Living Longer, Living Better

Navigating, Leveraging and Measuring the Pathways to Longevity

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Marschall S. Runge, M.D., Ph.D.
Proposal architect / originating author

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EVP Medical Affairs · CEO Michigan Medicine · Dean UMMS
Proposed PIs: Steven L. Kunkel · Brian D. Athey
With: Sachin Kheterpal · Scott W. Ballinger · Ryan E. Mills · Greg Farnum

The question

How long is long enough?

Aging is a dynamic, modifiable process. Behavioral, environmental, and socioeconomic forces shape healthspan as powerfully as genetics.

The longevity marketplace today: influencer protocols, supplement stacks, biological reductionism dressed up as science.

What's needed: rigorous, evidence-based biomarkers grounded in mechanism and validated in human cohorts.

Aging-genomics — the natural extension of pharmacogenomics

Pharmacogenomics asks
Which drug is right for which person, given their genome?

Aging-genomics asks
Which way of living and which interventions are right for which person, given their genome, epigenome, mitochondrial state, and real-time physiology?

Same paradigm. Different question. Same clinical infrastructure (decision support, EHR alerts, CPIC-style guidelines) ready to extend.

Mechanism: mitochondrial-inflammaging axis

- Dysfunctional mitochondria release mtDNA-DAMPs + reactive oxygen species
- Activate NLRP3 inflammasome / NF-κB / chronic inflammation
- Drives cellular senescence, tissue damage, accelerated aging
- Lifestyle modulates this axis through epigenetic regulation of inflammatory + mitochondrial genes
- Maternal mtDNA inheritance + numts (Mills) determine the starting equilibrium

Three decades of Ballinger-Runge atherogenesis work establishes the mechanistic spine.

The proposal — three aims

Aim 1 · LCI Longevity & Cardiovascular Health Index — predict outcomes from WGS + CRF + BioButton + clinical risk

Aim 2 · EMHP Epigenetic & Mitochondrial Health Panel — profile biological-age trajectory; CRISPR Perturb-seq finds actionable targets

Aim 3 · Therapies Targets, Therapies, and Precision Longevity Programs — modulate via lifestyle decision-support and pharmaceuticals

Closed loop

measure → model → intervene → re-measure, with the rigor pharmacogenomics has brought to oncology.

Aim 1 — Longevity & Cardiovascular Health Index (LCI)

Inputs:

- Nuclear + mitochondrial WGS (haplogroups, heteroplasmy, copy number, numts; pangenomic alignment)
- Cardiorespiratory fitness (METs from exercise stress test)
- Standard clinical risk factors
- BioIntelliSense BioButton continuous physiology (HRV, sleep, activity, stress)

Cohorts: MGI ($\sim$90K) · MPOG (millions, Kheterpal) · DoDSR / USAFSAM / Cooper / VETS · validated against Oracle Health 150M EHR.

Outcome: Patented Ellison-branded predictive index, embedded in Oracle Health clinical decision support.

Aim 2 — Epigenetic & Mitochondrial Health Panel (EMHP)

Phase 1 — focused panel, calibrated against BioButton-paired blood draws bracketing real-world states (sleep deprivation, exercise, illness, vacation):

- IL-6, IL-1β, TNF-α, NLRP3, ASC, caspase-1
- VCAM-1, ICAM-1, PGC-1α, TFAM, sirtuins, GDF-15, FGF-21
- DNA methylation $\times$ expression $\times$ circulating protein

Phase 2 — genome-wide EPIC arrays, RRBS/WGBS, ATAC-seq, plus CRISPR Perturb-seq in patient-derived iPSCs $\rightarrow$ distinguishes biomarkers from actionable therapeutic targets.

Aim 3 — Targets, Therapies, Precision Longevity Programs

Network analysis prioritizes:

- DNMTs, TETs, HDACs, sirtuins (epigenetic enzymes)
- Mitochondrial regulators
- Non-coding RNA modulators

Therapeutic pipeline: repurposing screen + small-molecule / biologic discovery; EMHP + LCI as pharmacodynamic readouts; BioButton as continuous responder-monitor.

Precision longevity programs: aging-genomics decision framework (Athey-architected) outputs individualized lifestyle prioritization + therapeutic-candidate identification, integrated into Oracle Health workflows and EIT-affiliated longevity clinics.

Cohort tiers — five orders of magnitude

Tier	N	Use
WGS training cohort	10K–20K	Aim 1 LCI training
MGI (UM, recontactable)	∼90K	Aim 1+2 sub-cohort
Federal exercise-stress-test	750K	Decades of follow-up
MPOG (Kheterpal, 85+ hospitals)	5M+	BioButton sub-cohorts
Oracle Health (Ellison)	150M	LCI external validation

Commercialization roadmap (Years 1–7+)

- **Phase 1 (Y1–3) Discovery:** biomarker discovery, panel feasibility, target identification. Initial patents.
- **Phase 2 (Y4–6) Product + Regulatory:** EMHP IVD, FDA 510(k) / de novo, CE Mark, pre-clinical drug optimization.
- **Phase 3 (Y7+) Launch + Therapeutics:** EMHP via Oracle Health, personalized longevity programs, therapeutic Phase 1–3 trials.

Team

Marschall Runge Architect; cardiovascular-translation arm; EIT/Oracle channel

Steve Kunkel Proposed PI; inflammaging axis; Aim 2 & 3 lead

Brian Athey Proposed co-PI; LCI architect; decision framework

Sachin Kheterpal MPOG operational lead; multicenter sub-cohorts

Scott Ballinger mtDNA genetics; conplastic mouse foundation

Ryan Mills Numts methodology; pangenome

Greg Farnum OCI bioinformatics; ML pipeline

What we need from PIs

1. First submission target. NIA R01 recommended (4-axis aging fits NIA program review naturally).
2. PI delegation confirmation. Doc 1 places Kunkel as PI, Athey as co-PI, with Runge as senior collaborator.
3. Ellison + Oracle Health terms. Aim 1 LCI external validation depends on this.
4. PI biosketch refresh (eRA-Commons format).
5. MPOG governance terms (Sachin) for BioButton sub-cohorts.
6. Real budget numbers from EVPMA office + IRB protocol from Athey.

Dashboard — everything is one click away

single-molecule-sequencing.github.io/longevity-platform-grant

- 28 funding-mechanism PDFs ready to download
- 8 auto-generated figures + 4 reference tables
- Both source drafts linked at the top
- "What we need from PIs" status grid
- Rebuilds on every push to `main`

Thank you.

Marschall S. Runge, M.D., Ph.D.
marschallrunge@umich.edu