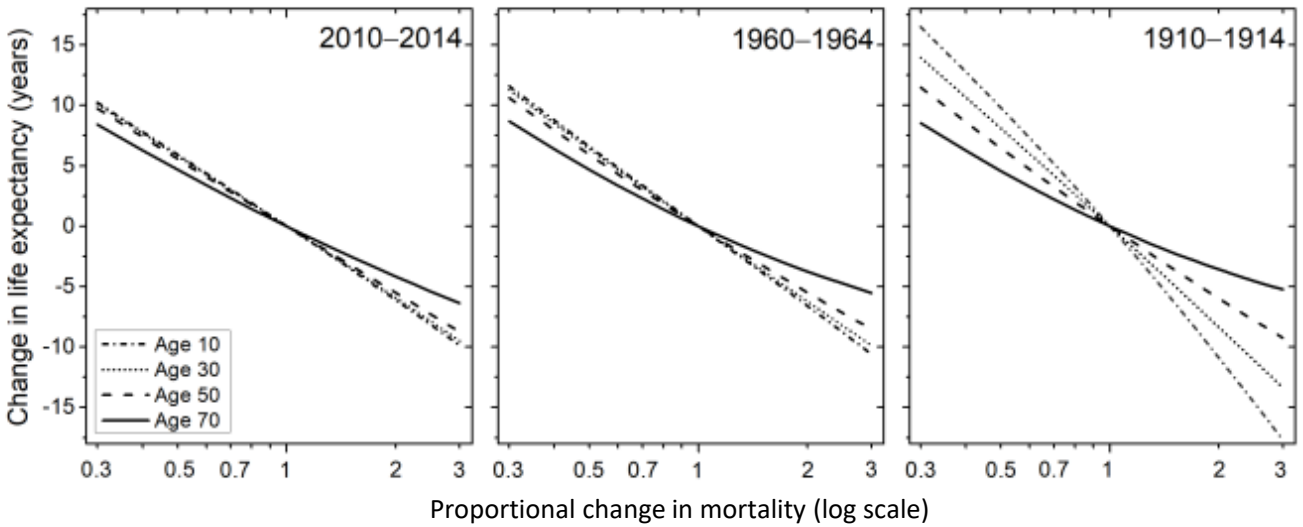
Proportional Changes in Mortality Produce Predictable Changes in Life Expectancy

Change in life expectancy at age a; a = 10, 30, 50, and 70 as a function of a proportional change of the mortality rate



DEMOGRAPHIC RESEARCH

VOLUME 39, ARTICLE 23, PAGES 671–684
PUBLISHED 27 SEPTEMBER 2018
http://www.demographic-research.org/Volumes/Vol39/23/
DOI: 10.4054/DemRes.2018.39.23

Formal Relationship 27

The impact of proportional changes in age-specific mortality on life expectancy when mortality is a log-linear function of age

Michael Væth

Mette Vinther Skriver

Henrik Støvring

"… the change in life expectancy is approximately linear in the logarithm of the proportional change of the mortality." [Swedish women data]

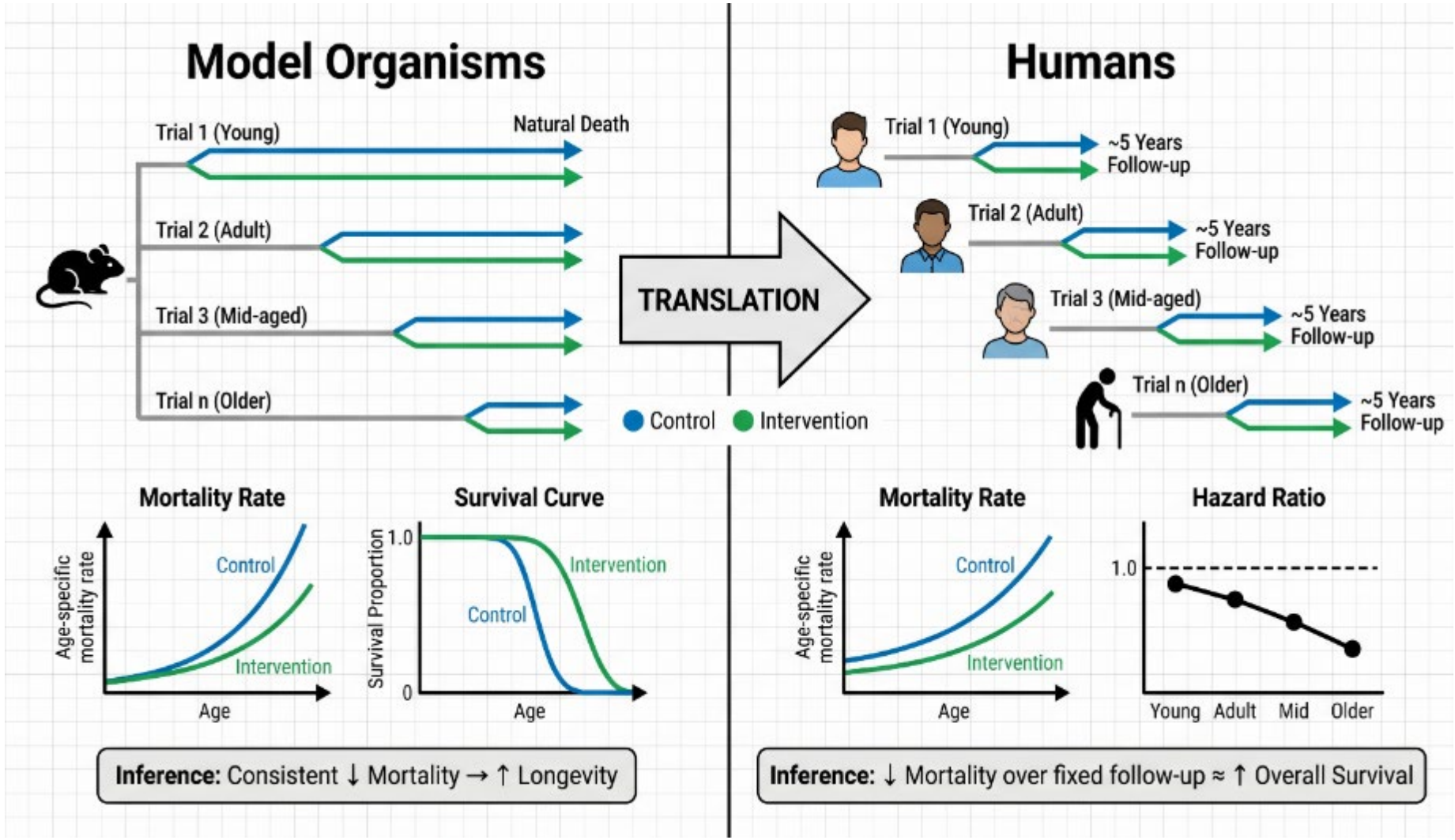
Can Mortality Rate Substitute for Longevity?

Mortality rate could meaningfully and confidently be used as a substitute for longevity if the following two conditions hold:

- Preclinical: analyses across multiple rodent longevity studies show that drug-induced changes in interval mortality rate predict changes in overall longevity across archival datasets with different drugs

- Clinical: the intervention shifts mortality rate in the same direction at each time interval in humans, with participants enrolled across the full adult lifespan

From Longevity to Mortality: A Feasible Trial Strategy



Potential issues:

- Low power at younger ages
- Age-dependent effect size
- Timing vs exposure confounding

Infographic created using Gemini 3.1

Assumptions and Heterogeneity

“Treatment Response Heterogeneity (TRH)" refers to inter-individual variation in response to a given treatment across individuals and is a fundamental concept in precision medicine.

Heterogeneity – the effect of intervention on mortality rate at early age (e.g., 30 years) is not same as its effect at older age (e.g., 80 years).

- It is important to distinguish between two sources of different effects.
  - age at which the effect is observed.
  - age at which the treatment is implemented.

Zoh et al. (2023). *Obesity Reviews*

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Conclusion – What Would Convince Us?

- No current proxy is fully convincing.
- Longevity is the gold standard; but impractical in human trials.
- Mortality is measurable, mechanistically linked to lifespan, consistent across model systems.
- Consistent reductions in age-specific mortality across well-designed trials provide credible evidence of increased longevity.

“…let us take this path through the woods…”

~ Jean-Jacques Rousseau

謝謝您

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Children's Nutrition Research Center

Baylor College of Medicine

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REAGAN-UDALL FOUNDATION FOR THE FDA

John Beard, MBBS, PhD

Irene Diamond Professor
Columbia University Mailman School of Public Health

Intrinsic Capacity

John Beard

COLUMBIA | MAILMAN SCHOOL OF PUBLIC HEALTH

Why do we need a new way to measure health?

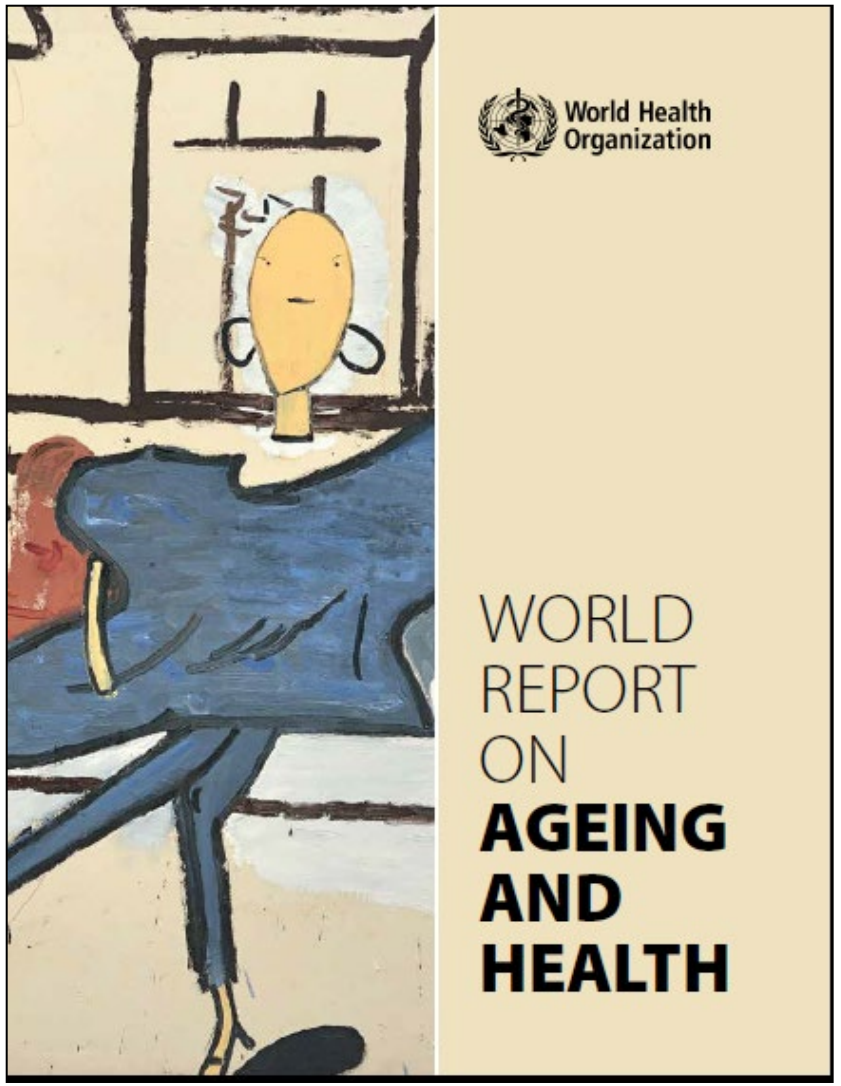
- Geroscience
  - Biomarkers
  - complexity
- Health is a continuum
  - Need to detect subtle incremental change
- But disease is dichotomous, late-stage and takes a long time to emerge
- Big data
  - Wearables etc etc
- Artificial intelligence

How can intrinsic capacity help?

- Need to link biomarkers to clinically meaningful measures of healthspan
- Functioning is the outcome prioritized by older adults
- Intrinsic capacity is a measure of individual level functioning
- Because it is continuous -potential to measure incremental change across the life course

Origins of Intrinsic Capacity

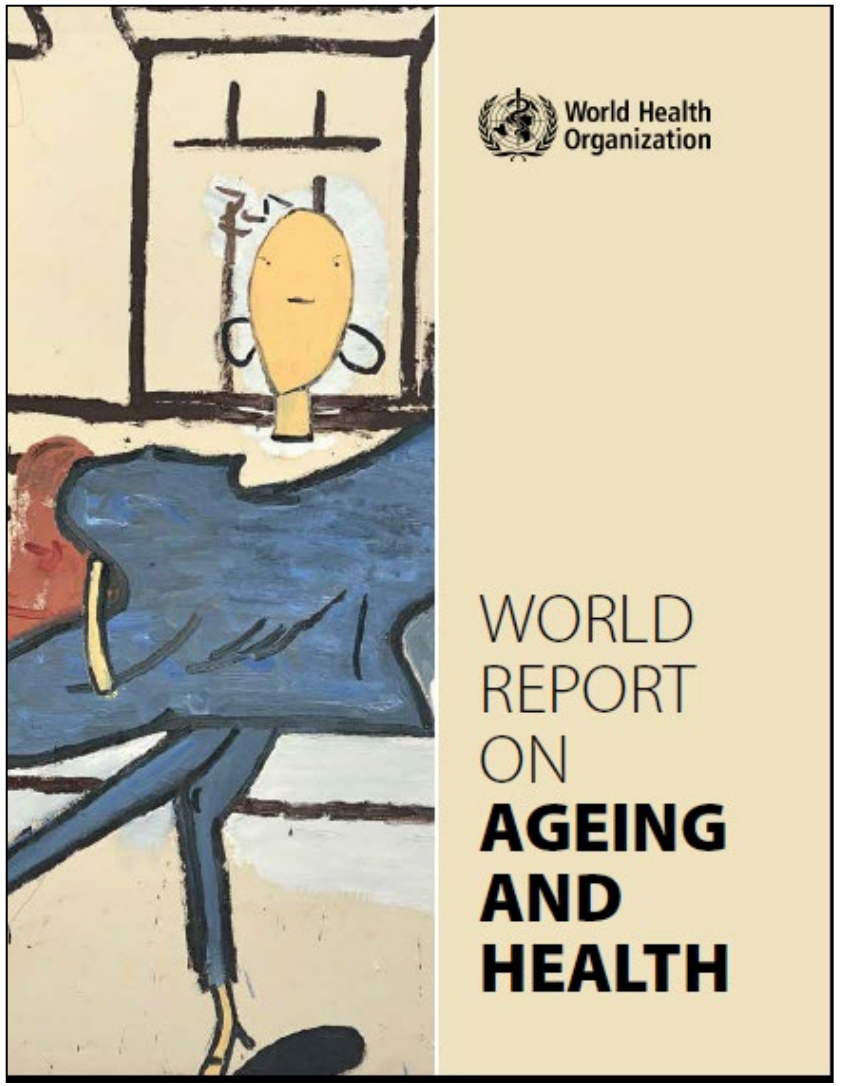
Action oriented around building and maintaining the functional ability of people to be and do the things they value



Beard JR et al, *the Lancet,* 2015

Origins of Intrinsic Capacity

Action defined not by chronological age but by functional state



Beard JR et al, *the Lancet,* 2015

Structure of intrinsic capacity

- 4 expressed subdomains:
  - Cognitive capacity
  - Locomotor capacity
  - Sensory capacity
  - Psychological capacity
- Vitality

Cesari M et al 2018 *J Gerontol A*
Beard JR, Jotheeswaran AT, et al. *BMJ Open* 2019

Structure of intrinsic capacity

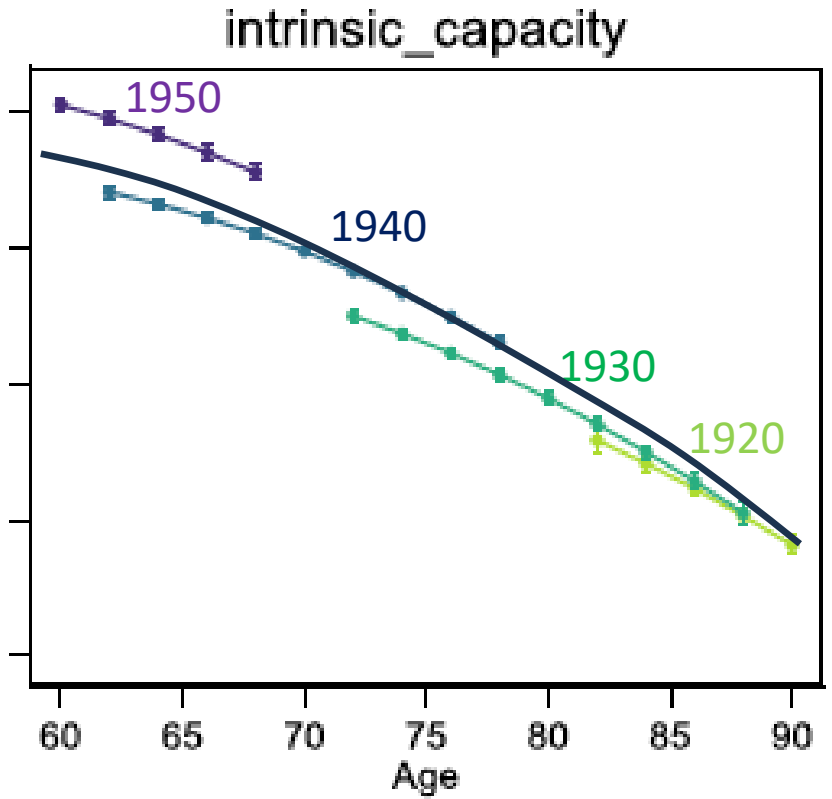
- 4 expressed subdomains:
  - Cognitive capacity
  - Locomotor capacity
  - Sensory capacity
  - Psychological capacity
- Vitality

Powerful predictor of future mortality and care dependence after accounting for age, sex, SES and multimorbidity

Distribution of capacity by age and sex in SHARE countries

Chen et al, JAMA Network Open 2025

Cohort trends in Intrinsic Capacity in ELSA



Beard et al 2024, Nature Aging

Trajectories of Intrinsic Capacity

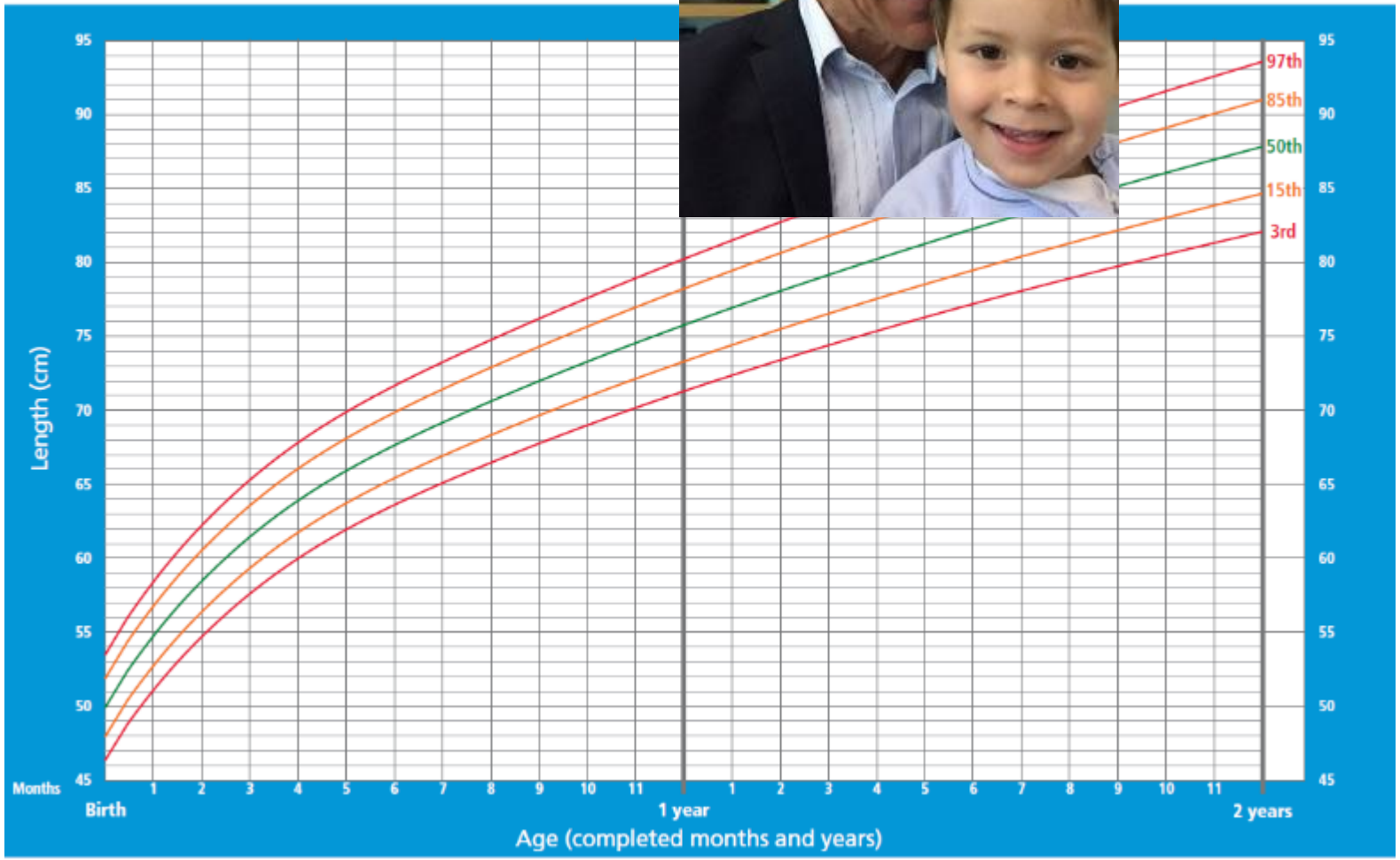
Great for observing and comparing patterns, trends and determinants at a population level…….

But what about for individual level research and clinical care?

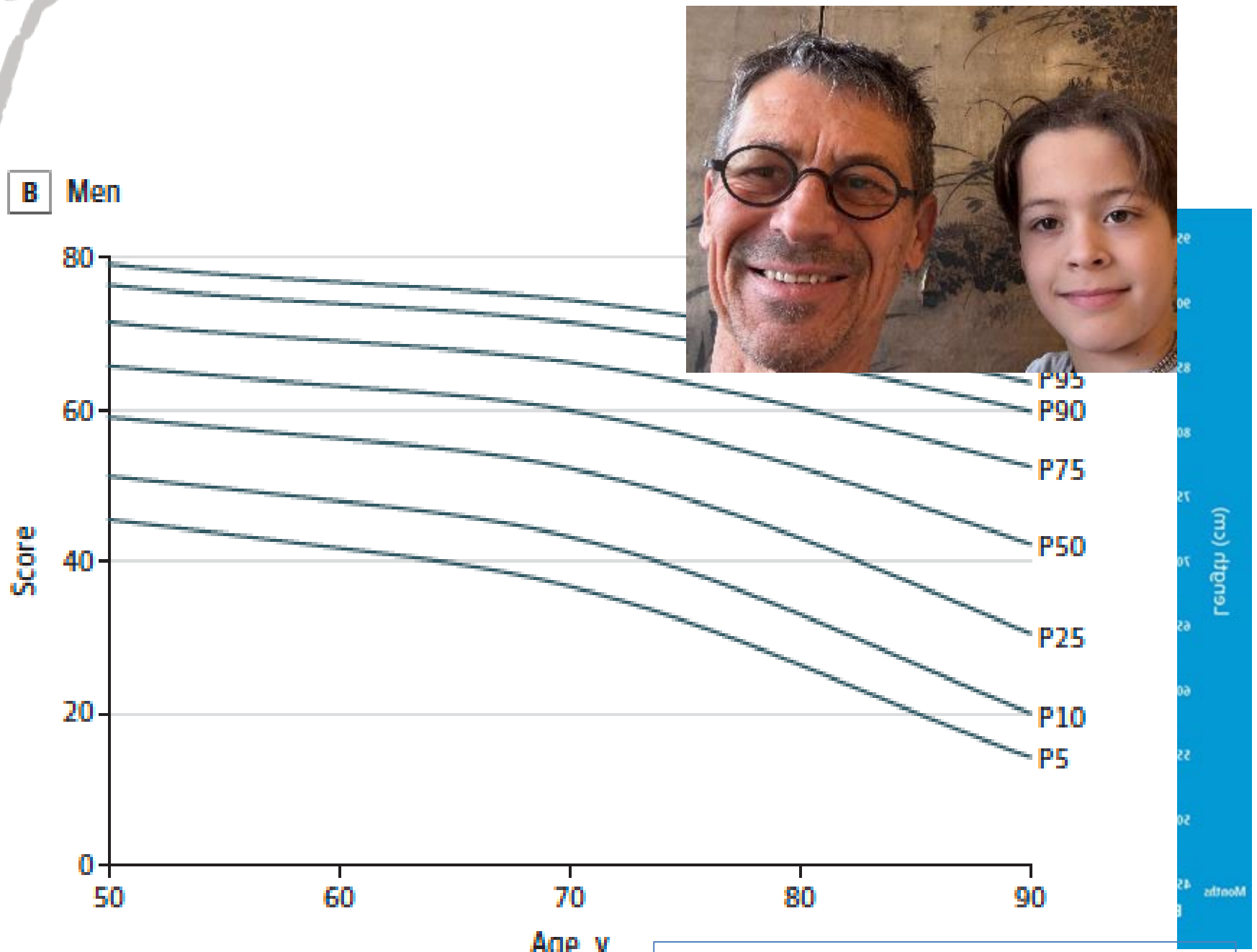
Length-for-age BOYS

Birth to 2 years (percentiles)

World Health Organization



WHO Child Growth Standards



Chen et al, JAMA Network Open 2025

Trajectories of care aligned with trajectories of capacity

Beard JR, Nature Aging 2024

ICOPE

INTEGRATED CARE FOR OLDER PEOPLE

Handbook

Guidance on person-centred assessment and pathways in primary care

World Health Organization

Where to now?

- Already an ICD code but can we formalize this as an outcome for clinical research and care?
- Measurement
- Biomarkers
  - Biological change
  - Of intrinsic capacity
- Medicine is built around thresholds, not continuums. Will need a significant shift in how doctors and researchers are trained and practice

Collaborators

Columbia University
Warren Coons
Xin Ma
Science of Health Group

World Health Organization
Matteo Cesari,
Islene Araujo de Carvalho,
Jotheeswaran
Amuthavalli Thiyagarajan

Toulouse University
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Philipe de Souto Barreto,
Christelle Cantet,
Yves Rolland,
Sandrine Andrieu,
Bruno Vellas

University College London
Moreno, Dario

University of New South Wales
Katja Hanewald,
Bingqin Li,
Hazel Bateman
Yafei Si,
Zhixin Liu,
Lynn Chenoweth

Macquarie University
Yuanyuan Gu
Meimei Chen

Adelaide University
Azmeraw Amare
Renuka Visvanathan
Melkamu Beyenne

Funding support:
Velux Foundation

REAGAN-UDALL FOUNDATION FOR THE FDA

Kelly Anderson, PhD

Scientific Engineering and Technical Advisor
ARPA-H

ARPA-H-hosted Consensus Meeting on Intrinsic Capacity

Kelly Anderson, PhD

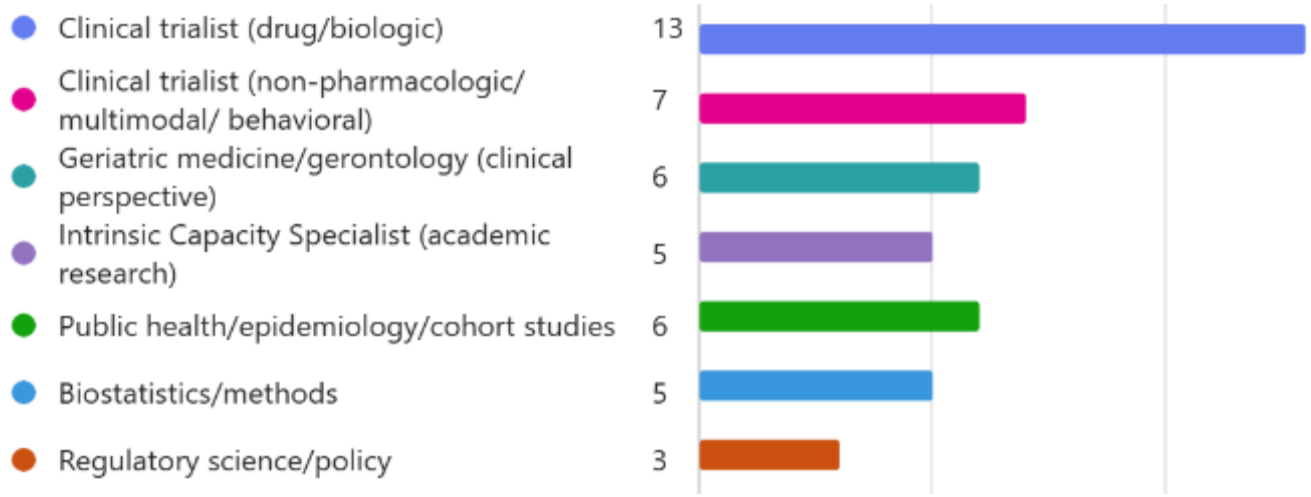
ARPA-H SETA, CTR

ARPA-H

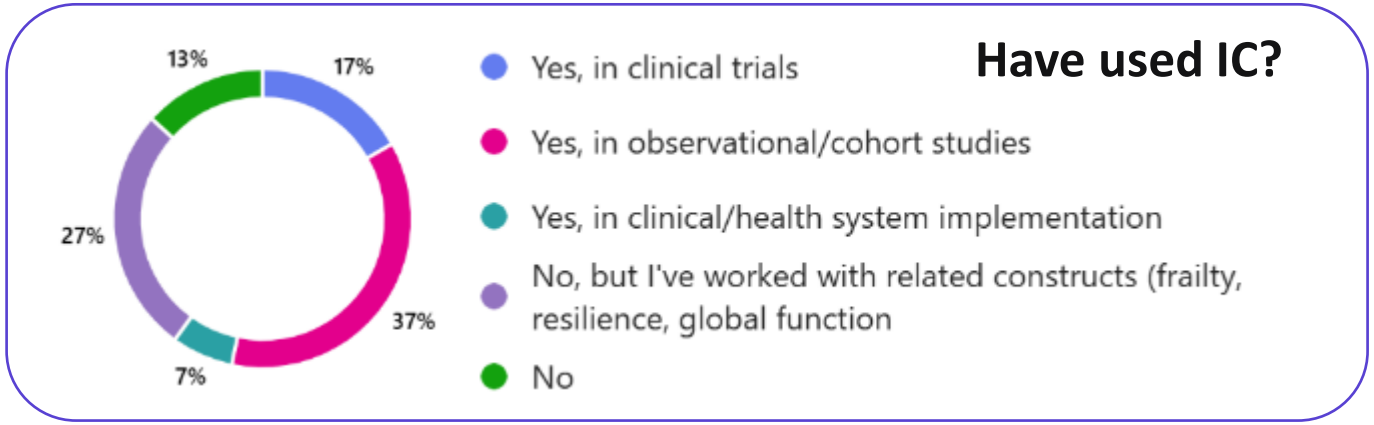
Building a Consensus for Intrinsic Capacity v1.0

- Goal: enable testable, FDA-relevant approaches to targeting aging biology
- Need: no standardized trial framework for measuring intrinsic capacity
- Aim of IC v1.0
  - Standardized measurement and analysis in trials
  - Generate consistent, comparable evidence
  - Support constructive dialogue with FDA and other regulators

Key Opinion Leader area of expertise



Have used IC?



IC Consensus Statement Scope

Proposes

- IC as a multi-domain clinical outcome framework
- Initial use in older, community-dwelling adults with early decline in intrinsic capacities but not disease
- Near term use for:
  - Domain-specific endpoints
  - Secondary outcomes
  - Enrichment/stratification

Does not propose

- IC as a validated surrogate endpoint (yet)
- A single global IC composite as a universal primary registration endpoint
- Replacement of established frailty or disease-specific endpoints

Principal Scientific Conclusion

Domain-level use is the most defensible near-term approach

- IC framework includes 5 domains: locomotor, cognitive, psychological, sensory, vitality.

- Consensus view:
  - Domain-specific changes are clinically meaningful and interpretable
  - Early programs should prioritize domain-level analyses
  - Broad gerotherapeutic claims would require additional evidence:
    - Multi-domain effects
    - Association with major health outcomes

Core Trial Battery v1.0

Domain	Tier 1 Measures
Locomotor	Gait speed; SPPB
Cognitive	MoCA plus processing speed/executive function measure
Psychological	Brief depression measure plus anxiety/distress coverage; optional wellbeing
Sensory	Visual acuity; basic hearing assessment
Vitality	Candidate reserve-oriented measures such as grip strength, respiratory function, and context-appropriate nutritional/appetite or biologic reserve measures

* Selected to balance feasibility, interpretability, scalability, and familiarity in clinical research. Tier 2 measures available for context-specific enhancement

Recommended Initial Contexts of Use

1. **Enrichment and stratification**
   - Identify higher-risk participants
   - Support subgrouping and balance across arms
2. **Secondary outcomes**
   - Characterize multi-domain functional effects
   - Build evidence across trials
3. **Domain-specific primary endpoints**
   - In selected programs with strong mechanistic rationale
   - Especially locomotor or cognitive composites

* Default use of a global IC composite as a standalone primary endpoint was not recommended at this stage

Scoring, Reporting, and Interpretation Principles

- **Domain scores should be:**
  - Measured separately
  - Analyzed separately
  - Reported separately
- **If a global IC score is used:**
  - Simple normalized unweighted composite is the provisional v1.0 approach
  - Use as secondary/exploratory endpoint
- **Meaningful change:**
  - Primarily defined in terms of patient-important differences
  - Prioritize domain-level interpretation first
  - Use anchor-based approaches where possible

Proposed Path Forward

- **Retrospective analyses in existing cohorts and trials**
- **Prospective incorporation into geroscience/healthspan studies**
- **Evaluation of:**
  - Responsiveness
  - Ceiling/floor effects
  - Meaningful change
  - Links to disability, independence, hospitalization, mortality
- **Early and ongoing FDA dialogue on fit-for-purpose contexts of use**


ARPA H

REAGAN-UDALL FOUNDATION FOR THE FDA

Nicholas Schork, PhD

Director, Quantitative Medicine & Systems Biology HonorHealth Research Institute

HONORHEALTH Research Institute

Reagan-Udall Foundation: Affecting Aging Trajectories
Hybrid Symposium; Washington DC: 5/27/2026

HONORHEALTH Primary Clinical Affiliate
ASU John Shufeldt School of Medicine and Medical Engineering
Arizona State University

Emerging Designs for Clinical Trials Vetting Geroprotective Interventions

Nicholas J. Schork, PhD

(HRI, ASU, TGen, Scripps Research)

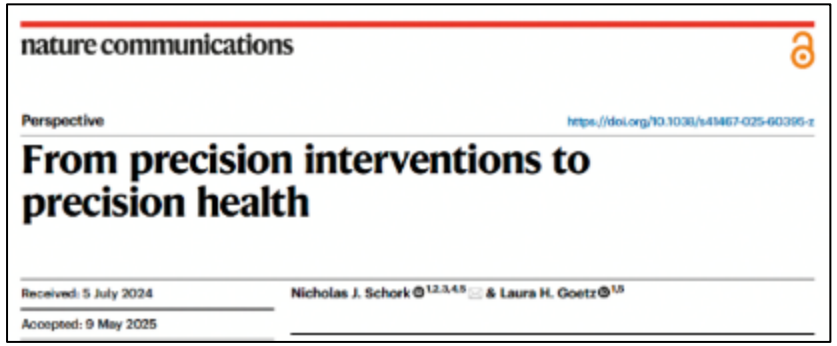
1. Different orientation
2. Defining response
3. Statistical methods
4. Integrative Approaches

Acknowledgements: NIA Longevity Consortium (U19AG023122; Schork, Girke co-PIs; Program officers: Evan Hadley, Chhanda Dutta); NIA Precision Aging Network (U19AG065169; Lee, Huentelman, Barnes co-PIs; Program officer: Molly Wagster); CIRM (Stuart Lipton, PI); HaDEA/HERA (Gingko Biosecurity, Prime)

Trials that Focus on Individual Health Improvement; *Mega* vs. *Mini* Trials

Different perspectives re: motivation/design of a trial:

- Rare disease (small N, trial phases not appropriate)
- Clinical translation (will it benefit the patient participant?)
- Phase I oncology trials: patients, not volunteers…


nature communications

Perspective

https://doi.org/10.1038/s41467-025-60395-z

From precision interventions to precision health

Received: 5 July 2024

Accepted: 9 May 2025

Nicholas J. Schork & Laura H. Goetz

Mega-trials "can provide definitive evidence about the mortality *(or morbidity)* reduction afforded by a class of therapy so that broad changes in clinical practice can be justified."

Mini-trials "can explain why a treatment is effective to allow development of more effective approaches attacking the identified mechanisms."

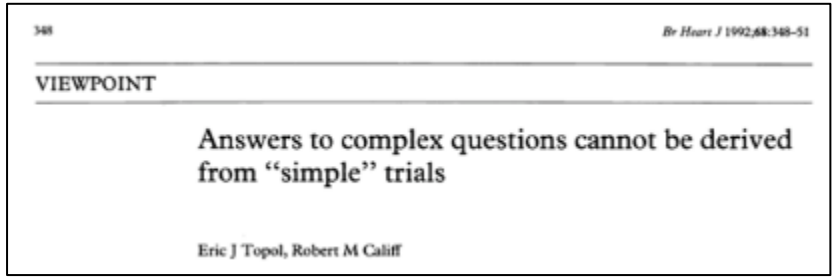
Further Complementarity: the mechanistic and comprehensive "rationale for mega-trials and the 'fine-tuning' of minor adjustments in treatment will be the task of the mini-trials."

Especially Repurposed Drugs

Mega-trials -> **Mini-trials**

Mini-trials -> **Mega-trials**

Real World Evidence + Evidence Synthesis


348

Br Heart J 1992;68:348-51

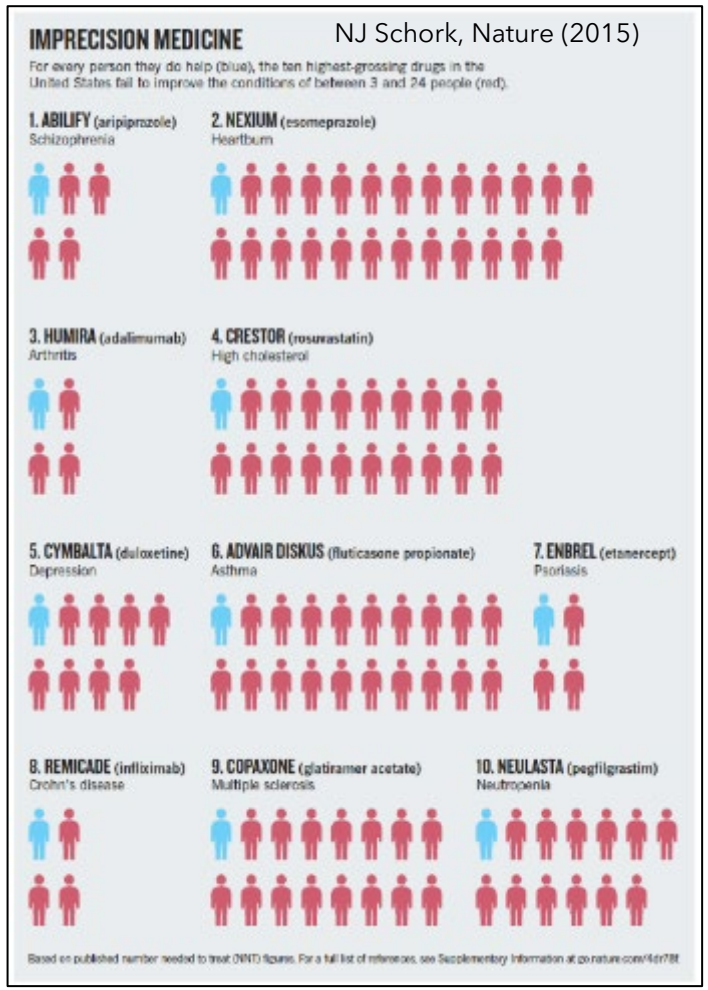
VIEWPOINT

Answers to complex questions cannot be derived from "simple" trials

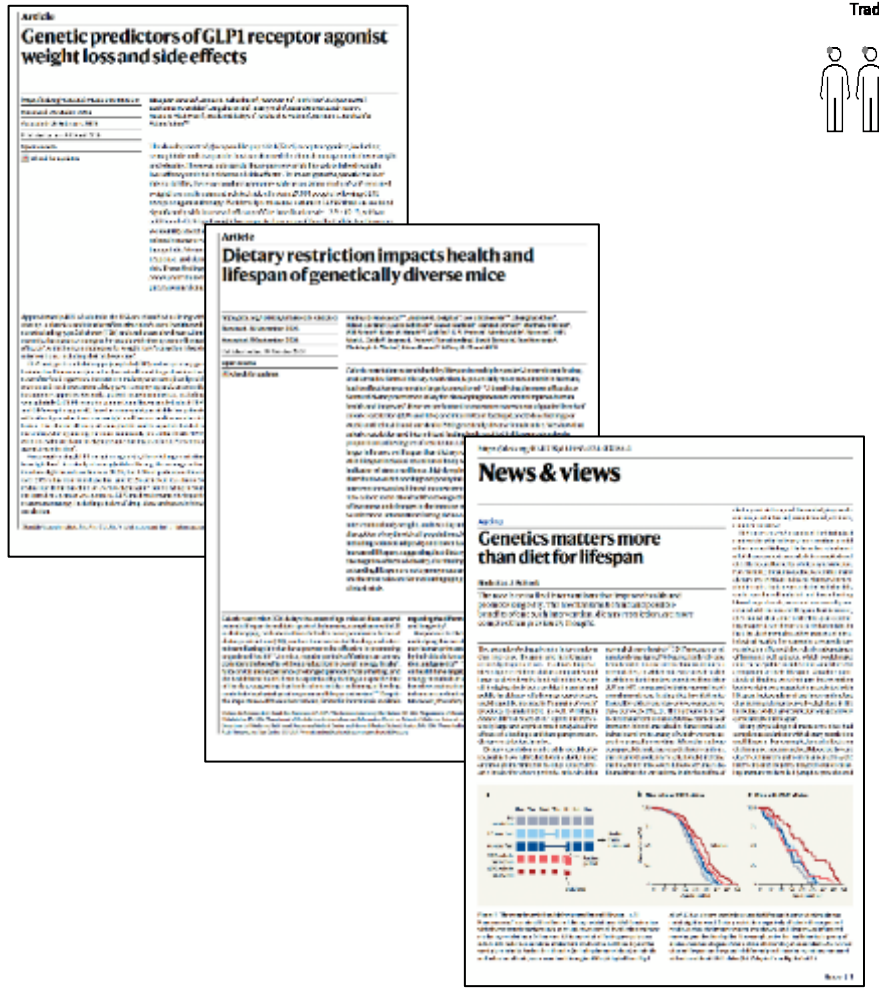
Eric J Topol, Robert M Califf

Inter-Individual Variation in Intervention Response

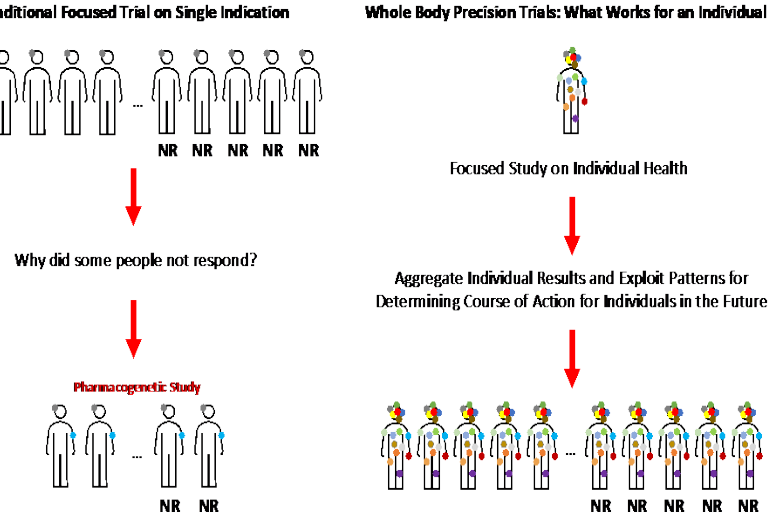
Population trials reveal poor response rates

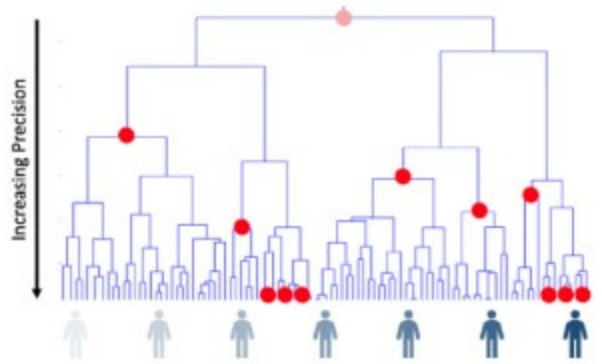


Recent studies on genetic basis of geroprotector response



Need built-for-purpose trials and infrastructure





Schork, Goetz et al. PMIDs: 40447582; 37255593

Defining Response: Population Level vs. Individual Level

Traditional target effect sizes may not adequately capture important clinically-relevant individual response info:

- Mortality rates
- Morbidity rates
- Average change in IC or, e.g., a surrogate endpoint
- Multivariate phenotype defining overall health

Response criteria could be defined *a priori* using available data sources (e.g., natural history or cohort studies, etc.)

- Age reversal
- Life tables
- Clinical assessments
- Participant concerns
- Aging clock dial

Use of *a priori* criteria for response by developing a response distributions has elements of a Bayesian design (“Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products;” https://www.fda.gov/media/190505/download)

Simple 2 x 2 Table Formulation

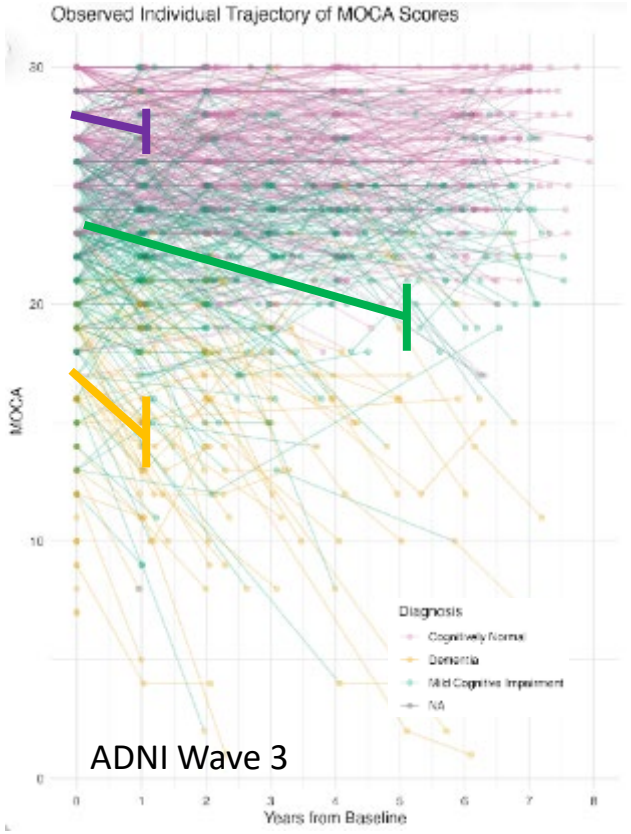
- Hypothesis: $C_R << I_R$
- Define criteria so that C_R is small
- Multiple criteria = C_R even smaller

Studies Using *A Priori* Defined Response Criteria

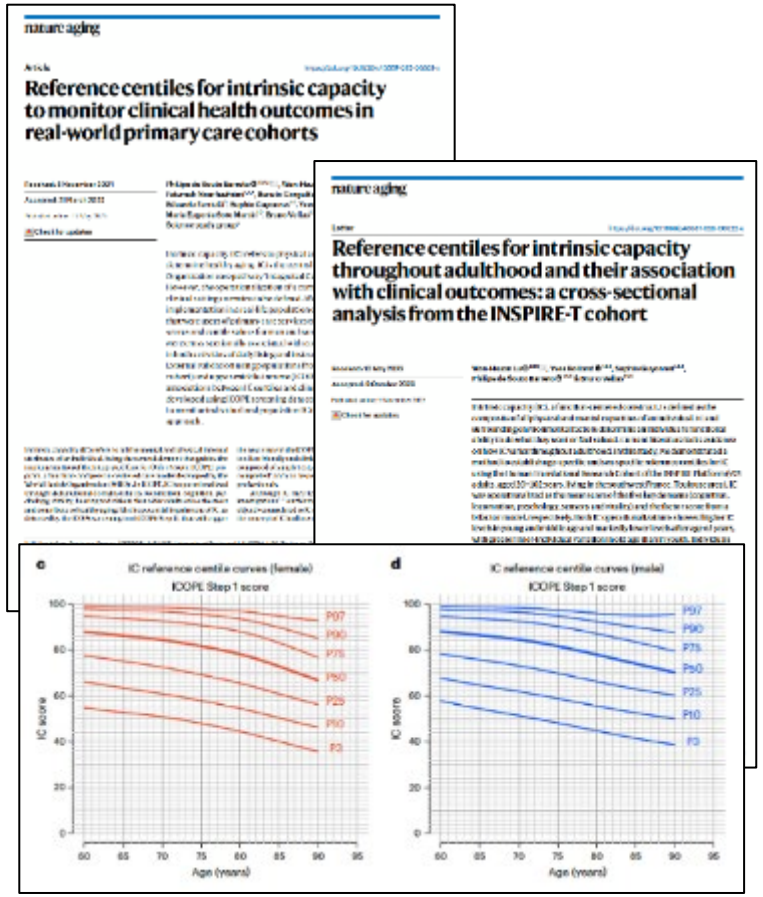
Defining Response: “Age-Reversal” Criteria

- Explore variation in trajectories
- Determine changes that would amount to age-reversal in years
- Determine the probability of achieving changes by chance

- Meaningful changes could be ’individualized’ via covariate use (XPRIZE Healthspan competition)
- Post-hoc tests of quantitative changes can always be pursued



- Intrinsic capacity could be used
- Define responses for each domain
- Non-linearity and ceiling effects



Multivariate Studies: Aging Affects *Multiple* Phenotypes…

- If a multivariate effect hypothesis is true, then multivariate tests are more powerful than univariate tests
- Multivariate tests can assume *each variable* exhibits a minimal effect (% variance explained by a treatment)
- Correlations between the measures can have a substantial effect on power and the nature of the test

Upper panel: Multivariate test (Hotelling's T-square) vs. univariate test (paired t-test) with Bonferroni correction

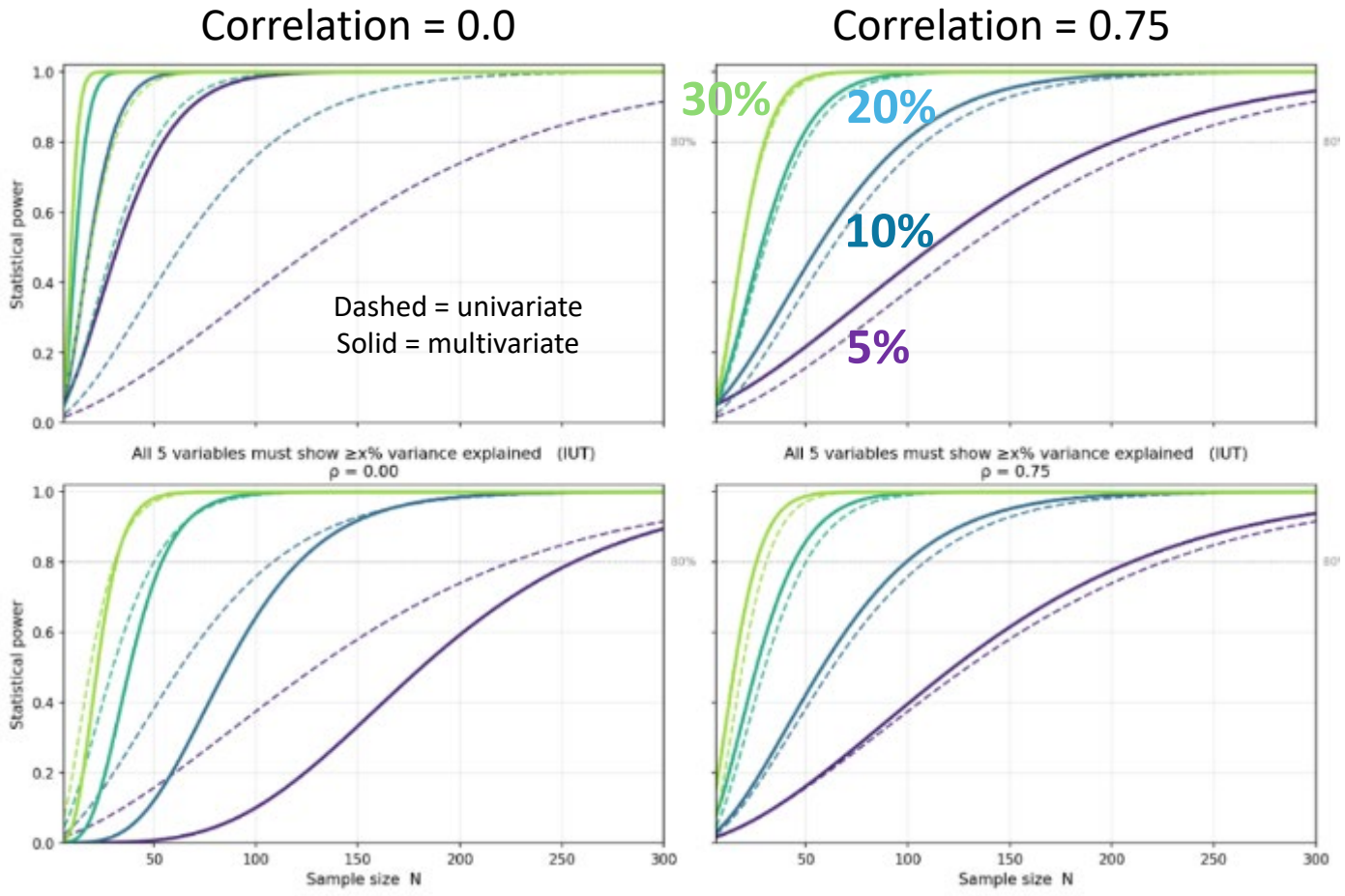
- 5 variables assumed
- Type I error rate of 0.05

Lower panel: Union-intersection test (i.e., each variable exhibits and effect) vs. univariate test (paired t-test)

Am. J. Hum. Genet. 63:1190–1201, 1998

Multiple Phenotype Modeling in Gene-Mapping Studies of Quantitative Traits: Power Advantages

David B. Allison,[1] Bonnie Thiel,[2] Pamela St. Jean,[2] Robert C. Elston,[2] Ming C. Infante,[1] and Nicholas J. Schork[2,3,4,5]



Single Case Experimental Designs (SCEDs): Heterogeneity Studies

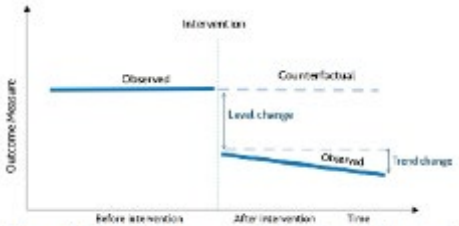
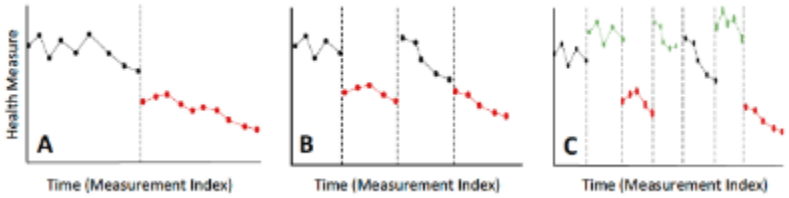
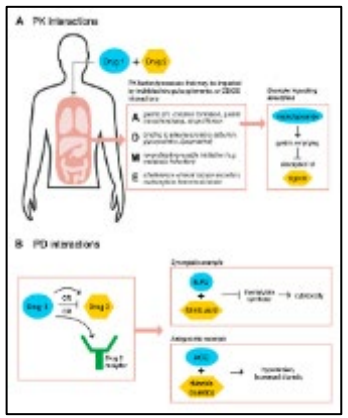


Figure 1 Diagrammatic representation of single interrupted time series.



Testing Average Effect vs. Variation in Effect

- Traditional randomized clinical trials (RCTs) typically focus on **average** effects of interventions not individual responses
- Power derives from number of longitudinal measures not individuals
- Major advantages of SCEDs and **aggregated** SCEDs:
  - ✓ Intervention effects (standard average effect analyses)
  - ✓ Variation in response effects using, e.g., mixed models
  - ✓ Causal relationships between PK-like biomarkers and responses
  - ✓ Validate surrogate endpoints and prognostic vs. predictive biomarkers
  - ✓ Identify clinically-relevant patterns from aggregated data using AI/ML
  - ✓ **Identify phenomena that benefit patients *in real time***

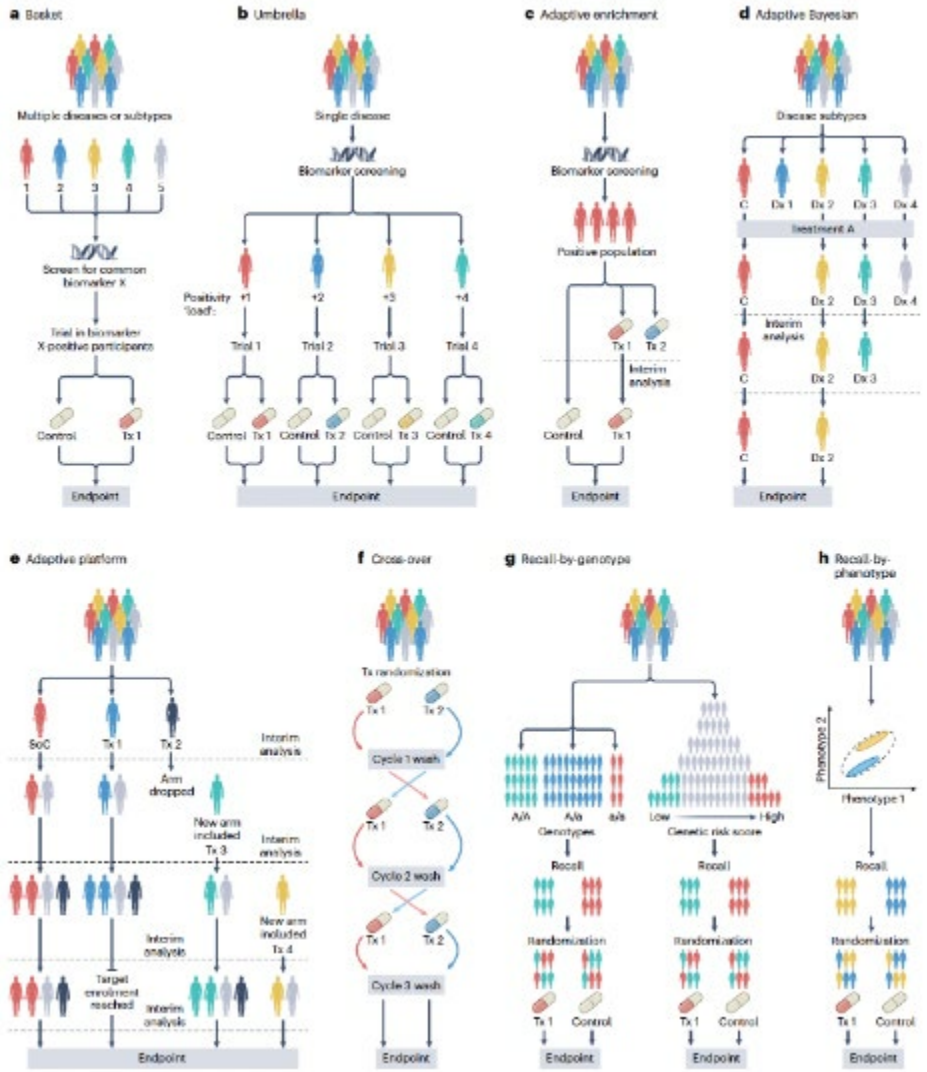


- **Punchline**: More observations on fewer individuals are more powerful than fewer observations on more individuals for detecting **variation** in treatment response (with total number of observations fixed)
- Mediation effects and surrogate endpoint analysis can be accommodated as well

Schork (*Manuscript in Preparation*); Schork et al. *Harv Data Sci Rev*. 2022;2022(SI3)

Other Large-Scale Designs and Infrastructure

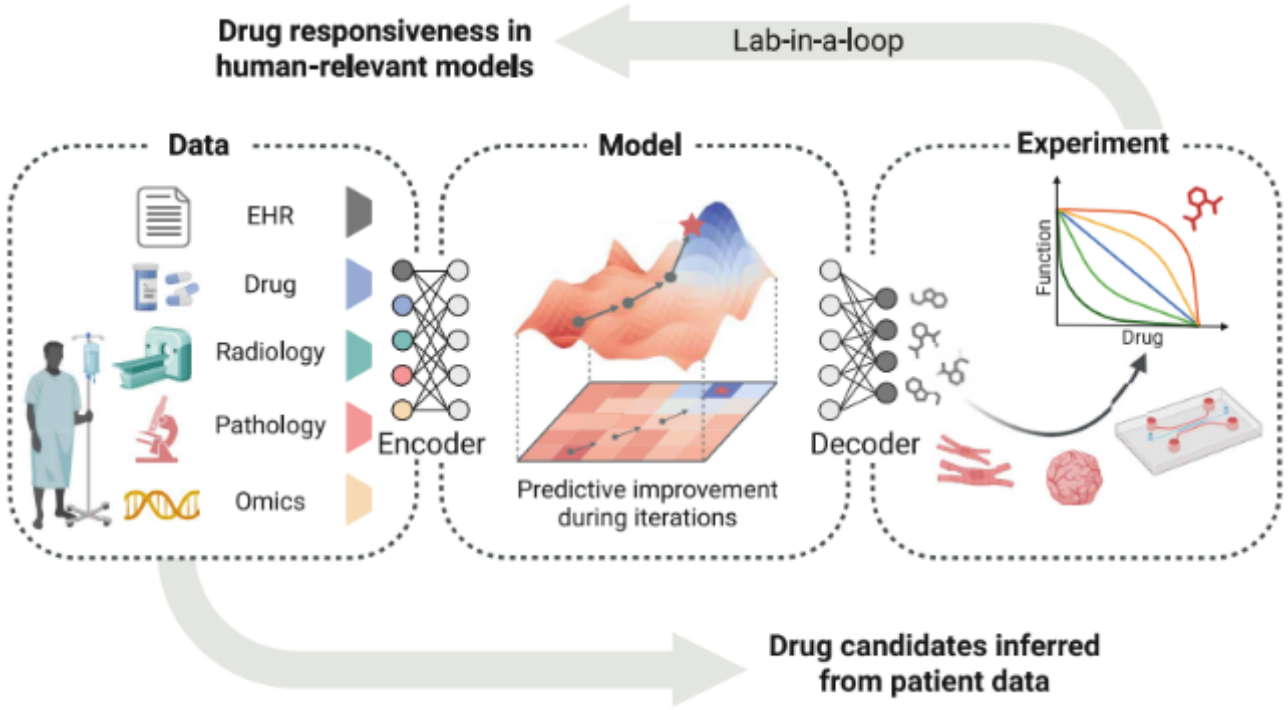
Platform Trials: Multi-Intervention, Matching, etc.



Franks PW et al. Nat Med. 2026 Apr;32(4):1211-1222 (PMID: 41872601)

New Approach Methodologies (NAMS): Precision Trials

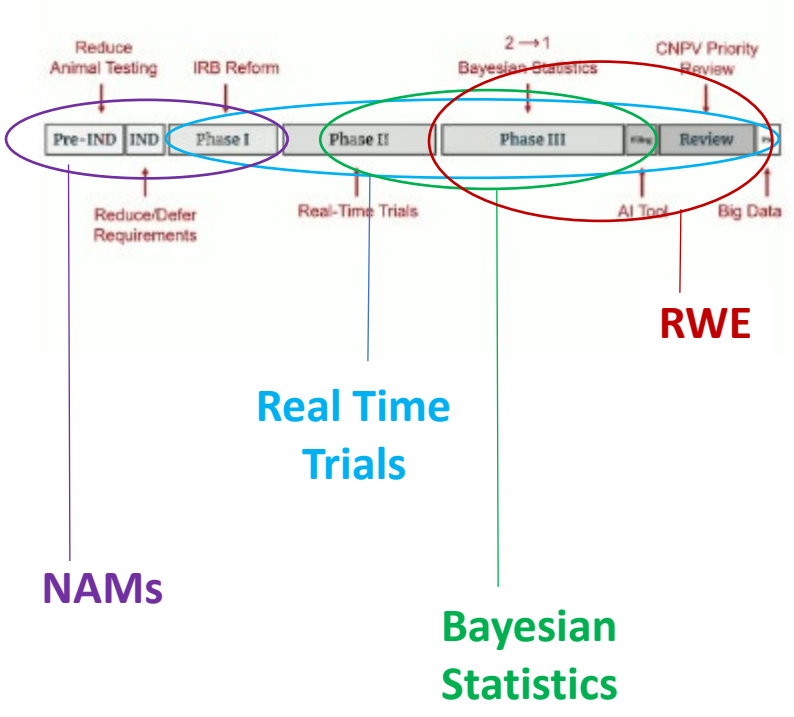
- Replace animal models
- Could be used to screen drugs with appropriate assays
- Could be used to guide intervention choice (e.g., cancer)
- Different tissues and can remove iPSC stage
- Problem: non-cell autonomous activity can be missed



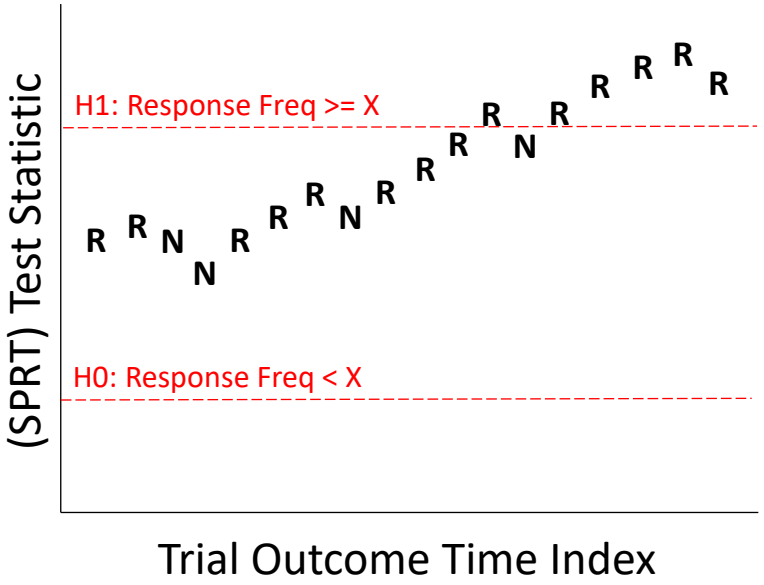
Science. 2026 Apr 23; 392(6796): 371-378 (PMID: 41990130)

Sequential Aggregation of SCED Results: *Real Time* Analyses

Real-Time Clinical Trials



Sequentially Aggregated Trials



- Boundaries for accepting/rejecting H0 set in advance based on Type I, II error rates, H0, assumed variation
- Type I error rate defining response in a single trial must be balanced with type I for testing response frequency

Sampling Burden Reductions

- 100 simulated modified SPRTs using N-of-1 trials
- 4 intervention comparison periods with 50 measurement (no washout periods, randomization, serial correlation, or carry over effects)

Schork et al. *Harv Data Sci Rev*. 2022;2022(SI3)

Integrating AI Prediction Models with SCEDs Within a Learning System

Epidemiology	Clinical (EHR) Data	Model Organisms	Cellular Constructs
↕	↕	↕	↕
Biomarker Specific Studies	Clinical Epidemiology Studies	Physiological Studies	*In vitro* biomarker analyses
↕	↕	↕	↕
Emulated Clinical Trials	Population-Based Trials	Non-Human Intervention Trials	Cell Perturbation Studies

Large Language Model (LLM)?

Response Prediction Models
(e.g., Digital Twin Analyses)

Pink Sheet – FDA's Califf On Real World Evidence: 'Use It For The Right Purposes'

Single Case Experimental Designs (SCEDS)

↕

Aggregated SCED Results

↕

Broad Population-Level Comparative Trials

- Intervention matching
- Better monitoring devices
- Patient engagement strategies
- Biomarkers/Surrogate endpoints
- Causal relationships

Learning System

Adapted from Schork and Goetz, *Nature Communications* (PMID: 40447582)

REAGAN-UDALL FOUNDATION FOR THE FDA

Lunch

We will resume at 1:05pm ET

XPRIZE Healthspan and PROSPR Awardees:
Evidence Being Built at Scale

REAGAN-UDALL FOUNDATION FOR THE FDA

Dr. Jamie Justice, XPRIZE Healthspan

Presenters

- **David A. Brown, PhD**, Chief Scientific Officer, Stealth BioTherapeutics
- **Zahi A. Fayad, PhD**, Lucy G. Moses Professor of Medical Imaging and Bioengineering, Icahn School of Medicine, Mount Sinai
- **Blake Rasmussen, PhD**, Professor and Chair, UT San Antonio Long School of Medicine

Dr. Andrew Brack, ARPA-H PROSPR

Presenters

- **Brianna Stubbs, PhD**, Director of Translational Science, Buck Institute for Research on Aging
- **James Peyer, PhD**, Founder & CEO, Cambrian Bio
- **George A. Kuchel, MD, CM, FRCP**, Director, UConn Center on Aging, University of Connecticut

XPRIZE Healthspan

REAGAN-UDALL FOUNDATION FOR THE FDA

Jamie Justice, PhD

Executive Director, XPRIZE Healthspan
XPRIZE Foundation

XPRIZE Healthspan and PROSPR Awardees
Evidence Being Built at Scale

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD | GSK

PRIZE PURSE

$101 MILLION PRIZE

$10 MILLION BONUS

BREAKTHROUGH

Seven year global competition to advance proactive, accessible therapeutics that can improve function and increase human healthspan.

TESTING & JUDGING

10+ Finalist Teams will begin 1-year randomized controlled clinical trials in 2026.

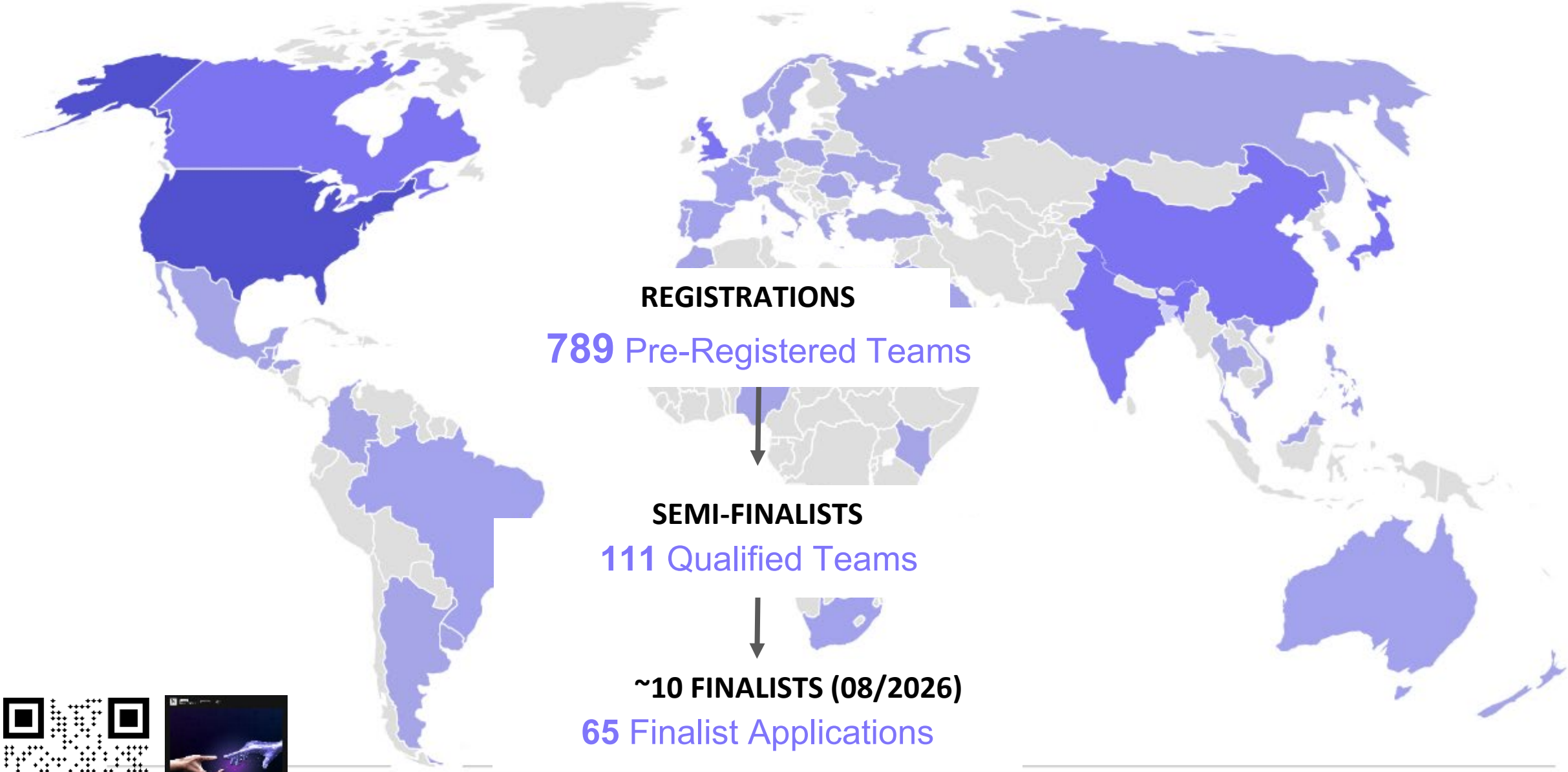
The **WINNING TEAM** must demonstrate that their therapeutic treatment restores muscle, cognitive, and immune function in older persons. The therapeutic treatment must take 1-year or less.

Awarding of the best team is indexed to **response thresholds** that surpass age-related declines expected over 10 years, 15 years, or 20 years in referent populations.

THE XPRIZE HEALTHSPAN TIMELINE

QUALIFYING SUBMISSION		SEMI-FINALS		FINALS
Research & Development	100+	Proof-of-Concept Clinical Studies	10+	1-Year Clinical Trials in Older Adults
Milestone 1 $10M	40 TEAMS	Milestone 2 $10M	10 TEAMS	Grand Prize Up to $81M
AWARDED **2025**		AWARD IN **2026**		AWARD IN **2030**

https://www.xprize.org/competitions/healthspan#guidelines



REGISTRATIONS

789 Pre-Registered Teams

SEMI-FINALISTS

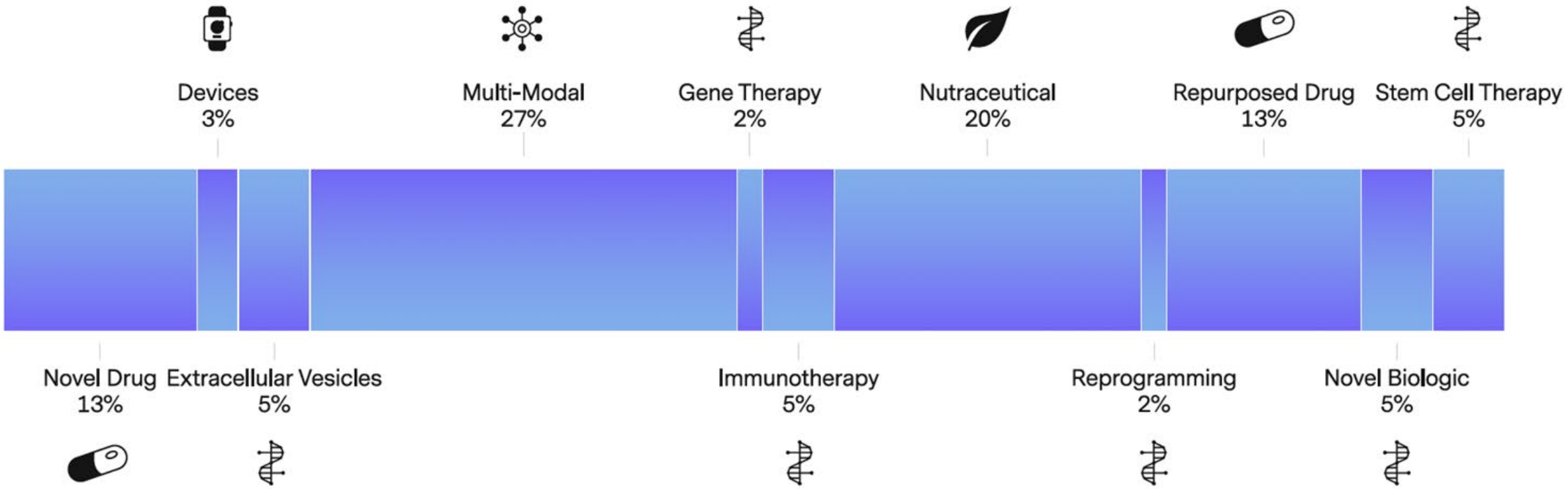
111 Qualified Teams

~10 FINALISTS (08/2026)

65 Finalist Applications

1-5 6-20 21-50 50+

XPRIZE HEALTHSPAN- PROPOSED MODALITIES



2025 Innovations Landscape Report

REAGAN-UDALL FOUNDATION FOR THE FDA

David A. Brown, PhD

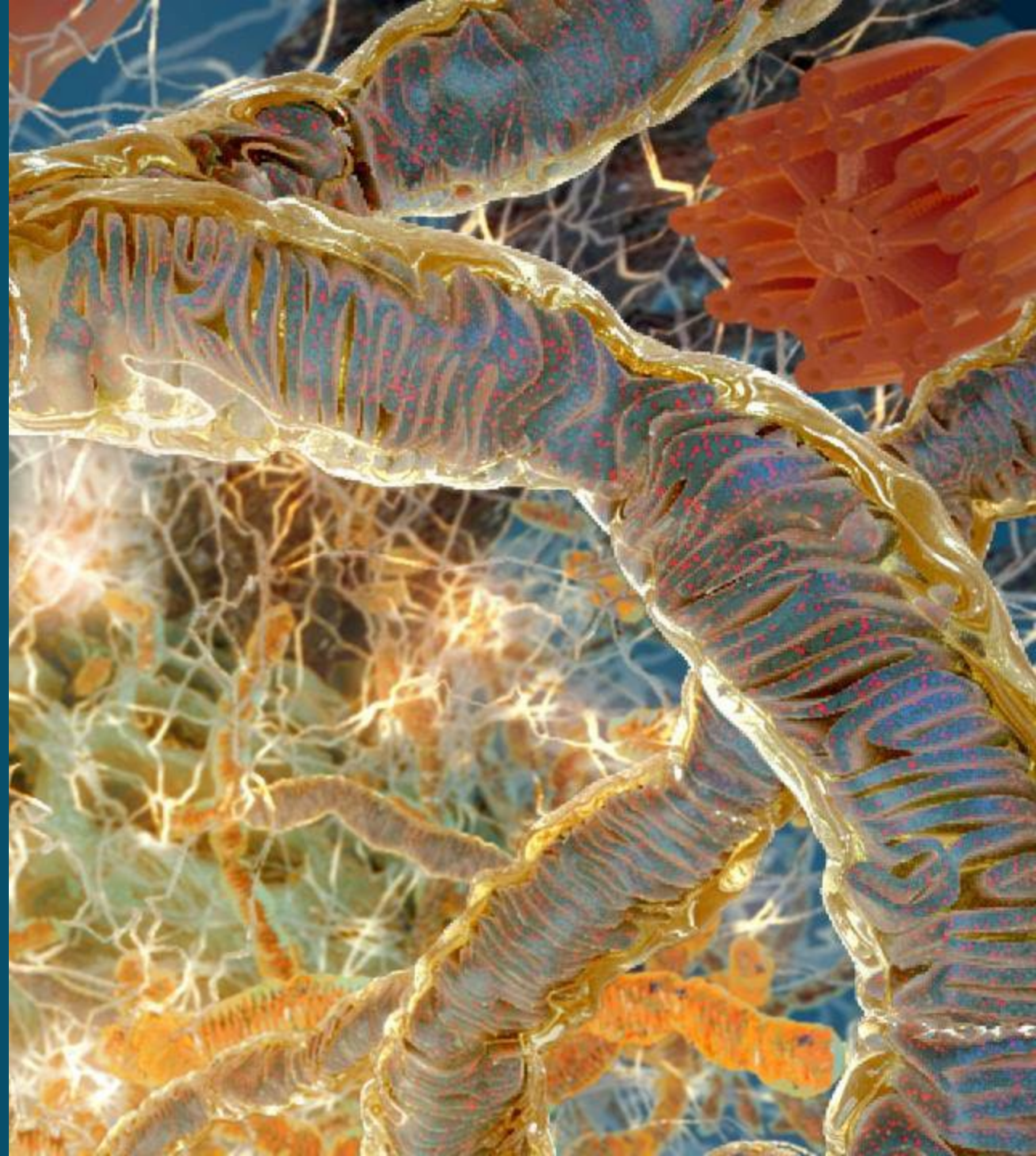
Chief Scientific Officer
Stealth BioTherapeutics

Stealth BIOTHERAPEUTICS

Influencing Healthspan by Targeting Mitochondria

David A. Brown, Ph.D.
Chief Scientific Officer
Stealth BioTherapeutics

On behalf of: *The Mitochondrial All-Stars*
XPRIZE Healthspan Semi-finals Team



Forward-Looking Statements

We are an “emerging growth company” as defined under the Securities Act of 1933, as amended (the “Act”).

These presentation slides are intended for educational purposes only. Any discussion of investigational uses, unapproved indications, or compounded drugs does not imply FDA approval or endorsement. The use of this material for promotional purposes is strictly prohibited.

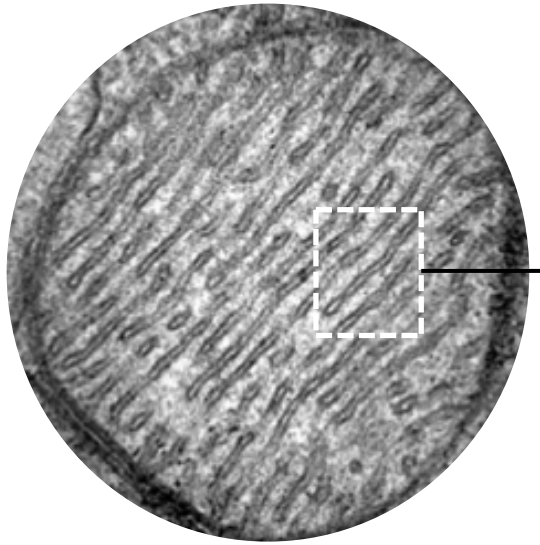
These slides and the accompanying oral presentation contain forward-looking statements. All statements other than statements of historical fact contained in this presentation, including statements regarding our future results of operations and financial position, business strategy and plans and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements by terms such as “may,” “should,” “expects,” “plans,” “anticipates,” “could,” “intends,” “target,” “projects,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negative of these terms or other similar expressions. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. The forward-looking statements contained in this presentation reflect our current views regarding future events, and we do not assume any obligation to update any forward-looking statements.

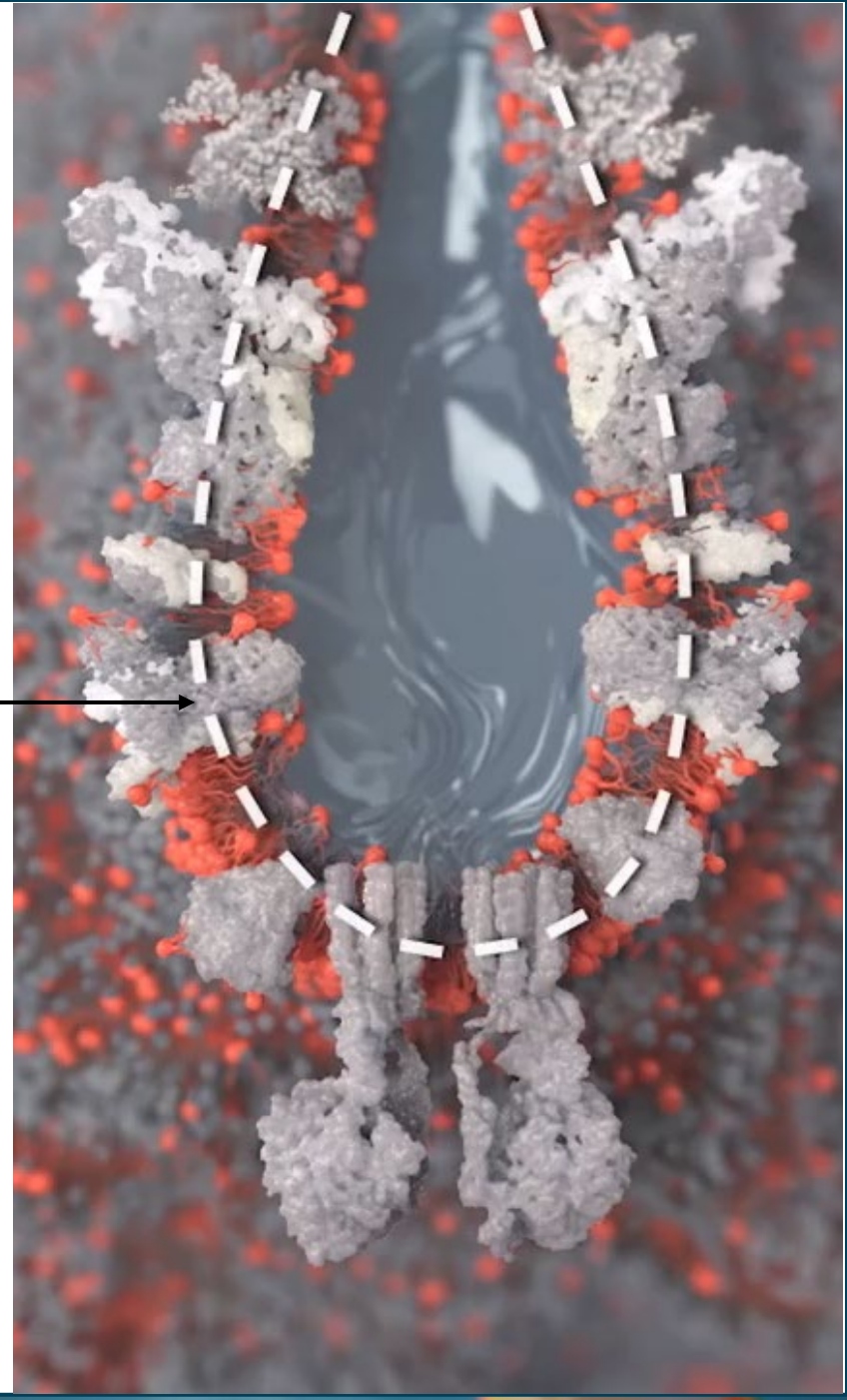
Certain data in this presentation was obtained from various external sources. We do not make any representation as to the accuracy or completeness of that data or undertake to update such data after the date of this presentation. Such data involves risks and uncertainties and are subject to change based on various factors.

Mitochondria Power Biological Life

Stealth BioTherapeutics is at the forefront of mitochondrial medicine

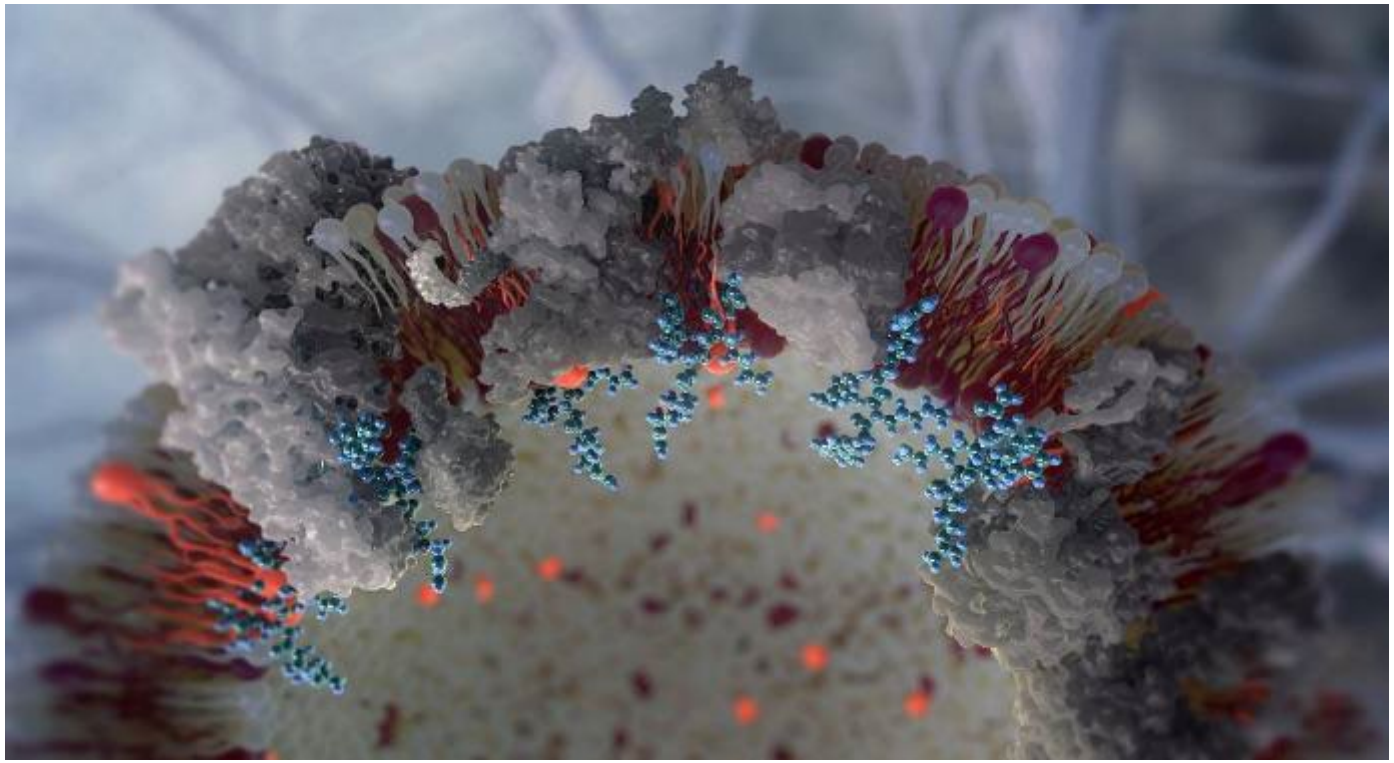
- **FOUNDED** on the premise that mitochondrial dysfunction is integral to Healthspan
- **FASCINATED BY MITOCHONDRIA** and the potential to *transform* Healthspan pathologies
  - Intracellular energy grid that influences nearly every aspect of cell/organ function
  - Mitochondrial dysfunction is a central driver for aging & age-related diseases
- **LEADING MITOCHONDRIAL MEDICINE**
  - Decades of experience developing mitochondrial- targeted therapeutics
  - Small molecules at various stages of development





Targeting Mitochondria with Elamipretide

Accelerated approval for an ultra-rare syndrome in 2025; extensive evaluation in preclinical aging models



Elamipretide is a mitochondria-targeting peptide that binds to cardiolipin in the inner mitochondrial membrane and improves mitochondrial structure-function

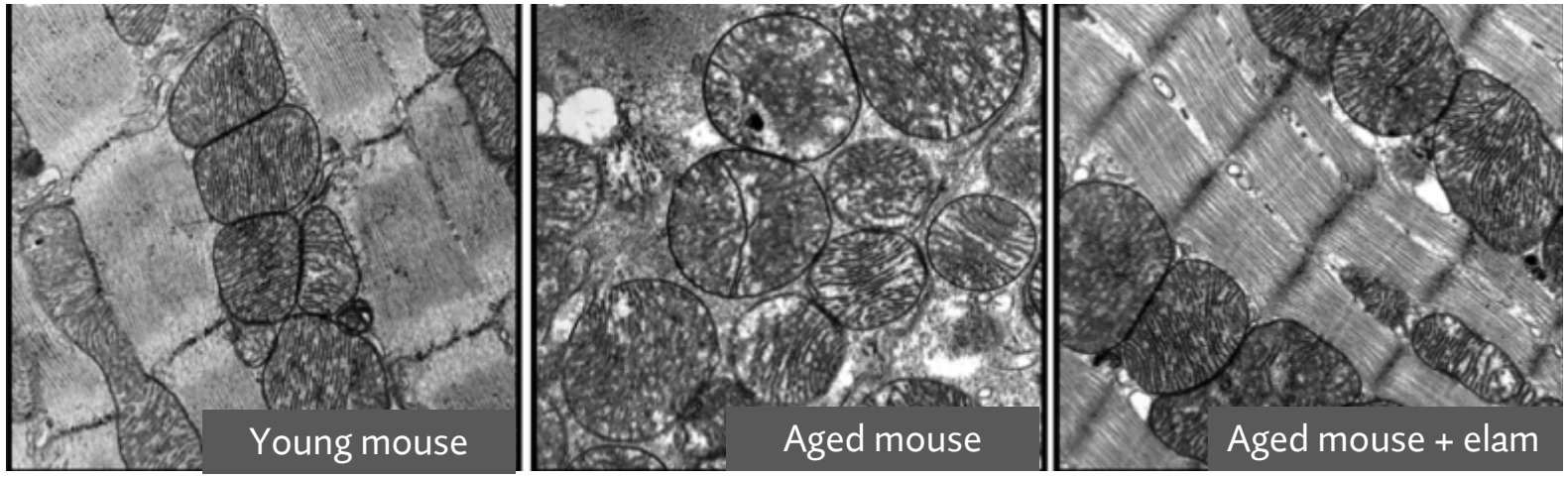
- Assessed in many preclinical models of aging and disease*
- Well-characterized clinical safety profile (>1700 individuals; >400 patient years)
- First and only FDA-approved mitochondria-targeted therapy
  - Approved in Sept 2025 under Subpart H (accelerated approval) for an ultra-rare disease
- Encouraging Phase 2 data in dry age-related macular degeneration
  - Leading cause of blindness in older adults
  - Phase 3 clinical trial fully-enrolled

* e.g., Hao et al., Oncotarget, 2017; Liu et al., Front. Aging Neurosci, 2021; Zhao et al, Journal of Neuroinflammation, 2019; Alam et al., Dis Model Mech. 2022; Whitson et al., Gero Science, 2021; Chiao et al., eLife, 2020; Sweetwyne et al., Kidney Int. 2017; Nickel et al., Aging Pathobiology and Therapeutics, 2022; Campbell et al., Free Radical Biology and Medicine, 2019; Siegel et al., Aging Cell, 2013

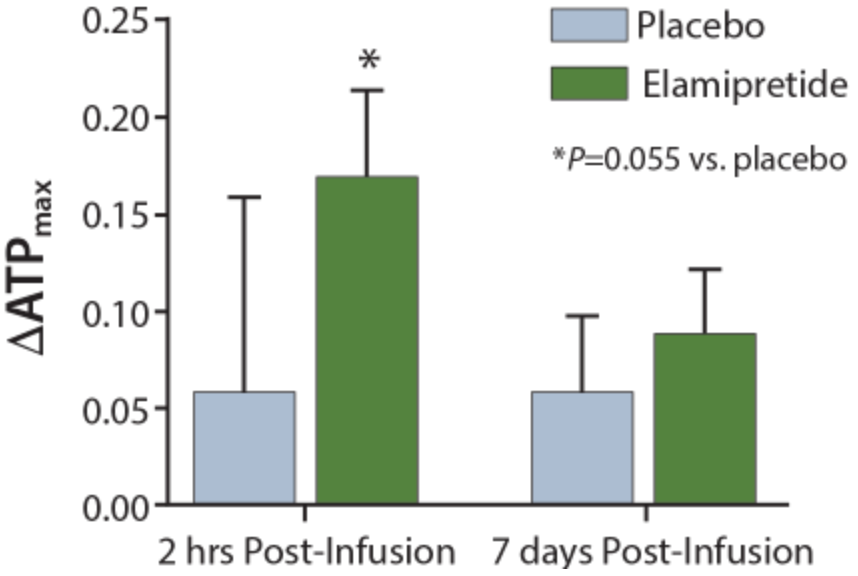
Elamipretide May Influence Age-Related Mitochondrial Dysfunction

Scientific validation from pre-clinical models and a small pilot study in humans

Muscle Mitochondrial Morphology in Aged Mice



Muscle ATP Production in Aged Adults (MOTION Trial)



- Elamipretide improved age-related heart, kidney, muscle, eye & brain dysfunction across non-clinical models (>50 peer-reviewed publications from independent investigators)
- Improved muscle ATP production rate in elderly subjects receiving acute elamipretide treatment (single IV infusion)
- Published studies also showed reduced markers of inflammation and improved cognitive function in animals

Szeto, Birk, Clin Pharm & Ther, Dec 2014; Szeto, Liu, ABB, 2018; Roshanravan et al. 2020

“Mitochondrial All-Stars” Team

XPRIZE Healthspan Semi-Finalists

XPRIZE HEALTHSPAN | HEVOLUTION | SOLVE FSHD

Chief Clinical Officer

Stealth BIOTHERAPEUTICS

HEALTHY AGING & LONGEVITY RESEARCH INSTITUTE

UNIVERSITY of WASHINGTON NATHAN SHOCK CENTER

Study of Healthy Aging and Physical Function with Elamipretide (SHAPE)

Mitochondrial All Stars successfully executed on aggressive XPRIZE Healthspan competition deadlines

SCREENING (28-days)	TREATMENT PERIOD (4-weeks)				END OF STUDY	FOLLOW-UP
n=35 screened; n=23 enrolled	Visit 1 baseline (BL)	Visit 2 baseline (BL)	Mid-treatment (phone)	Visit 3 (EOT)	Visit 4 (EOS)	EOT + 2 wks (Phone)
• Male/female age≥65-80 years • VO2peak ≤ 37.3ml/kg/min (men)/ ≤ 25.7ml/kg/min (women) (below 50% standard for 65 year old) • Ambulatory/able to complete 6MWT	• 6MWT • Demographics, vitals, ECG • Blood draw • CPET exercise test	• Muscle strength & fatiguability – knee extensor • Cognitive function • Elamipretide (IMP) dispensed, first treatment	• Check injection compliance • Subject experience	• Demographics, vitals, ECG • 6MWT • Blood draw • CPET exercise test	• 3-7 days after Visit 3 • 6MWT • Muscle strength & fatiguability • Cognitive function	• Safety follow-up • Subjective subject experience
	Elamipretide 40 mg 1X daily SC (single arm, open label)					

Study Objectives

Demonstrate our high-quality execution capability

- SHAPE was a Phase 2a investigator-initiated study conducted by Drs. Marcinek and Jayadev at University of Washington
- Kick-off June 2025; IND exemption received October 2025; FPFV November 2025; LPLV March 2026

Primary objective: evaluate safety and tolerability of daily SC elamipretide.

Secondary objectives: assess changes in inflammatory biomarkers, cognitive function, and skeletal muscle health

SHAPE Study Semi-Finals Data

Acceptable safety profile; interesting trends observed on muscle and cognitive function

Safety: Elamipretide was well tolerated; the most common treatment-emergent event was mild injection-site discomfort (33%). All participants (100%) completed the study and reported willingness to enroll in future clinical trials.

- Interesting trends, albeit in an open label, single arm study
- Supports initiation of a randomized placebo-controlled study to control for placebo/learning effects, etc.
- Broader data set to be presented by Drs. Marcinek and Liu at the upcoming American Aging Association Meeting (June 2026)

Next Steps To Advance Mitochondrial Medicine for Aging

XPRIZE Healthspan Finals proposal summer ’26; access requires clarity on regulatory pathway(s) for aging therapies

✓ Early Proof-of-Concept Studies:

Does one-time elamipretide treatment improve energy production and influence muscle fatigue in aged individuals?

✓ X-Prize Semi-Finals:

Can daily elamipretide for 1-month influence age-related declines/inform study design for a larger trial? Aged 60-85 years, n=23.

X-Prize Final Round:

Can daily elamipretide treatment for one year impact the loss of muscle, cognitive, and immune function in aged individuals?

Thank You

REAGAN-UDALL FOUNDATION FOR THE FDA

Zahi A. Fayad, PhD

Lucy G. Moses Professor of Medical Imaging and Bioengineering
Icahn School of Medicine, Mount Sinai

XPRIZE HEALTHSPAN · FINALS APPLICATION

HEALTHSPAN NYC-VITA 2030

Exercise, spermidine, and rapamycin to correct systemic inflammaging and extend healthspan

Phase 2 · Randomized 2:1, controlled, open-label
180 participants, ages 50–90 · 12-month intervention
BioMedical Engineering and Imaging Institute (BMEII)

Miriam Merad, MD, PhD · Zahi A. Fayad, PhD · Thomas Marron, MD · Fanny Elahi, MD, PhD · Ryan Walker, PhD

Icahn School of Medicine at Mount Sinai

Aging drives a systemic shift toward inflammatory myeloid biology

Our hypothesis:

Aging progressively replaces protective resident tissue macrophages with inflammatory, poorly reparative cells — a “macrophage shift” that drives decline across brain, muscle, and immune systems.

Recent literature has strengthened this model: the shift is reversible, and interventions that reduce inflammatory myeloid output restore function.

OUR STRATEGY

Rebalance hematopoiesis · reduce SASP · restore tissue homeostasis

BRAIN

Inflammatory myeloid cells drive neuroinflammation and degeneration

MUSCLE

Loss of resident macrophages impairs repair and regeneration

IMMUNE

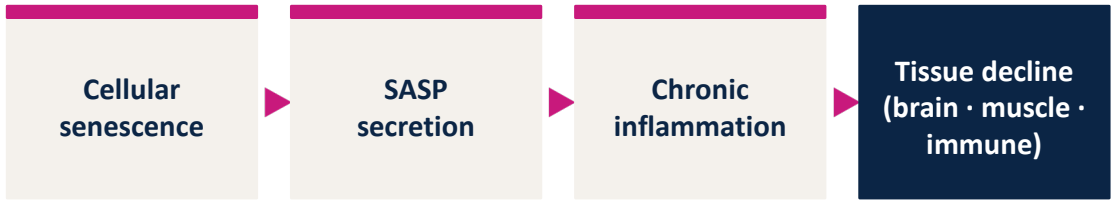
Skewed myeloid output suppresses adaptive immune competence

SASP: the senescence-associated secretory phenotype

Senescent cells stop dividing but don't die quietly.

They secrete a cocktail of pro-inflammatory cytokines, chemokines, growth factors, and proteases — the **senescence-associated secretory phenotype** — that drives chronic low-grade inflammation in surrounding tissue and across the body.

SASP is the mechanistic bridge between cellular senescence and **inflammaging** — and reducing it is the most tractable therapeutic lever in geroscience.



Reduce SASP → break the chain

OUR COMPOSITE SASP SCORE

Mean fold-change across 12 plasma analytes (Olink)

AREG *growth factor*	**HGF** *growth factor*	**TGFA** *growth factor*
FGF23 *growth factor*	**CCL7** *chemokine*	**CCL13** *chemokine*
CXCL13 *chemokine*	**IL-1α** *inflammasome*	**IL-1β** *inflammasome*
IL-18 *inflammasome*	**MMP12** *ECM remodeling*	**OLR1** *metabolic*

WHY THIS PANEL

Captures the breadth of the senescent secretome — growth factors, chemokines, inflammasome cytokines, ECM remodeling, and metabolic enzymes — in a single composite metric.

TERM COINED BY *Coppé, Desprez, Krtolica & Campisi · Annual Review of Pathology, 2010*

Two agents acting on complementary points of the macrophage shift

mTOR INHIBITOR

RAPAMYCIN

FINALS DOSE

Weekly · 2→4→6 mg

MECHANISM

Low-dose, intermittent mTOR inhibition dampens inflammation-driven HSPC proliferative drive and myeloid skewing. The 2–6 mg weekly window enhances rather than suppresses immune function.

SEMI-FINALS SIGNAL

Broader SASP reduction · ↑ EPO · ↑ GZMB · ↑ FLT3LG

ADVANCED

POLYAMINE · AUTOPHAGY INDUCER

SPERMIDINE

FINALS DOSE

40 mg PO daily, with food

MECHANISM

Endogenous polyamine that induces autophagy, reduces myelopoiesis (GMPs), and lowers circulating IL-6, IL-1α/β, IL-18, IL-33. Source: Chrysea Labs (Finals supplier).

SEMI-FINALS SIGNAL

Plasma PK saturates at 40 mg · modulated brain-aging markers

ADVANCED

WHY THIS COMBINATION Distinct, complementary nodes — autophagy induction + mTOR restraint — converging on reduced inflammatory myeloid output.

Four independent signals chain into one story of restored resilience

01 STAGE 01

SASP

p = 0.029

Senescence-Associated Secretory Phenotype

WHAT IT IS

12-analyte composite of cytokines, chemokines, growth factors, proteases secreted by senescent cells

WHAT IT MEANS

Inflammatory pressure releases — rapamycin acts upstream on senescence translation (Laberge, Nat Cell Biol 2015)

02 STAGE 02

EPO

p = 0.063

Erythropoietin

WHAT IT IS

Renal hormone driving RBC production; suppressed by chronic inflammation (HIF-2α axis)

WHAT IT MEANS

Tissue oxygenation signaling recovers — prerequisite for VO_2max and brain function

03 STAGE 03

FLT3LG

trend

FLT3 Ligand

WHAT IT IS

Cytokine driving differentiation of hematopoietic progenitors into dendritic cells

WHAT IT MEANS

Dendritic cell production machinery responding — bridge between innate and adaptive immunity

04 STAGE 04

GZMB

p = 0.06

Granzyme B

WHAT IT IS

Serine protease used by cytotoxic $CD8^+$ T cells and NK cells to kill targets; plasma levels = functional cytotoxicity

WHAT IT MEANS

CD8 cytotoxic killing returns — adaptive immune competence restored (Mannick, Lancet HL 2018)

CONVERGENT BIOLOGY

Inflammatory pressure releases → oxygenation axis recovers → DC signaling responds → CD8 killing function returns

PHASE 2 DESIGN

Finals trial design: 180 participants, 2:1 randomization, 12-month intervention

180

participants enrolled
ages 50–90

2:1

INTERVENTION · n = 120 (108 evaluable)

Spermidine 40 mg PO daily · Rapamycin weekly (2→4→6 mg escalation) ·
Structured exercise: 2× HIIT (20 min) + 3× resistance (40 min) per week, home-based with Fitbit

CONTROL · n = 60 (54 evaluable)

Lifestyle modification counseling (AHA/CDC minimums) + Fitbit + matched visit schedule

STRATIFICATION

Age (50–69, 70–90) and sex; <60:40 sex cap

RANDOMIZATION

REDCap blocked, 30 days post-consent; two baselines

POWER

85% power, α = 0.05, responder rates 30% vs 10%

OVERSIGHT

Independent DSMB: Bhatt, Zitvogel, Terrier, Friedman

CONTROL ARM · WHAT IT ACTUALLY CONSISTS OF

AHA / CDC physical activity guidelines, delivered as structured counseling

THE GUIDELINE · HHS/AHA/CDC ADULT MINIMUMS

≥ 150 *min/week*

Moderate-intensity aerobic activity

or ≥75 min vigorous, or equivalent combination

≥ 2 *days/week*

Muscle-strengthening activity

All major muscle groups, moderate intensity or greater

≥ 3 *days/week*

Balance training (older adults)

Plus gradual ramp-up if previously sedentary

HOW WE DELIVER IT

01

Baseline counseling session

20–30 min, delivered by study exercise physiologist using the 5 A's framework (Ask · Advise · Assess · Assist · Arrange). Personal weekly target set against the guideline.

02

Standardized materials

CDC "Move Your Way" guide + AHA "Healthy for Good" brochure provided at consent. No prescribed regimen, no progression, no supervised sessions.

03

Passive reinforcement at visits

Guidelines re-stated and Fitbit data reviewed at each clinic visit. No active coaching or goal revision between visits.

04

Measured, not assumed

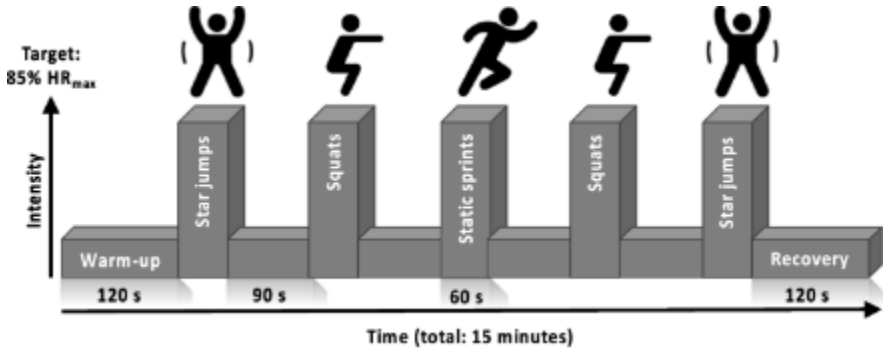
Fitbit weekly active-minutes tracked descriptively against the 150-min threshold — characterizes contrast rather than assuming sedentary controls.

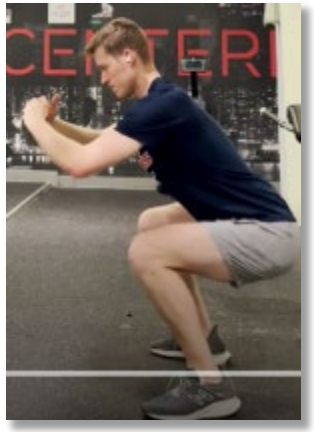
THE CONTRAST **Structured, supervised, progressive HIIT + resistance + drugs** *vs* **unsupervised, self-directed activity at guideline minimums**

Exercise design (5 times per week for 12 months)

2 x/week: high intensity interval training (HIIT)

- 3 exercises (no equipment needed)
- Sessions target 85% age-predicted HR max





Warmup (5min)

Exercise (~15min)

Cool down (5min)

3 x/week: resistance training

- 6 core exercises (resistance bands)
- Progressive repetitions and load

Lower Body

Movement	Exercise
Lower Body extension	squat
hip hinge	deadlift
lateral rotatory	lateral walk

Upper Body

Movement	Exercise
horizontal push	modified press up
full-body extension	push press
Horizontal pull	seated row

PRIMARY ENDPOINTS

Composite responder endpoint across the three XPRIZE domains

A participant is a responder if they achieve clinically meaningful improvement in **≥1 of 3 domains** at 12 months.

MUSCLE FUNCTION

VO_2max

≥ 3 mL/kg/min

Improvement over averaged baseline at 12 months. Gold-standard cardiorespiratory fitness via Vyntus CPX metabolic cart.

Secondary endpoints

Keiser leg press · 6MWT · HGD · MRI body composition

BRAIN FUNCTION

Processing speed

Stabilize or ≥ +10%

Cogstate composite — stabilization if MOCA 22–26, ≥10% improvement if MOCA >26. Supplemented with NeuroUX home monitoring.

Secondary endpoints

Plasma NfL & GFAP (NULISA + Simoa orthogonal)

IMMUNE FUNCTION

HSPC reduction

≥ 30% decrease

Circulating $CD34^{+}CD38lo/–CD49f^{+}$ HSPCs at 12 months vs averaged baseline (Park et al., Science 2024).

Secondary endpoints

CyTOF, scRNA-seq, Olink, T-cell functional assay (OCCAM)

SECONDARY ENDPOINTS · FULL DETAIL

Deep phenotyping across muscle, brain, and immune domains

MUSCLE FUNCTION

- **Keiser pneumatic leg press**
  Peak lower-extremity strength and power
- **6-minute walk test (6MWT)**
  Validated VO_2max estimate
- **Hand grip dynamometry (HGD)**
  Whole-body muscular strength surrogate
- **FRAIL scale (5-item)**
  Frailty phenotype assessment
- **Quantitative MRI (baseline + 12 mo)**
  Skeletal muscle volume · intramuscular fat fraction · visceral & subcutaneous adipose volumes

BRAIN FUNCTION

- **Plasma NfL (NULISA)**
  Neurofilament light chain — neuronal injury
- **Plasma GFAP (NULISA)**
  Glial fibrillary acidic protein — astroglial activation / neuroinflammation
- **Quanterix Simoa HD-X**
  Orthogonal confirmation with absolute quantification
- **NeuroUX (smartphone, between visits)**
  Higher-frequency processing speed and executive function sampling
- **Mixed linear effects models**
  Intra-individual biomarker trajectories controlling for age, sex, baseline

IMMUNE FUNCTION

- **CyTOF immune phenotyping (HIMC)**
  High-dimensional cellular profiling
- **Single-cell RNA-seq**
  Transcriptional state of immune subsets
- **Olink 48-plex (2 µL plasma)**
  IL-1β, IL-6, IL-18, IL-2, IL-7, IL-15, IFNγ + SASP index
- **Olink Explore HT (exploratory)**
  ~5,400 proteins for unbiased discovery
- **OCCAM T-cell functional assay**
  PMA/ionomycin → IFNγ/TNFα/IL-17 across $CD4^+$/$CD8^+$; CMV-peptide for immune reserve

ALSO EXPLORATORY Monocyte functional assays · Metabolomics · Microvascular angiogenesis · **Multi-omic integration via DigiTwin**

Execution plan: recruitment infrastructure, timeline

TIMELINE

RECRUITMENT INFRASTRUCTURE

- Mount Sinai primary & specialty clinics
- BioMe + Mount Sinai Millions biobank registries (pre-consented for contact)
- Mount Sinai Healthspan Program + Sinai Well clinical network
- Longevity Docs physician network + MyChart campaigns + community mailings

WHY WE'LL DELIVER

A rational intervention, biological signal at 60 days, and the infrastructure to scale.

01

Mechanism-led

Exercise + spermidine + rapamycin act on complementary points of the macrophage shift — each with human signal.

02

Signal-driven

Semis showed broader SASP reduction with rapamycin, plus EPO, granzyme B, and FLT3LG gains pointing to restored resilience.

03

Built to scale

BMEII, HIMC, OCCAM Immune, and the DigiTwin platform deliver standardized, reproducible immune, muscle, and brain readouts.

Miriam Merad, MD, PhD · Zahi A. Fayad, PhD · Thomas Marron, MD · Fanny Elahi, MD, PhD · Ryan Walker, PhD

Icahn School of Medicine at Mount Sinai

REAGAN-UDALL FOUNDATION FOR THE FDA

Blake Rasmussen, PhD

Professor and Chair
UT San Antonio Long School of Medicine

Low-Intensity Ultrasound for Healthy Aging

UT Health San Antonio

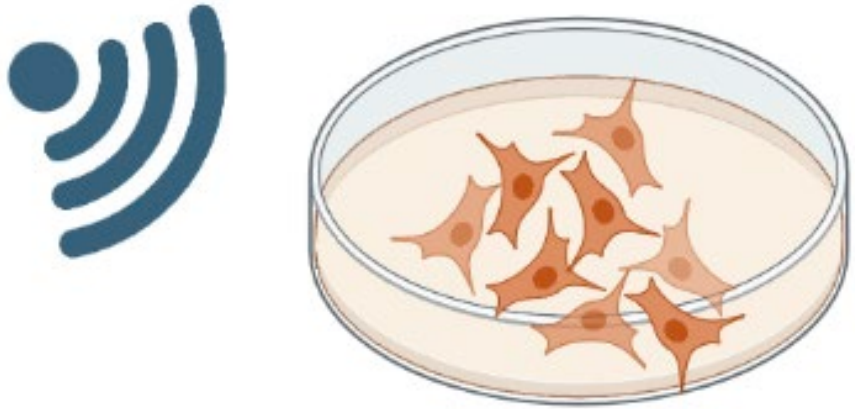
Barshop Institute for Longevity & Aging Studies

Blake B. Rasmussen, PhD
Professor & Chair
School of Medicine
Department of Cellular & Integrative Physiology

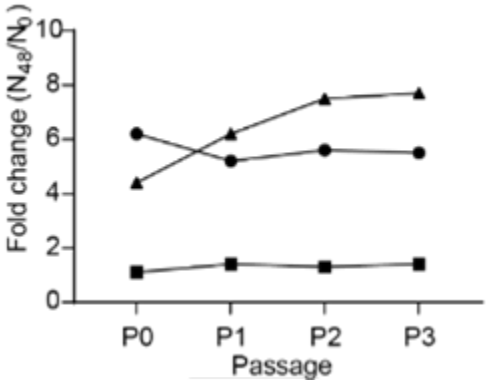
THE UNIVERSITY OF TEXAS AT SAN ANTONIO

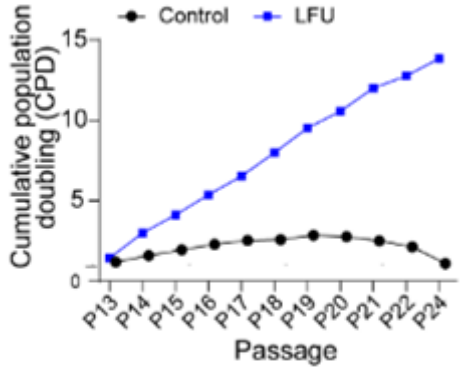
UT Health San Antonio
The University of Texas at San Antonio

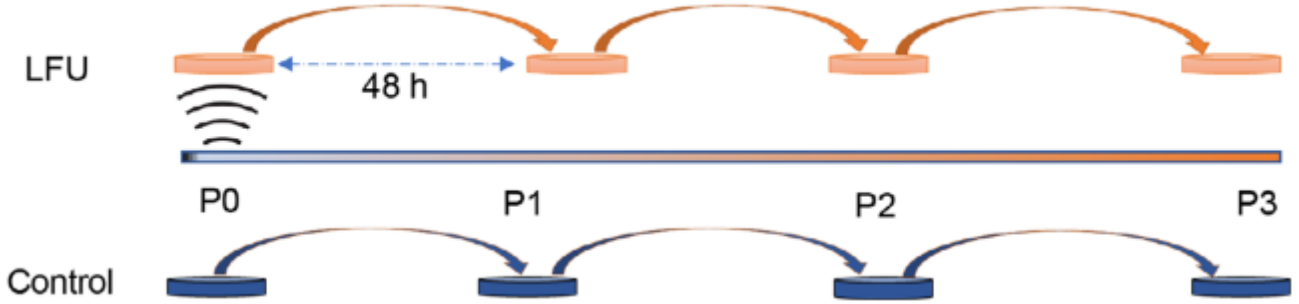
Rejuvenation of Senescent Cells *In Vitro* by Low-Frequency Ultrasound



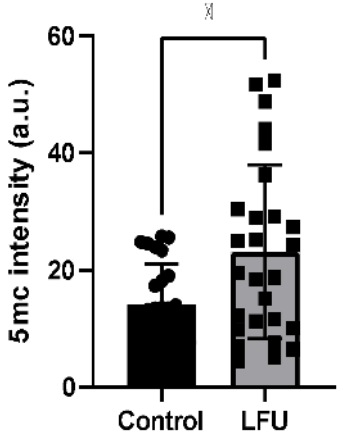
LFU reverses induced and replicative senescence

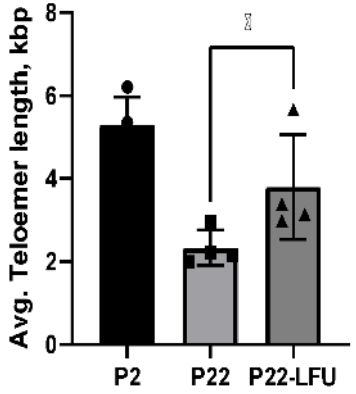






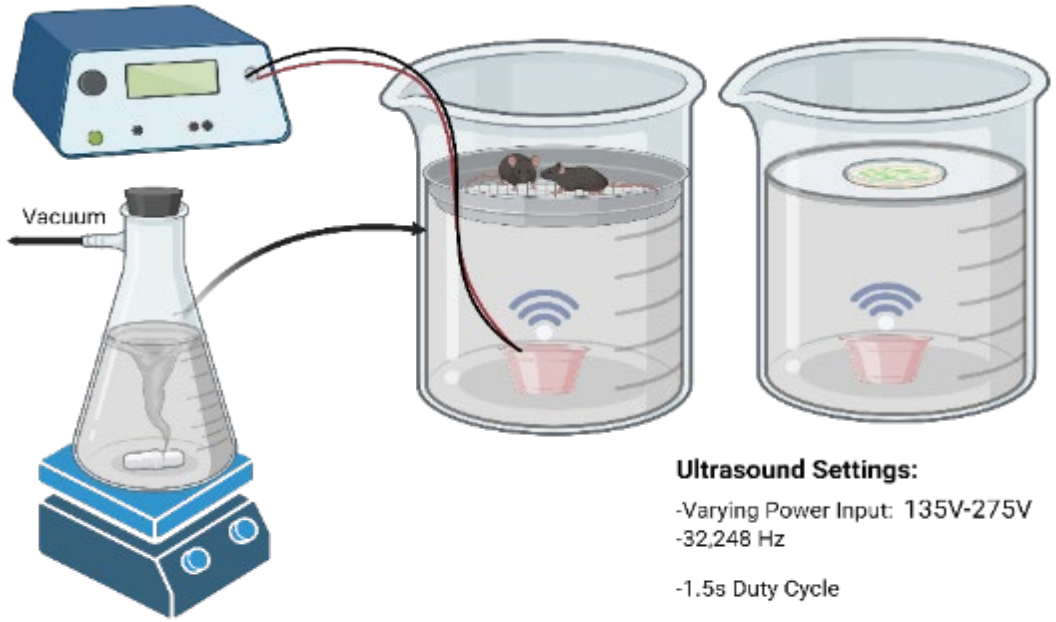
LFU increases DNA methylation/telomere length





Aging Cell 2025 Mar 3:e70008. doi: 10.1111/acel.70008

Rejuvenation of Senescent Cells *In Vivo* by Low-Frequency Ultrasound



Ultrasound Settings:

-Varying Power Input: 135V-275V
-32,248 Hz

-1.5s Duty Cycle

-30min Total (600 pulses)

-7-10cm above transducer

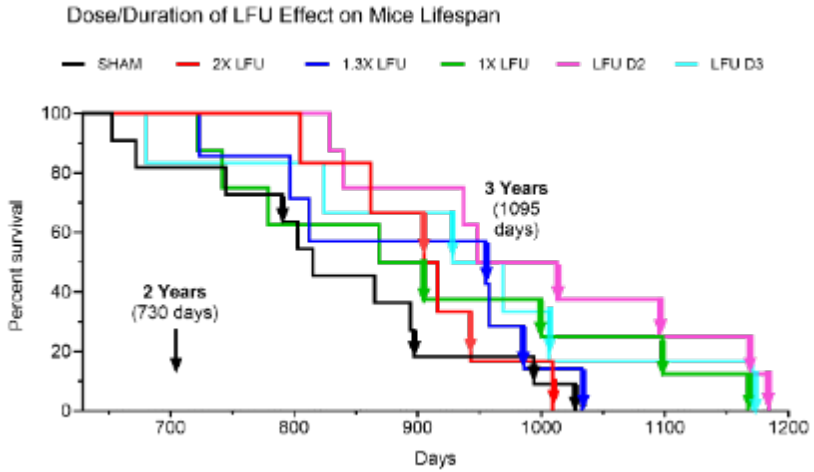
-Output power: 4-8Pa

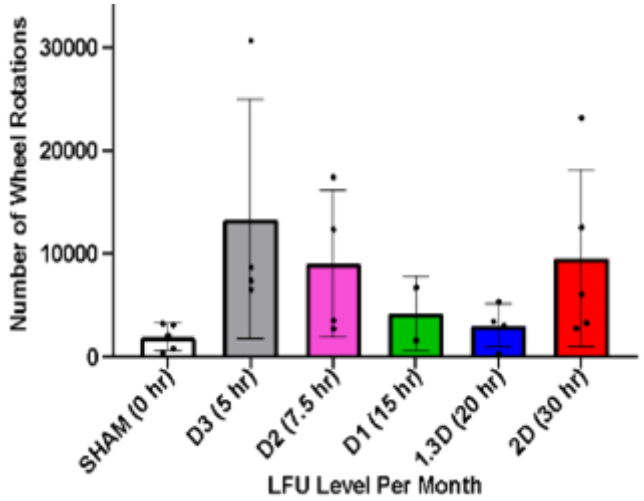
(d) 30-month-old control mice

(e)

30-month-old LFU treated mice

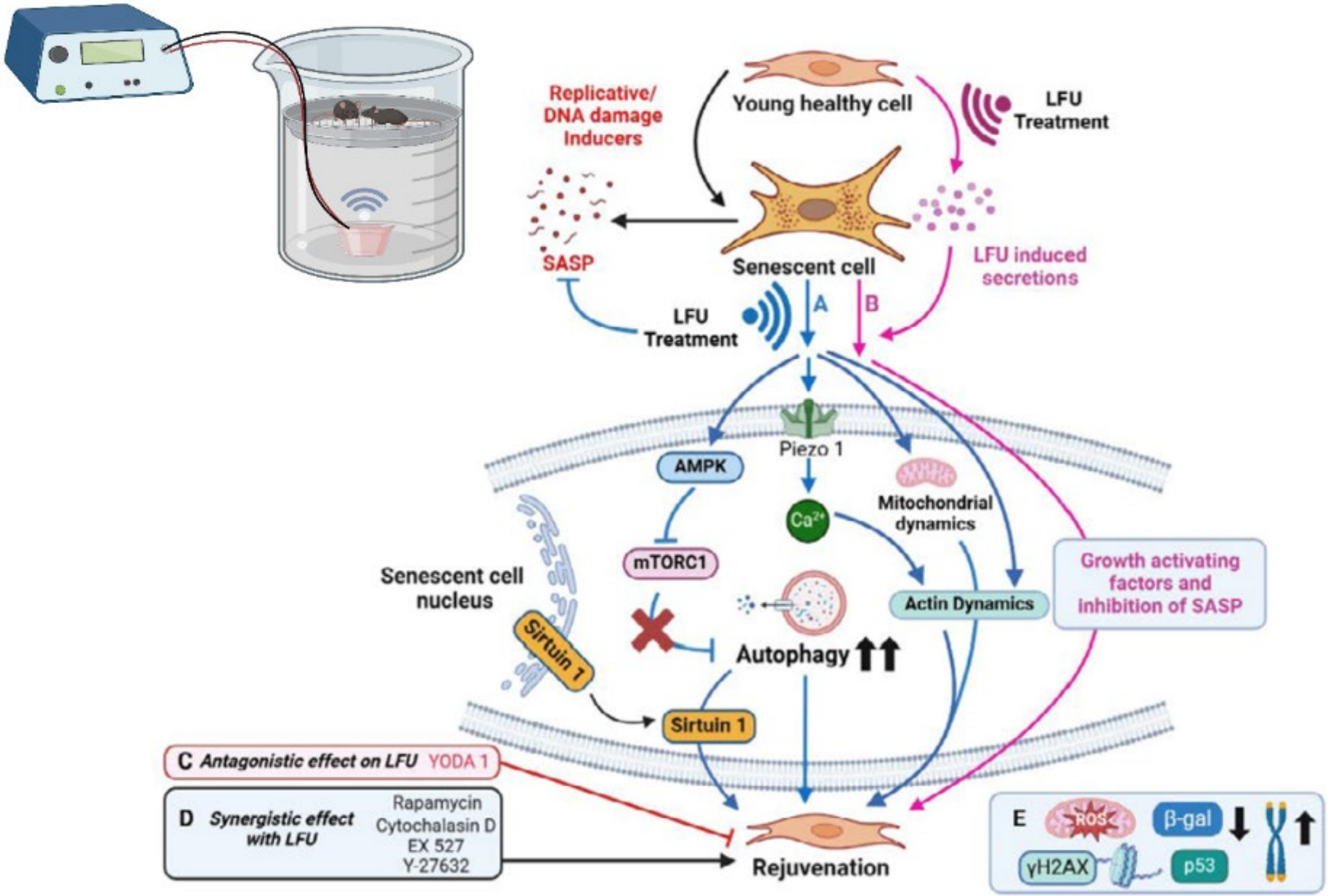
Optimum LFU increases lifespan and physical activity



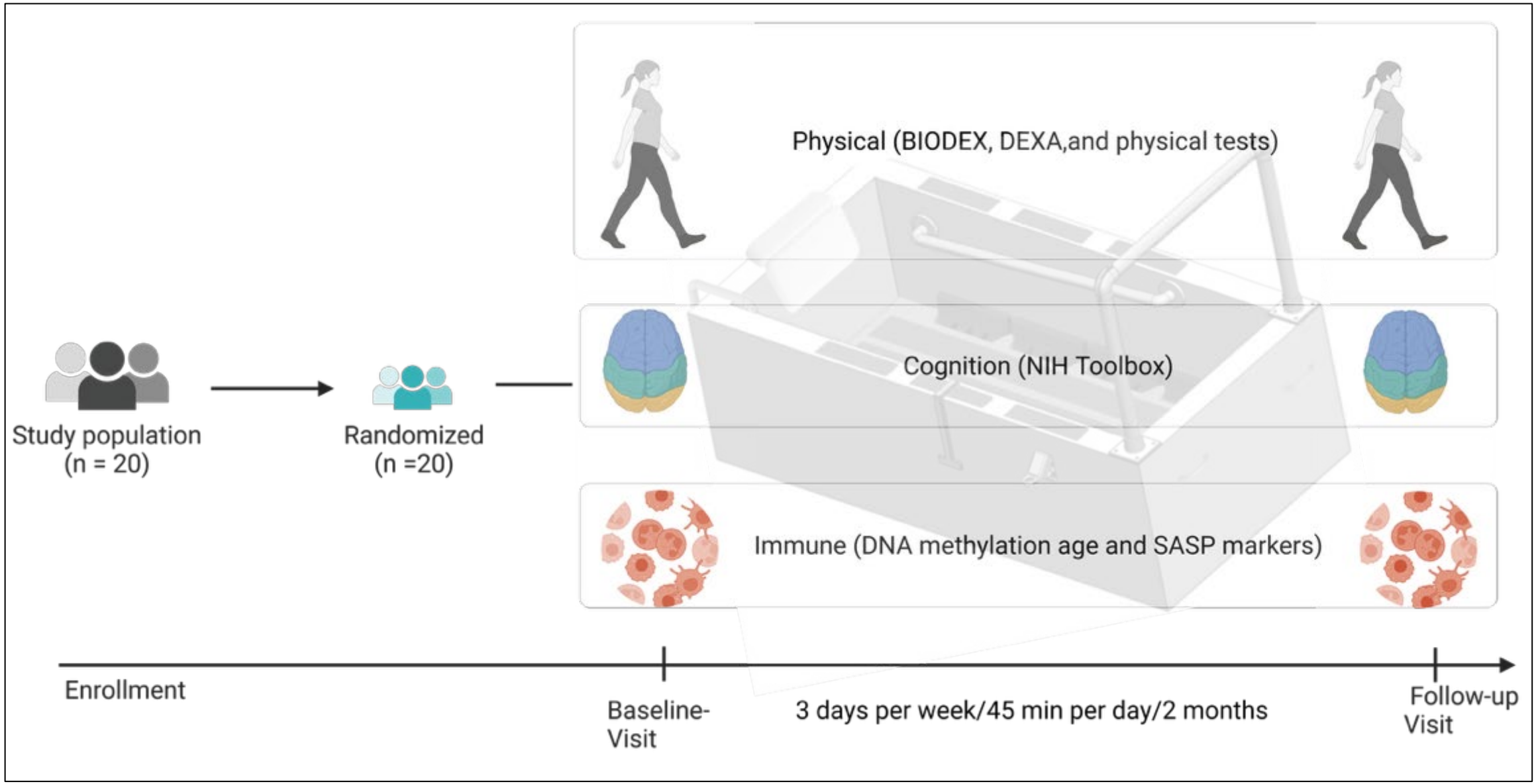


Aging Cell 2025 Mar 3:e70008. doi: 10.1111/acel.70008

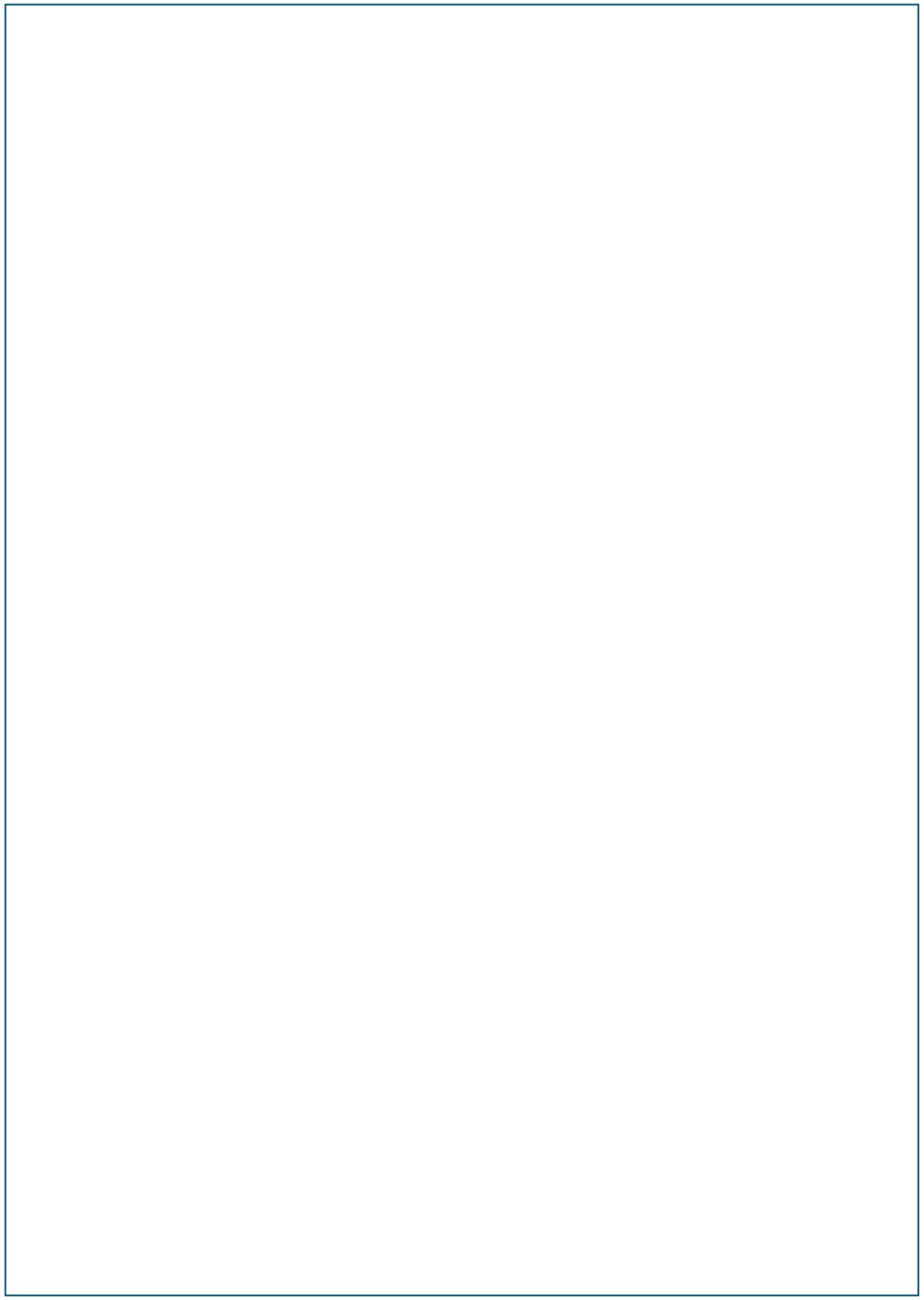
Mechanism of Action?



Current XPRIZE Semi-Finals Study Design



Proposed XPRIZE Finals Study Design



Low-Frequency Ultrasound for Healthy Aging

https://barshopinstitute.uthscsa.edu

Research Infrastructure for Basic Biology of Aging and Clinical Trials

NIA P30	San Antonio Nathan Shock Center of Excellence in the Biology of Aging
NIA P30	San Antonio Claude D. Pepper Older Americans Independence Center
NIA U01	San Antonio Center for Testing Potential Anti-Aging Interventions (NIH ITP)
NIAMS U01	Clinical Center for MoTrPAC (Molecular Transducers of Physical Activity Consortium)
VA	San Antonio GRECC (Geriatrics Research & Education Clinical Center)
ARPA-H	PROSPR VITAL-H
XPRIZE	Ultrasound for Healthy Aging

Business Partner: Novaquoustics, Inc.

PROSPR

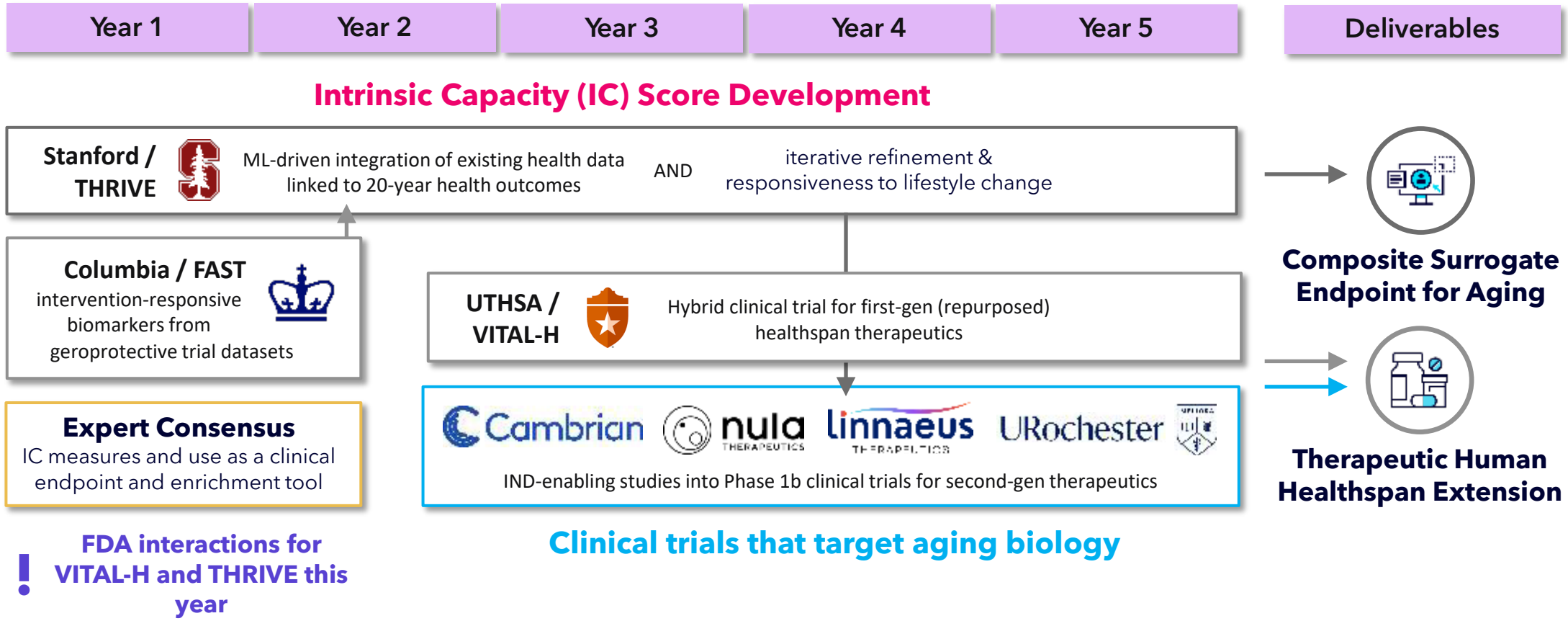
REAGAN-UDALL FOUNDATION FOR THE FDA

Andrew Brack, PhD

Program Manager, PROactive Health Office
Advanced Research Projects Agency for Health

XPRIZE Healthspan and PROSPR Awardees
Evidence Being Built at Scale

PROSPR is generating **FDA-relevant** therapeutics, trials, and touchpoints



REAGAN-UDALL FOUNDATION FOR THE FDA

Brianna Stubbs, PhD

Director of Translational Science
Buck Institute for Research on Aging

THRIVE: Intrinsic Capacity – Creating a Validated Measure

Brianna Stubbs, PhD Buck Institute for Research on Aging

Session: XPRIZE Healthspan and PROSPR Awardees: Evidence Being Built at Scale

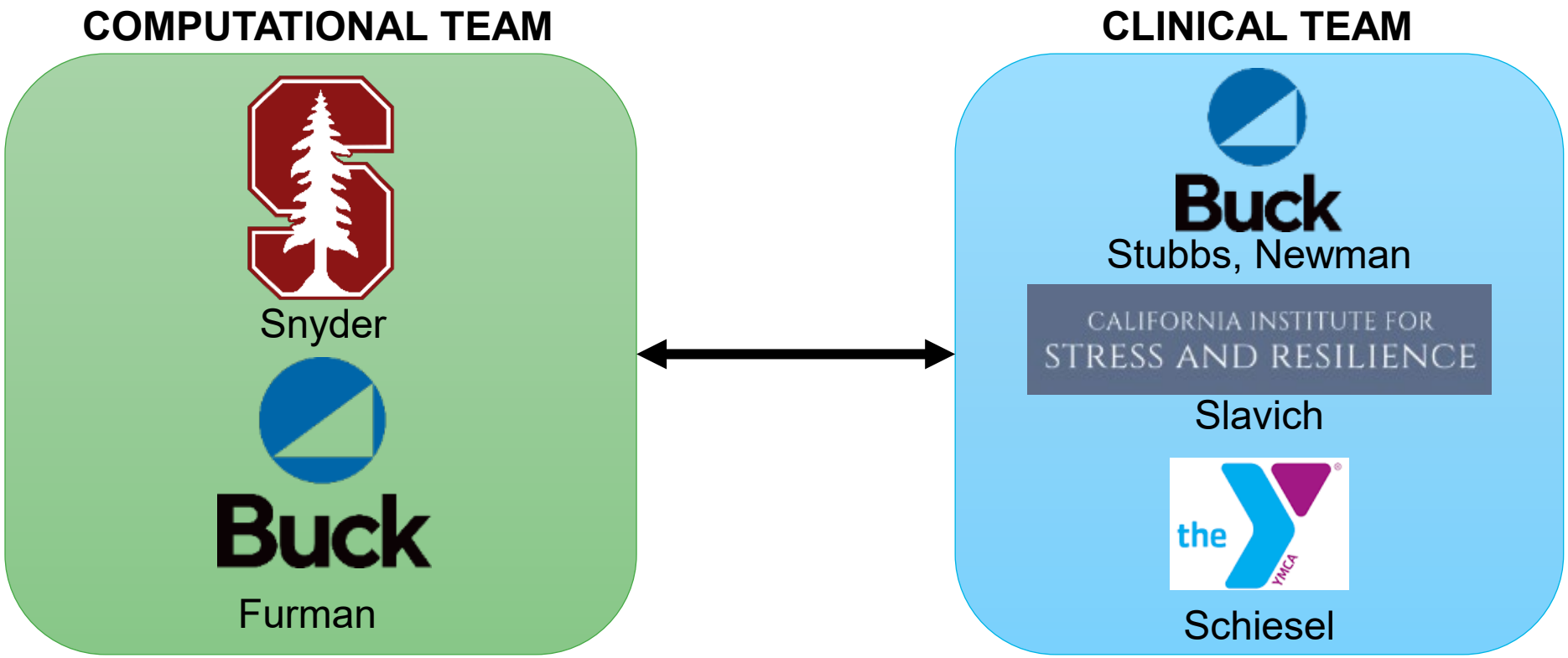
Reagan-Udall Foundation for the FDA May 27, 2026

Buck

Live better longer.

THRIVE Team

Prime Awardee: Stanford University; **Principal Investigator**: Mike Snyder



Methuselah Foundation

OpenCures

Buck

THRIVE is Pursuing Two Concurrent Regulatory Pathways

PATHWAY 1 — PROSPR IC SCORE

- **FDA Drug Development Tool / COA Qualification**
- **Route**: Pre-LOI > Type C meeting > Letter of Intent > Qualification Plan
- **Goal**: qualify PROSPR IC as a COA for gerotherapeutic drug trials
- **ICD-11 MG2A**: aging-associated IC decline is already a recognized diagnosis
- **If qualified**: standardized FDA-recognized endpoint for the whole field

PATHWAY 2 — AT-HOME IC TEST KIT

- **FDA De Novo Classification**
- **Route**: Pre-Sub (Q-Sub) → De Novo Classification Request (eSTAR)
- **Goal**: authorize at-home kit as a medical device
- **Kit**: app-based clinical assessments + wearable monitoring + blood multi-omic panel -> AI/ML IC Score. Submission structure (modular PCCP vs phased) subject to Pre-Sub response.

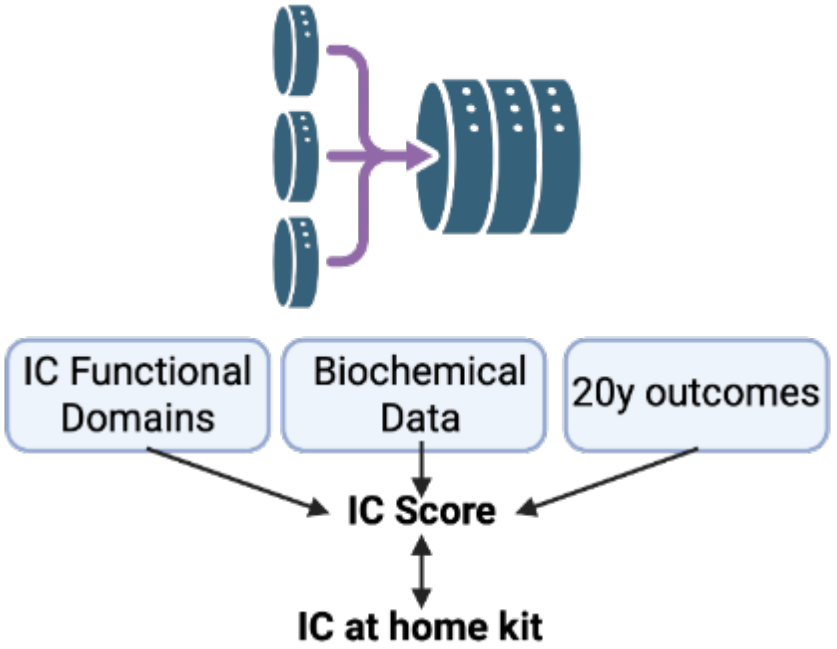
THRIVE clinical program generates evidence for both pathways

Dr John Newman, MD, PhD – jnewman@buckinstitute.org

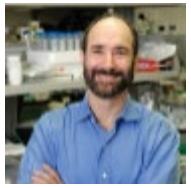
Buck

Stage 1: Build PROSPR IC Score from Longitudinal Data

- >20 international longitudinal cohorts harmonized (UK Biobank, INSPIRE-T, and others)
- All 5 IC domains: locomotor cognitive psychological sensory vitality
- **Data-driven scoring**: anchored to 20-year risk of disability, multimorbidity, and mortality
- **Output**: sex-specific composite PROSPR IC score + clinically interpretable domain sub-scores
- **Score development underway now – v1 ready ahead of clinical studies**



LOCOMOTOR | COGNITIVE | PSYCHOLOGICAL | SENSORY | VITALITY


Snyder


Furman


Poganik

Buck

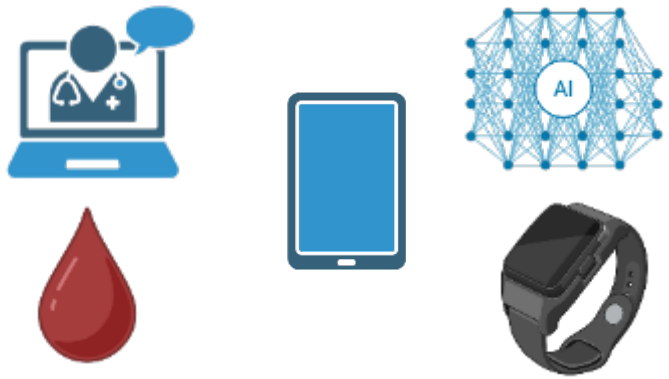
Stage 2: Pilot - Test At-Home Kit Feasibility

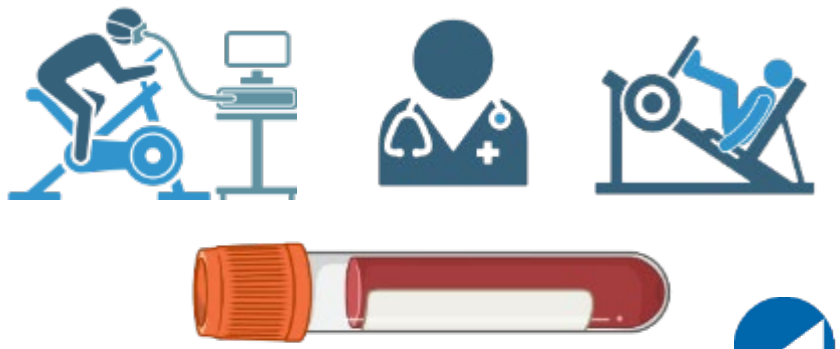
- **n=100 | single at-home IC assessment + 1 in-person clinic visit |**
- **Participants:** Generally healthy, aged 35 – 75 years
- **Goal**: early feasibility data + concordance between at-home and clinic-based PROSPR IC
- **At-home**: smartphone app (video, PROs), Whoop, blood micro-sampling
- **Clinic gold standard**: e.g., SPPB, 6-min walk, MoCA / MMSE, validated PerfO/PRO instruments, sensory testing
- Sets parameter estimates and informs any kit refinements before scaling

AT HOME KIT
App | Whoop | CGM | Biochemical assays

↔

IN-CLINIC (Gold Standard)
e.g., SPPB | 6MWT | MoCA | PerfO/PRO





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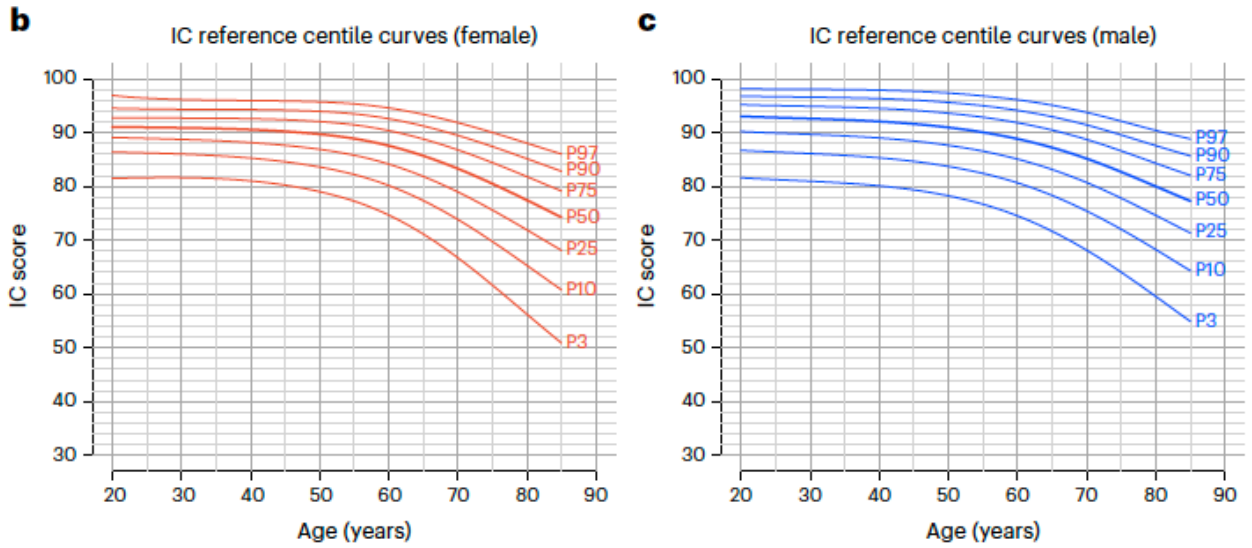
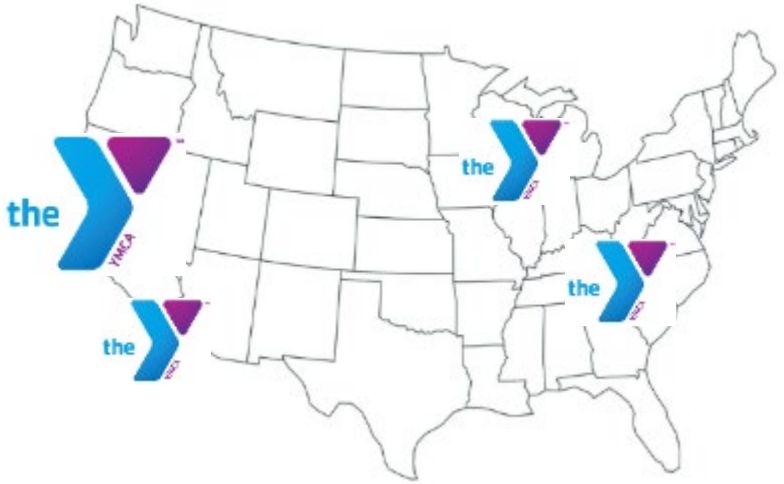
Stage 3: Observational Study - Generate The Adult Health Curve

- **Decentralized**: **n=1,200** recruited near YMCA sites in 4 cities – SF, San Diego, Minneapolis, Atlanta
- **Primary goal**: cross-sectional IC vs. age relationship across the adult lifespan
  - **Single at-home IC assessment**
- **Generates the normative IC reference** - the "Adult Health Curve"
- Continues at-home vs. clinic-grade IC validation at population scale
  - **Bay Area subset (n=100) with clinic visit**



Lu et at 2023, Nat. Aging



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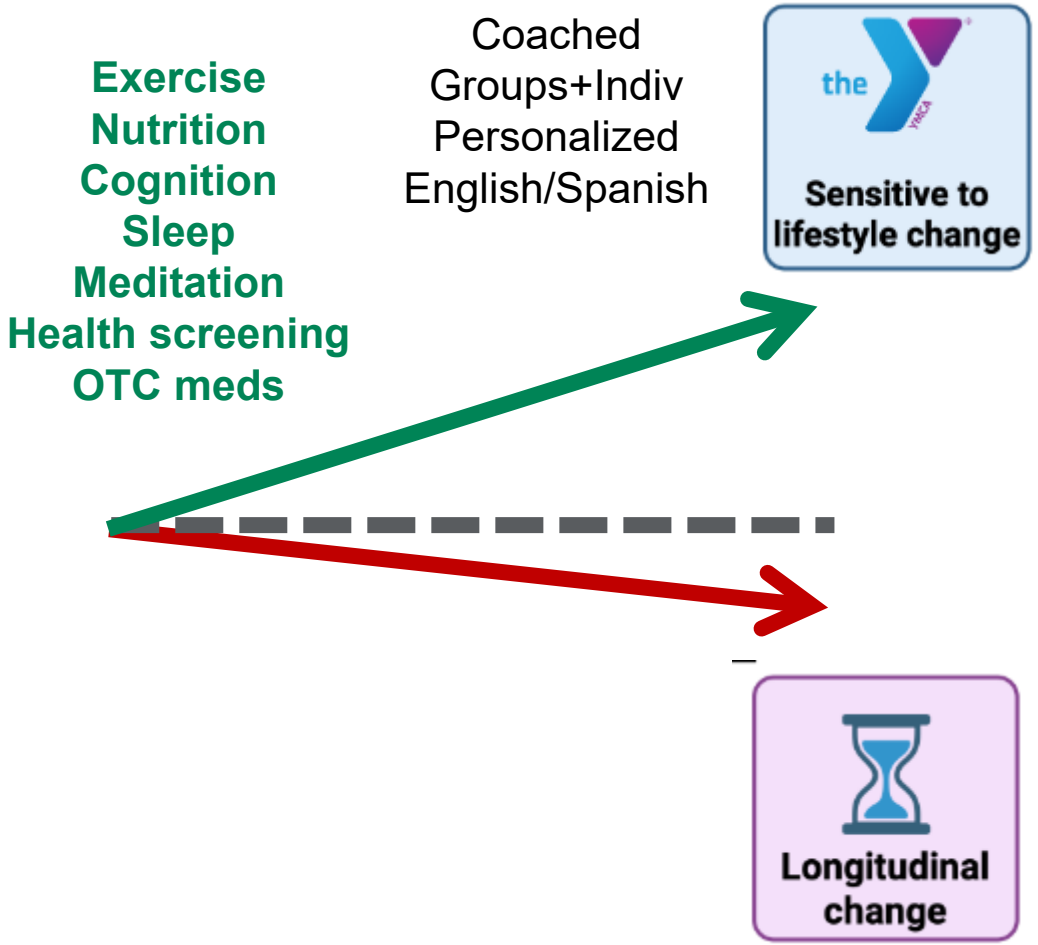
Stage 4: Interventional Study - Determine Score Responsiveness & Trajectory

- **n=1,700, participants continue from prior phases + additional recruits**
- **Decentralized throughout:** at-home PROSPR IC is the primary endpoint measurement (bi-monthly)
  - Bay Area subset (n=100) with clinic visit
- **Active (n= ~740, low IC):** YMCA-led coached multimodal lifestyle program -> tests responsiveness of PROSPR IC
- **Low IC control (n = ~480)**: longitudinal observation to detect natural IC decline over ~16 months
- **High IC control (n = ~480):** establishes natural trajectory as a reference



Buck

A qualified IC endpoint unlocks a new generation of aging trials.

THRIVE Team

Stanford: Snyder, Wyss-Coray,Delp, Babu, Mayer, Thorta, Zhai, Srivasta, Ying

Buck (Computational): Furman, Belic, Schneider

Buck (Clinical): Stubbs, Newman, Smith, Erram

California Institute of Stress and Resilience: Slavich, Mengelkoch, Alley

YMCA of Greater San Francisco: Schiesel, Clapperton, Price

Methuselah: Gobel, Paulson, Fiorenza

OpenCures: Perrot

ARPA-H

Andrew Brack

Kelly Anderson

Buck

Clinical Strategy: BStubbs@buckinstitute.org
FDA Strategy: JNewman@buckinstitute.org

Live better longer.

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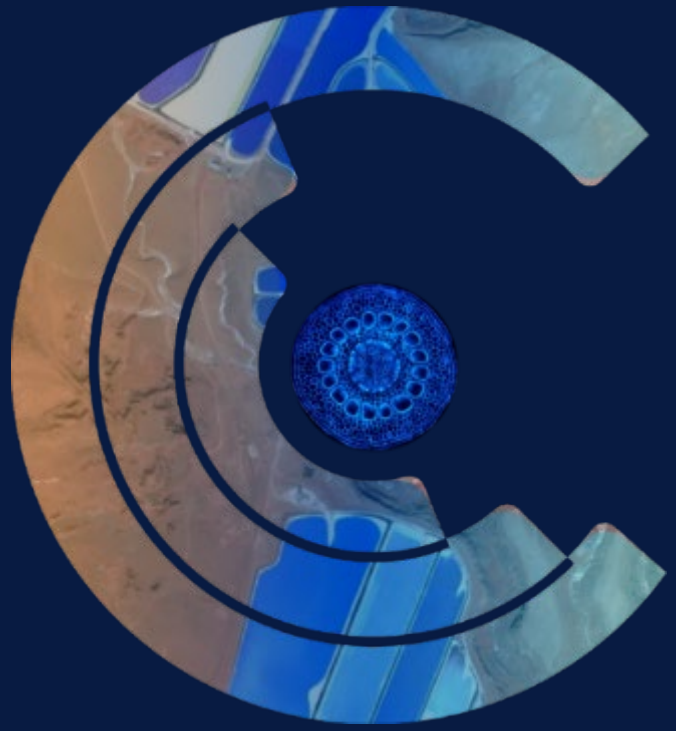
James Peyer, PhD

Founder & CEO

Cambrian Bio

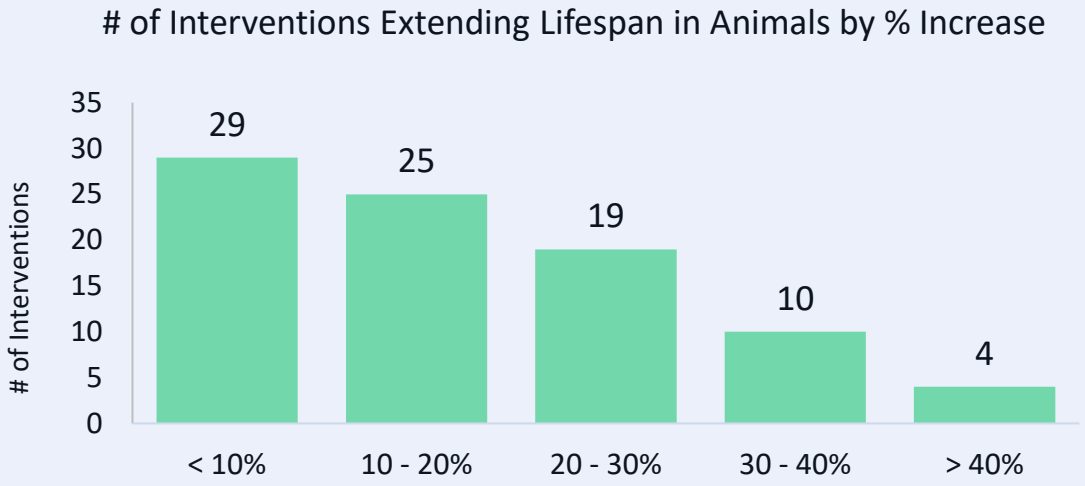


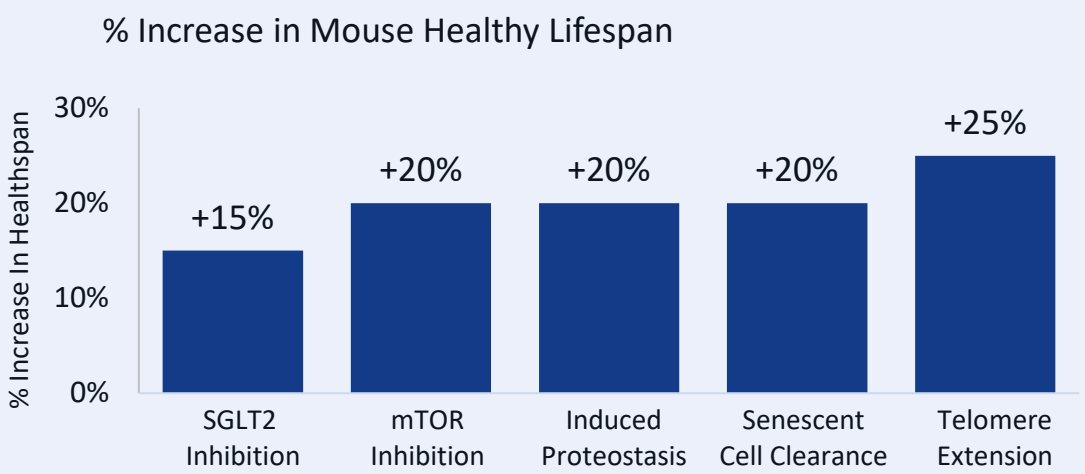
Cambrian

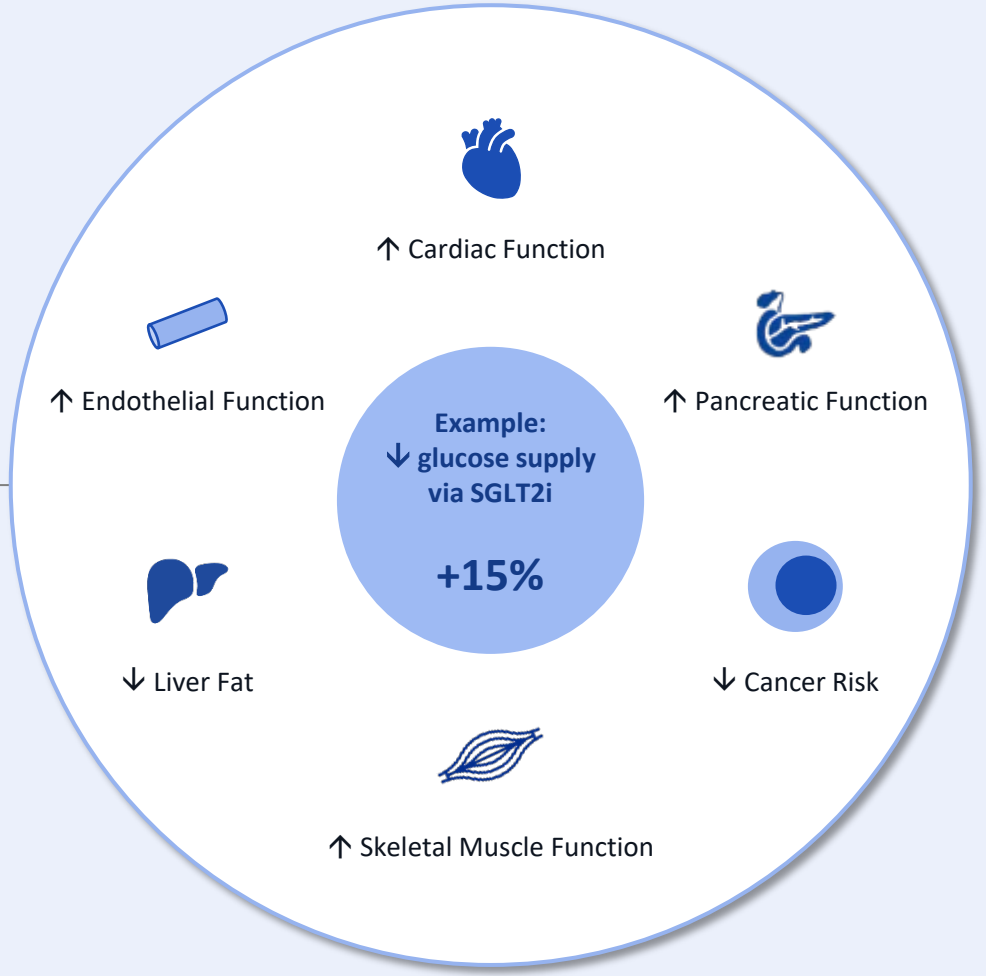
Affecting the Aging Trajectory
May 2026

James Peyer, PhD
CEO & Founder

80+ interventions extend healthy lifespan in animal models – how can we translate these discoveries to humans?



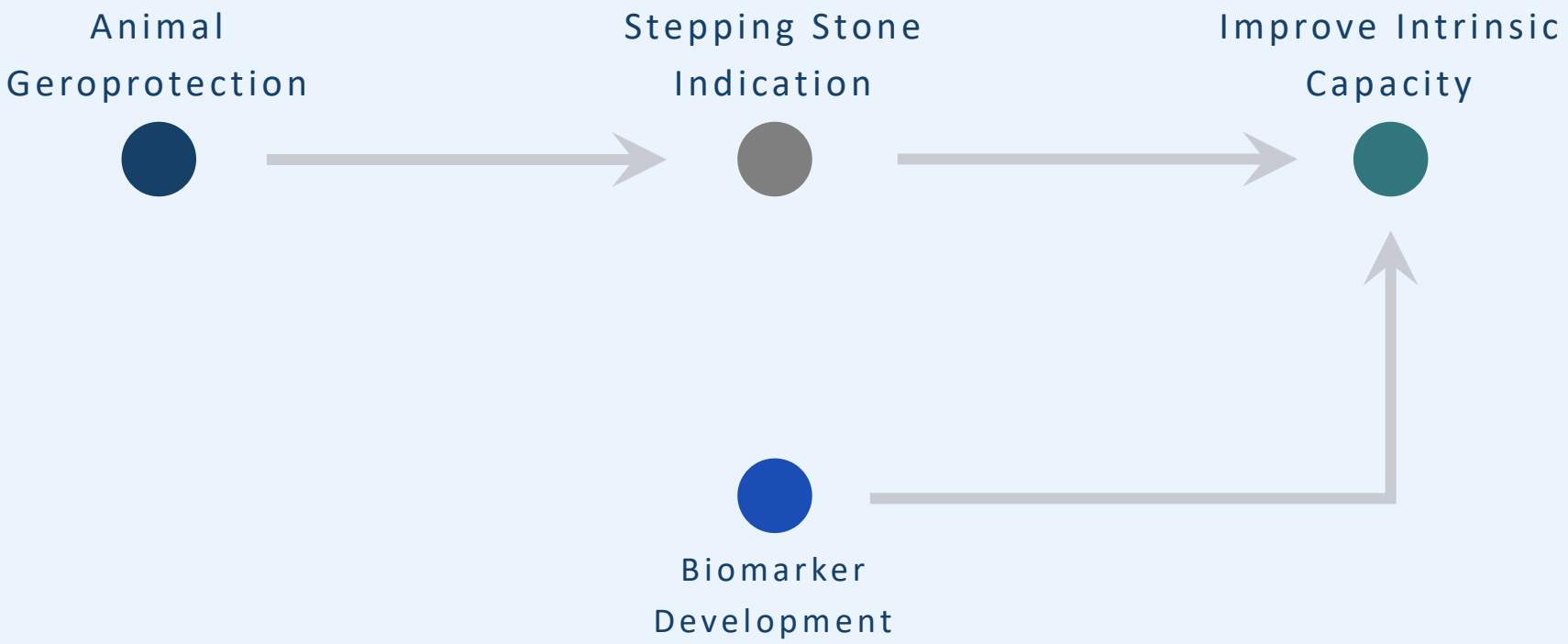




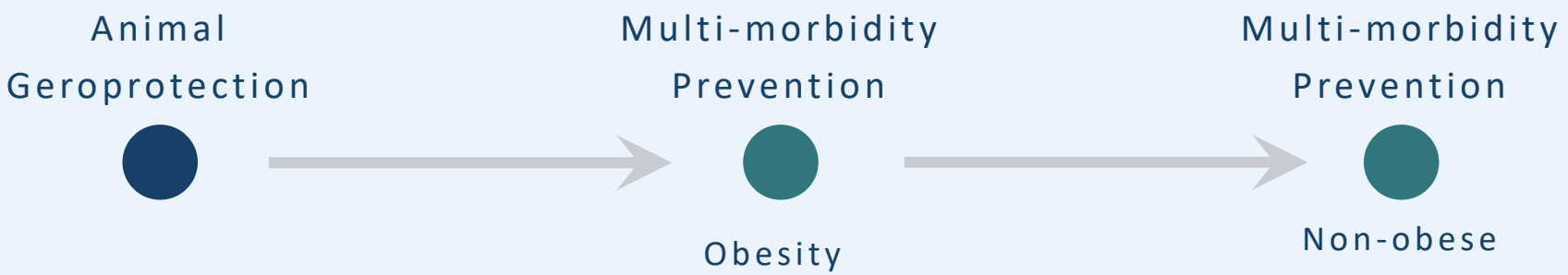
Cambrian

SGLT2 diagram adapted from Gao, Y. M.. et al. *eBioMedicine.* **2022**, 83. DOI: 10.1016/j.ebiom.2022.104215.
Other data aggregated from academic literature; more detail available in the appendix.

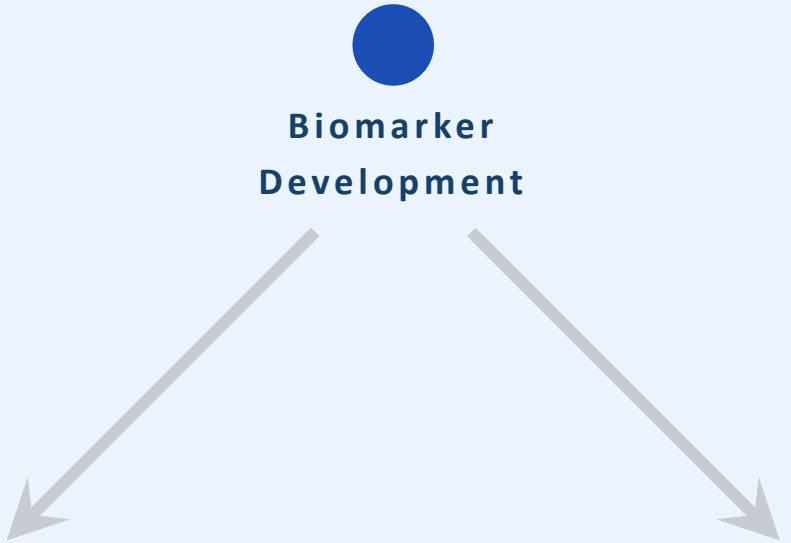
Cambrian has built the playbook for the Stepping Stone approach to gerotherapeutic development



Cambrian's first program, the AMPK & mitochondrial activator ATX-304, is using the Metabolic Shortcut of obesity as an existing biomarker of disease risk



New phenotypic or mechanistic biomarkers will be needed for most gerotherapeutics to become preventative medicines



Phenotypic

- Body weight
- Viral titer
- Bone mineral density
- Intrinsic Capacity?

Mechanistic

- Cholesterol
- Triglycerides
- Beta Amyloid
- AMPK activation / MTOR inhibition?

Inhibition of mTOR with rapalogs has the potential to improve the function of multiple aging organ systems

Reversal of aging-related immune dysregulation

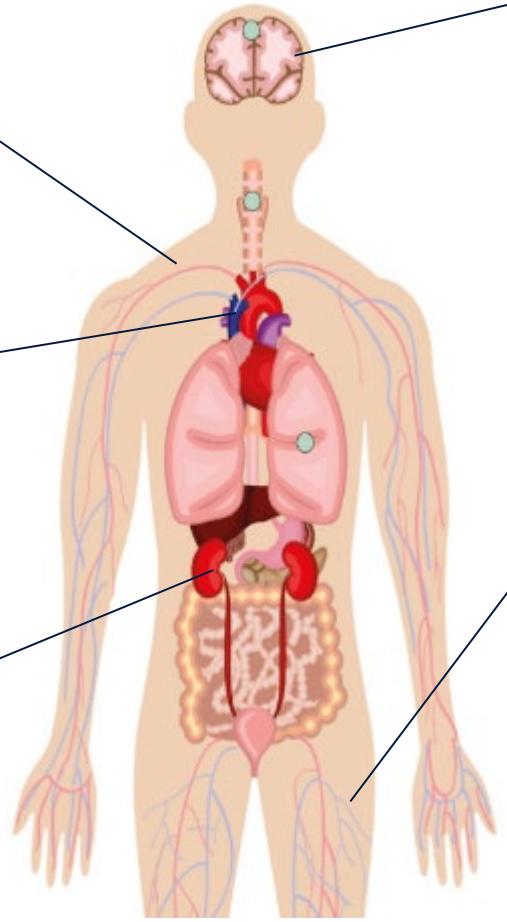
Chen et al., *Science Sig*, 2009
Selman et al., *Science*, 2011
Neff et al., *JCI*, 2013
Hurez et al., *Aging Cell*, 2015

Reversal of aging-related cardiac dysfunction

Flynn et al., *Aging Cell*, 2013
Dai et al., *Aging Cell*, 2014
Chiao et al., *Aging*, 2016

Improved Kidney Disease

Chen et al., *PLoS One*, 2012
Walz et al., *NEJM*, 2010



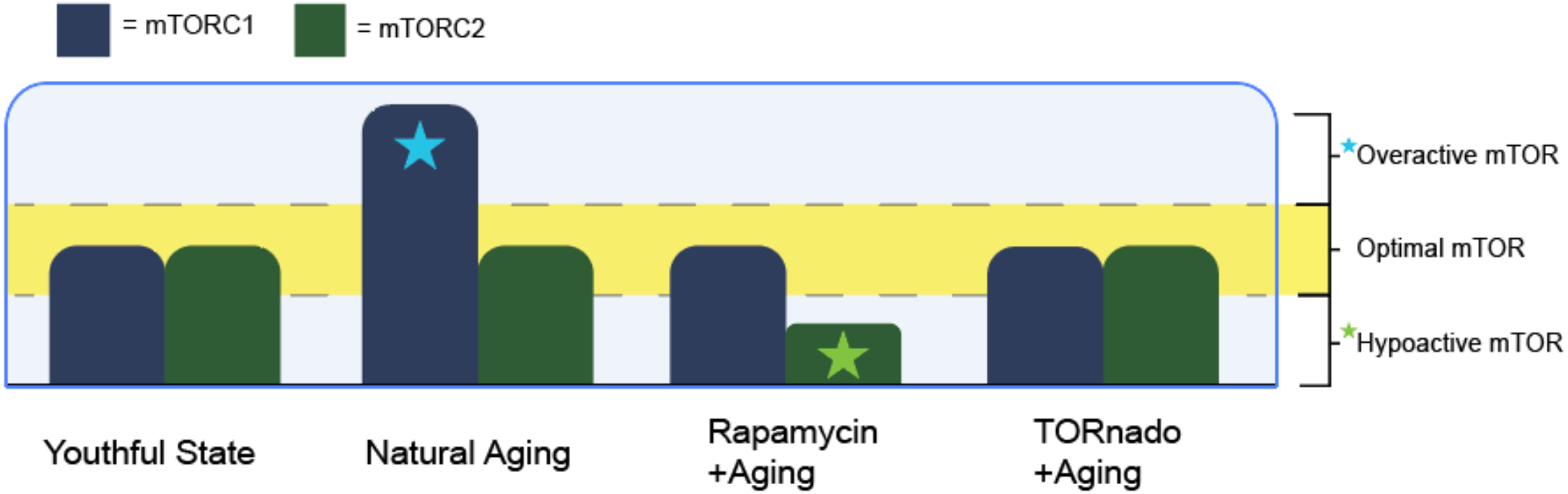
Improved neurologic function

Tain et al., *Nature Neuroscience*, 2009
Malagelada et al., *J Neurosci*, 2010
Spilman et al., *PLoS ONE*, 2010
Halloran et al., *Neuroscience*, 2012
Majumder et al., *Aging Cell*, 2012
Neff et al., *JCI*, 2013

Improved physical activity

Selman et al., *Science*, 2011
Harrison et al., *Nature*, 2009
Wilkinson et al., *Aging Cell*, 2014
Flynn et al., *Aging Cell*, 2013

MTORC1 but not MTORC2 is overactivated during aging

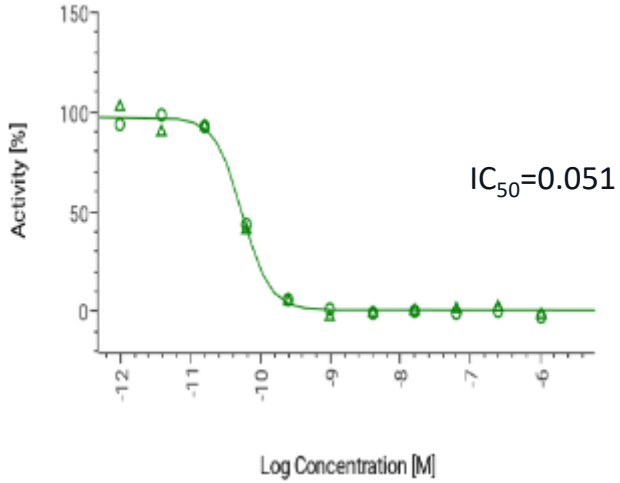


An ideal drug should inhibit mTORC1 but not mTORC2 to maximize the therapeutic window of mTOR inhibition

Cambrian's TORnado platform contains over a dozen mTORC1 selective rapalogs that do not inhibit mTORC2 at any concentration

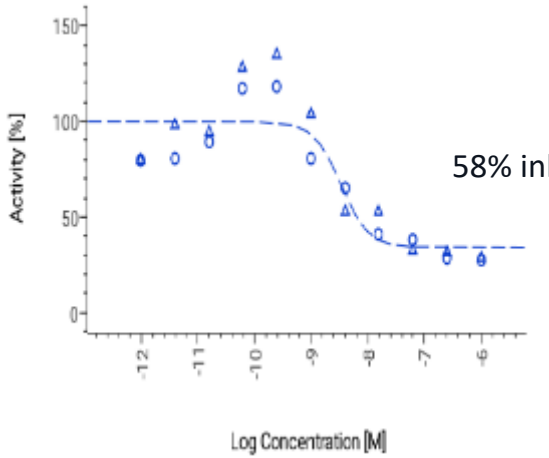
Everolimus (First generation rapalog that fully inhibits TORC1 and partially inhibits TORC2)

TORC1 Activity



IC_{50}=0.051 nM

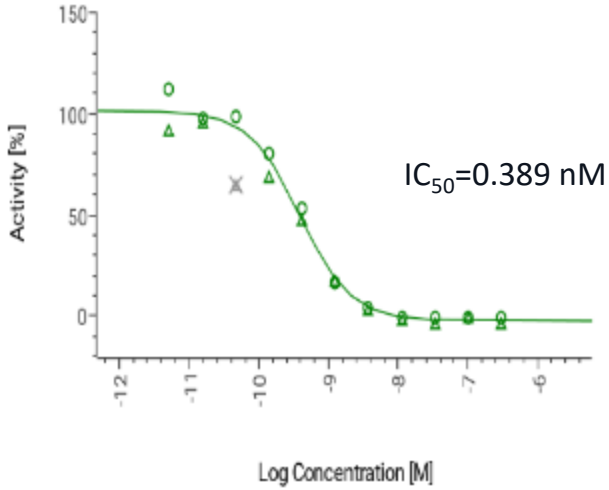
TORC2 Activity



58% inhibition

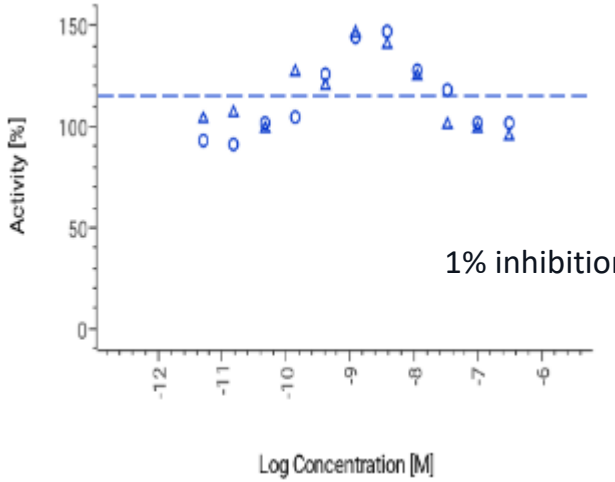
TOR-101 (TORC1-selective inhibitor)

TORC1 Activity



IC_{50}=0.389 nM

TORC2 Activity



1% inhibition

Soucre: Internal Cambrian Data.

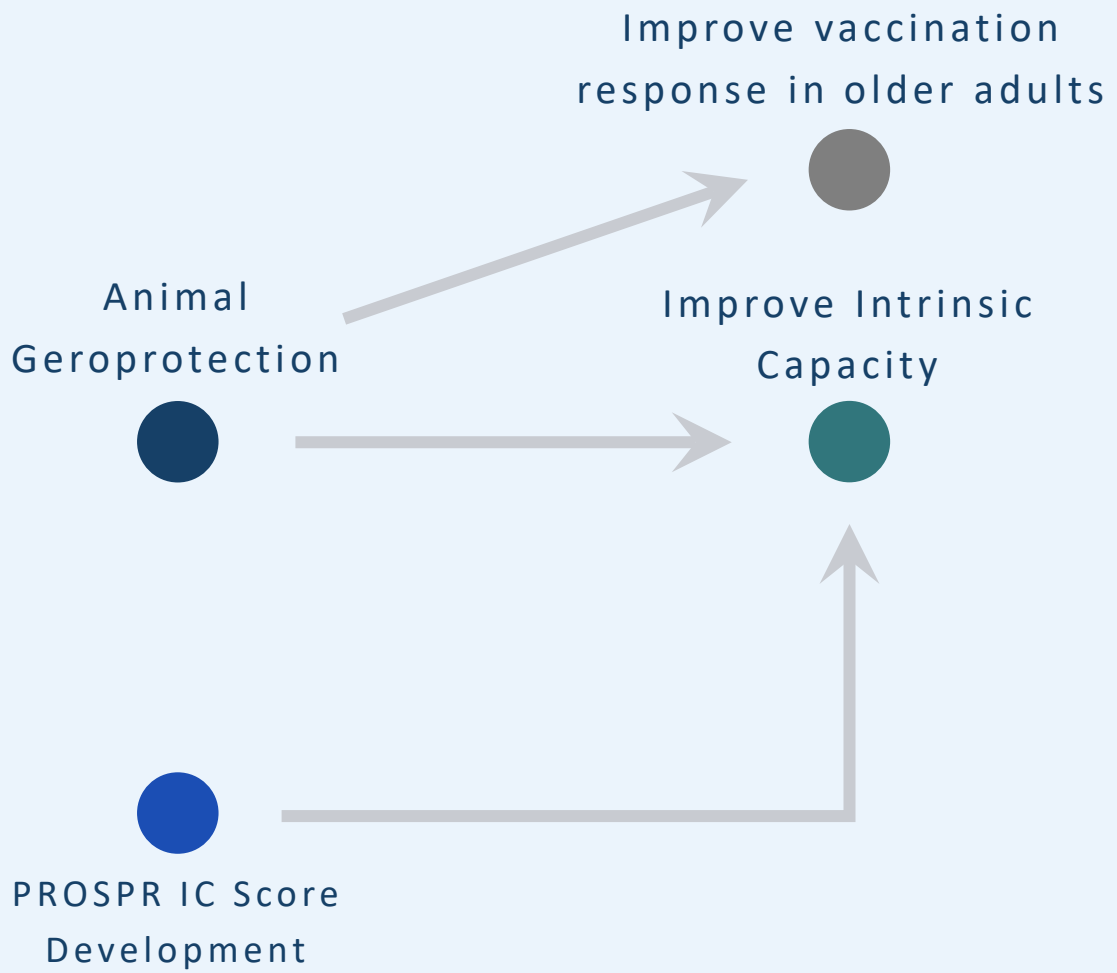
Unpublished results show benefits of mTORC1 selective inhibition in many disease models of aging

- **Cardiac health – improved ejection fraction and reversed age-related cardiac enlargement**
- **Cancer – prevention of tumorigenesis in cancer-prone mice**
- **Cancer – treatment of multiple tumor types**
- **Immune decline – improvement of antibody response to vaccination; no immunosuppression at any dose**

Soucre: Internal Cambrian Data.

Cambrian is working with ARPA-H PROSPR on its mission to establish a biomarker for intrinsic capacity

Development path for TOR-101



The Impact

Estimated 10+ year acceleration in starting to improve the lives of people who will develop severe age-related diseases

Cambrian

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REAGAN-UDALL FOUNDATION FOR THE FDA

George A. Kuchel, MD, CM, FRCP

Director, UConn Center on Aging
University of Connecticut

Repurposing Reverse Transcriptase Inhibitors to Treat Aging (RT-AGE)

George A. Kuchel, MD
Director, UConn Center on Aging
University of Connecticut

Presenting on behalf of the RT-AGE Team

University of Rochester (Prime Site)
Vera Gorbunova, Andrei Seluanov,
Kathi Heffner, Annette Medina-Walpole

Brown University
John Sedivy, Jill Kreiling

U Connecticut
George Kuchel, Iman Al-Naggar

UT Galveston
Alan Landay, Matt Mendoza

UT Houston
Jordan Lake

University of Nebraska
Kimberly Scarsi

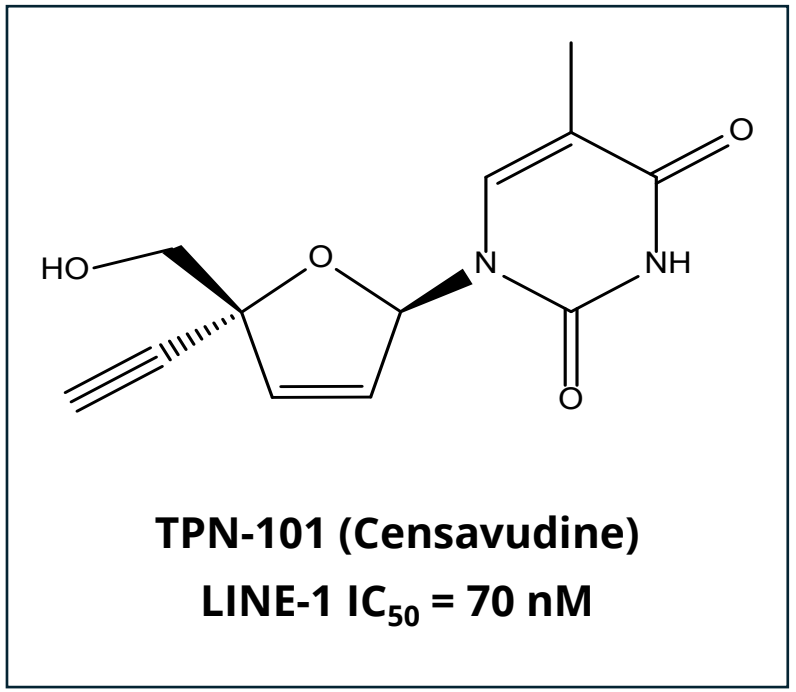
Transposon Therapeutics Inc.
Andy Satlin, Mark Mugerditchian

Background

- PROSPR TA3 Project
- Nucleoside reverse transcriptase inhibitors (NRTIs) used for HIV
- LINE-1 elements are main retrotransposons in humans
- Accumulate with and contribute to biological aging
- Censavudine (TPN-101): potent inhibitor of LINE-1 RT activity
- 2nd generation repurposed drug
- Academic-Industry partnership with Transposon Therapeutics Inc.
- Human safety and tolerability already established
- INDs obtained for treatment of neurodegenerative conditions (Progressive Supranuclear Palsy; Amyotrophic Lateral Sclerosis)

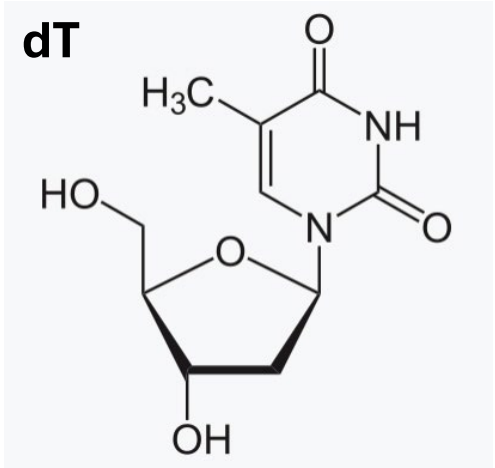
Censavudine is a potent LINE-1 reverse transcriptase inhibitor

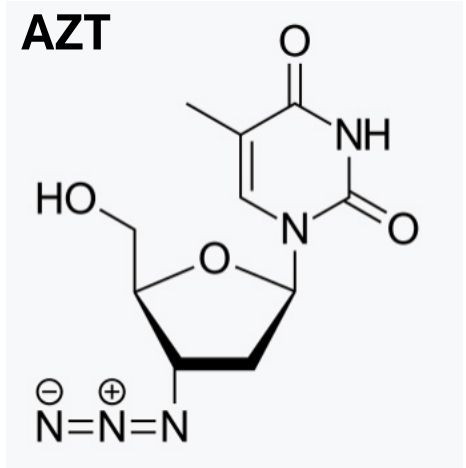
- **Safe and well-tolerated in 48 week clinical trial in HIV (n=222)**
- **Potent LINE-1 inhibitory activity**
  - >10 x more potent than generic NRTIs
- **Once per day oral dosing**
  - 95% bioavailability
  - Low protein binding
  - Excellent brain penetration

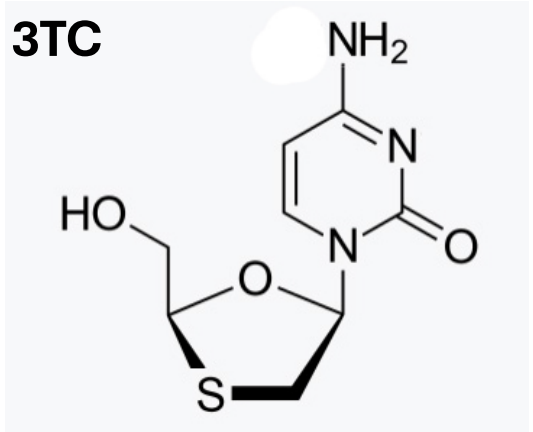


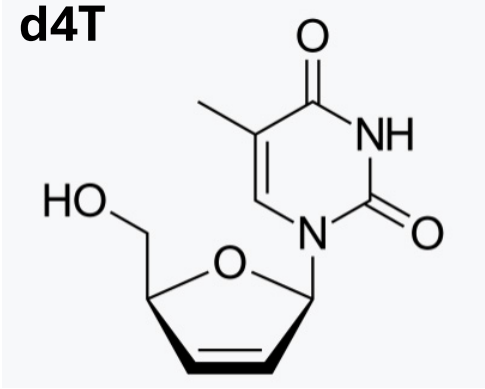
TPN-101 (Censavudine)

LINE-1 IC_{50} = 70 nM









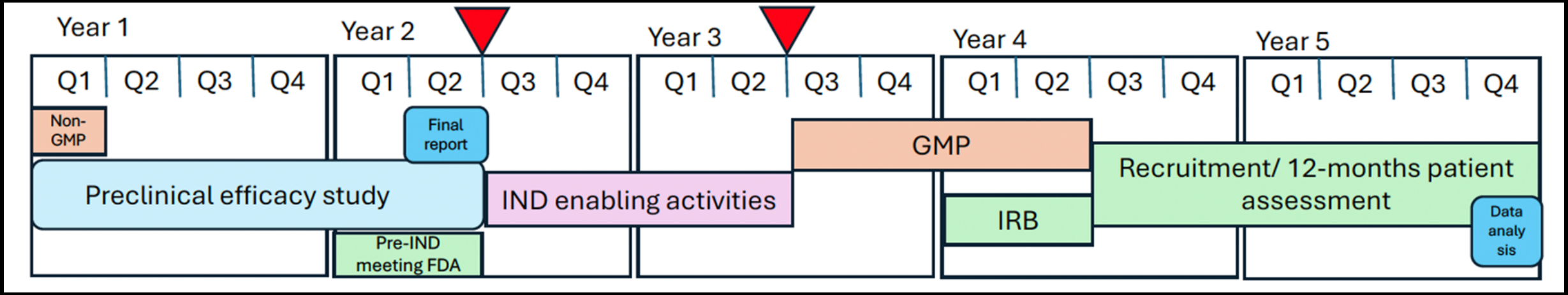
STAGE 1

- Preclinical mouse studies
- Test Censavudine effect on Intrinsic Capacity (IC) in mice
- Two doses tested in UM-HET3 outbred mice
- IC assessed via Vitality, Sensory, Locomotion and Cognition tests
- General health and molecular parameters
- 4 time points studied between ages of 15 and 24 months
- Studies replicated at 2 independent sites (U Rochester, Brown U)

STAGE 2

- Go/no-go decision point will occur in Q2 of Year 2
- Human trial at UConn, U Rochester, and U Texas Galveston
- Healthy men and women 60-65 years of age
- Censavudine 400 mg daily or placebo over 48 wks (n=100 per arm)
- Effects of Censavudine on PROSPR IC
- Sensory, vitality, psychological, locomotion and cognition domains
- Implement most current IC biomarkers from PROSPR TA1 findings
- Goal is to discern human healthspan effects

TIMELINES


Year 1
Year 2
Year 3
Year 4
Year 5
Q1 Q2 Q3 Q4
Non-GMP
Final report
Preclinical efficacy study
IND enabling activities
GMP
IRB
Recruitment/ 12-months patient assessment
Pre-IND meeting FDA
Data analysis

SUMMARY

- Innovative approach to testing 2nd generation repurposed drug
- Use of multidomain measures to capture impact on healthspan
- Benefit of existing INDs for disease indications
- Ability to move rapidly from mice to humans
- Potential pitfalls and challenges
- Timelines
- Human subject recruitment
- Clear rapid communication key both between and within teams

Regulatory Landscape

What Pathways Exist, Where They Break Down, and What Constructs Are Needed

REAGAN-UDALL FOUNDATION FOR THE FDA

Sandra Kweder, MD
Eliquent

G. Alexander (Zan) Fleming, MD
Kitalys Institute

Industry Perspectives

What Product Sponsors Need from FDA to Bring Gerotherapeutics to Market

REAGAN-UDALL FOUNDATION FOR THE FDA

Joshua Diamond, MD, MSCE
GSK

David Glass, MD
Regeneron

Evan Mills
Olink
Part of Thermo Fisher Scientific

Jill Lee, JD
Novo Nordisk

Next Steps to Designing Workable Regulatory Constructs for Gerotherapeutics

REAGAN-UDALL FOUNDATION FOR THE FDA

Andrew Brack, PhD
ARPA-H

G. Alexander (Zan) Fleming, MD
Kitalys Institute

Jamie Justice, PhD
XPRIZE Foundation

Jill Lee, JD
Novo Nordisk

Justin Penzenstadler, PharmD
CDER, FDA

Jeffrey Siegel, MD
CDER, FDA

Lisa Yanoff, MD
CDER, FDA

Thank you for joining us

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FOUNDATION
FOR THE FDA