Living Longer, Living Better: Navigating, Leveraging and Measuring the Pathways to Longevity

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Platform Pitch — Foundation & Philanthropic Funders

What we are asking you to fund

A 7-year program to operationalize *aging-genomics* — the natural extension of pharmacogenomics into healthspan — as a clinically-deployable platform: a predictive index that integrates genetics, epigenetics, real-time wearable physiology, and cardiorespiratory fitness into a single score; a blood-based diagnostic that tracks biological age over time; and a decision- support layer that translates each person's score into specific lifestyle and therapeutic recommendations.

Theory of change

The longevity / healthspan field is not technology-limited. The mechanistic biology (mitochondrial-inflammaging axis; epigenetic regulation by lifestyle; maternal mtDNA inheritance and numts) has been mature for two decades. Long-read sequencing, FDA-cleared continuous wearables, and CRISPR Perturb-seq for causal-flow discovery have converged in the last five years. The decision-support infrastructure exists in working clinical deployment via pharmacogenomics. **What's missing is not invention; it is disciplined translation.**

The field is also not capital-limited at the marketing end. The contemporary longevity marketplace generates substantial revenue from under-validated influencer-driven products. What is severely capital- constrained is the rigorously-validated infrastructure — the multicenter cohort design, the FDA-pathway IVD development, the decision-support deployment — that converts mature mechanism into deployed clinical impact. Foundation philanthropy, with its tolerance for long-horizon validation and its alignment with public-health- benefit rather than direct-to-consumer wellness, fills the gap that neither NIH (mechanism-fragmented) nor venture capital (short-horizon, consumer-marketing-driven) covers.

Why this team is uniquely positioned

Mechanism. Three decades of Ballinger-Runge collaboration established the mtDNA-atherogenesis foundation that anchors the mitochondrial-inflammaging axis at the heart of the proposal.

Infrastructure. Michigan Genomics Initiative (∼90{,}000 deeply-phenotyped recontactable patients), Multicenter Perioperative Outcomes Group (Kheterpal; 85+ hospitals; multicenter prospective trials at scale), federal exercise-stress-test cohorts (DoDSR, USAFSAM, Cooper, VETS), and the Ellison Institute / Oracle Health partnership giving access to the 150-million-patient EHR for external validation. No other academic institution combines these assets.

Translation. Athey's pharmacogenomics decision-support work demonstrates the ability to take methodology to clinical-deployment impact. The team's combined wet-lab + computational + multicenter- clinical-trial fluency is what aging-genomics demands at scale.

What you would get

A measurable program with explicit phase deliverables:

- **Phase 1 (Years 1–3).** Discovery + biomarker prioritization + initial patents on diagnostic algorithms.
- **Phase 2 (Years 4–6).** EMHP IVD development; FDA / CE- Mark dossiers; LCI external validation against Oracle Health 150M EHR; pre-clinical drug-lead optimization.
- **Phase 3 (Years 7+).** EMHP IVD commercial launch via Oracle Health channels; personalized longevity programs licensed to longevity clinics and employer/payer wellness programs; therapeutic candidates advancing through Phase 1–3 trials.

The platform also produces public-health-relevant outputs along the way: open-source analytical pipelines (6-month-delayed release), publicly-available summary statistics with each peer-reviewed publication, and an explicit refusal to participate in direct-to- consumer wellness marketing of unvalidated products.

What we are asking

A platform-level commitment that extends across the discovery → product → launch arc, not a single-aim short-horizon grant. The exact form (research grant, partnership, equity-aligned commitment, sponsored-research agreement) is appropriate to the funder's mechanism; we are open to structuring discussions accordingly. The through-line is the same: foundation capital fills the gap between mature mechanism and deployed clinical infrastructure that other funding sources do not cover.

Where to read more

Dashboard: `single-molecule-sequencing.github.io/longevity-platform-grant`. Both source documents (authored by Marschall S. Runge), all 26 atom- generated funding-mechanism PDFs, the slide deck, the A0 conference poster, the cabinet-briefing format, and a status grid showing what's authored vs. what needs PI input vs. what's blocked on partnership- governance terms.

Specific Aims

Goal: Develop commercially-viable diagnostic panels and identify therapeutic targets rooted in mitochondrial function, epigenetics, and cardiorespiratory fitness for promoting healthy longevity and reducing cardiovascular-disease (CVD) risk.

Premise: Aging-genomics extends the pharmacogenomics paradigm. Where pharmacogenomics personalizes therapy by genotype, aging-genomics personalizes the negotiation each individual conducts with their genes across genome, epigenome, mitochondrial state, and real-time physiology. The mechanistic core is the mitochondrial-inflammaging axis: mtDNA-derived damage-associated molecular patterns and reactive oxygen species activate the NLRP3 inflammasome and NF-κB, driving the chronic inflammation that accelerates biological aging. Lifestyle factors — physical activity, nutrition, sleep, social engagement, purposeful cognitive challenge — modulate this axis through epigenetic regulation of inflammatory and mitochondrial genes. Layered onto this axis is maternal mtDNA inheritance and numts (nuclear mitochondrial insertions, characterized methodologically by Mills) as under-recognized determinants of intrinsic longevity capacity.

Aim 1 — The Ellison Longevity & Cardiovascular Health Index (LCI). Develop and validate a clinically-deployable index integrating: (i) nuclear and mitochondrial whole-genome sequencing (polygenic scores for CVD, metabolic disease, longevity; mtDNA haplogroups, heteroplasmy, copy number; numts characterization); (ii) cardiorespiratory fitness measured in METs from exercise stress testing; (iii) standard clinical risk factors; and (iv) real-time phenotypic data from the BioIntelliSense BioButton wearable (heart rate variability, sleep architecture, activity, stress signatures). Cohort assembly leverages the Michigan Genomics Institute (MGI, $\sim$90{,}000 recontactable UM patients with deep phenotyping and WGS), the Multicenter Perioperative Outcomes Group (MPOG, millions of records across 85+ hospitals; Kheterpal Executive Director), and federally-funded military and veteran exercise-stress-test biorepositories (DoDSR, USAFSAM, Cooper Institute, VETS). Models are trained on Oracle Cloud Infrastructure using pangenomic alignment (to capture structural variation and reduce reference bias) and interpretability-constrained nonlinear machine learning (gradient boosting, deep learning, survival models), then validated against the Oracle Health 150-million-patient EHR. **Outcome:** A patented Ellison-branded diagnostic algorithm suitable for embedding in Oracle Health clinical decision support, population-health management, and employer/payer products.

Aim 2 — The Epigenetic & Mitochondrial Health Panel (EMHP). Discover and validate a clinically-practical blood-based panel quantifying epigenetic age and trajectory, inflammatory and mitochondrial status, and responsiveness to interventions. *Phase 1* starts from a small, carefully-selected set of inflammatory genes and closely-related mitochondrial regulators (IL-6, IL-1β, TNF-α, NLRP3 / ASC / caspase-1, VCAM-1 / ICAM-1, PGC-1α, TFAM, sirtuins, GDF-15, FGF-21). For each gene, assays capture DNA methylation at key CpGs, expression levels (targeted RNA-seq or qPCR), and where appropriate circulating protein/metabolite levels. In sub-cohorts wearing BioButtons, paired blood draws bracket defined behavioral/physiologic states (sleep deprivation, exercise bouts, acute illness, stress-heavy weeks, restorative vacations) to quantify acute transcriptional and epigenetic responses to real-world stressors — and to identify individuals whose responses are exaggerated or blunted (high-value resilience-vs-vulnerability phenotypes). *Phase 2* expands via genome-wide DNA methylation (EPIC arrays, RRBS, or WGBS where justified), selective chromatin profiling (ATAC-seq; histone-mark ChIP-seq), and CRISPR Perturb-seq in patient-derived iPSC and immune/vascular cell models to clarify causal flow in gene networks (upstream regulators vs. downstream reporters — distinguishing markers from actionable targets). **Outcome:** A clinically-deployable EMHP comprising a limited set of CpG sites and protein/metabolite markers with OCI-hosted interpretive software, output as epigenetic age, mitochondrial burden, and links

to recommended intervention frameworks.

Aim 3 — Targets, Therapies, and Precision Longevity Programs. Move from measurement to modulation. Network and pathway analysis across LCI, EMHP, WGS, methylation, BioButton, and Perturb-seq data identifies key epigenetic enzymes (DNMTs, TETs, HDACs, sirtuins), transcription factors, non-coding RNA regulators, and mitochondrial stress pathways whose perturbation most strongly shifts aging/recovery phenotypes. The therapeutic pipeline screens existing drugs and nutraceuticals (repurposing) and novel small molecules and biologics, advancing leads through pre-clinical efficacy and safety with EMHP and LCI as pharmacodynamic readouts and BioButton as continuous responder-monitor. In parallel, an aging-genomics *decision framework* (architected by Athey) integrates genotype + epigenotype + LCI + BioButton phenotypes to output individualized prioritization of lifestyle levers (sleep, movement, stress, diet, social/purpose) and to identify candidates for emerging therapeutics. The framework is built for integration into Oracle Health clinical workflows, population-health and employer/payer offerings, and EIT-affiliated longevity clinics. **Outcome:** A closed-loop *measure* $\rightarrow$ *model* $\rightarrow$ *intervene* $\rightarrow$ *re-measure* system, with a pipeline of pre-clinical drug targets and an evidence-based personalized-longevity decision-support layer.

Impact. Aging-genomics, like pharmacogenomics before it, can move precision medicine from reactive disease management to proactive healthspan extension — but only if grounded in rigorously-validated biomarkers and longitudinal data, not the silver-bullet rhetoric of the longevity-influencer marketplace. This program delivers the biomarkers, the decision-support, and the therapeutic pipeline that make aging-genomics clinically meaningful and commercially deployable at the scale of Oracle Health.

1 Significance

The longevity question — and the longevity-influencer problem

How long is long enough? As captured in a "hot mic'' moment reported by the BBC on September 3, 2025, Chinese President Xi Jinping and Russian President Vladimir Putin were overheard discussing the possibility of living to 150 years of age. The question is no longer hypothetical for individuals or for healthcare systems. Aging is increasingly understood as a dynamic, modifiable process rather than an inevitable decline, and behavioral, environmental, and socioeconomic forces shape healthspan at least as powerfully as the genetic blueprint.

This understanding compels a rigorous, evidence-based approach, especially in an era saturated with expensive, unproven, and often outrageous "cures'' for aging — influencer protocols, supplement stacks, and biological reductionism dressed up as science. Aging is not controlled by any one pathway; the silver-bullet rhetoric of the longevity marketplace is a categorical mismatch with the underlying biology, in which the drivers are *groups* of genes whose regulation is tuned epigenetically by the daily activities of life. Decades-long clinical trials of aging are infeasible: what is needed are scientifically-valid biomarkers for biological aging, and the analytical tools to translate the macro-level lifestyle and environmental factors known to extend healthspan (Blue Zones, Cooper Clinic exercise cohorts) into the micro-level cellular changes that either promote resilience or accelerate decline.

Mitochondrial dysfunction as a driver of inflammaging

The central role of mitochondria in cellular energy metabolism makes them a focal point for understanding aging. Beyond their canonical bioenergetic role, mitochondria are signaling hubs that

continuously monitor cellular stress and metabolic status. When their function is compromised, they switch from guardians of homeostasis to potent drivers of inflammation through three interconnected mechanisms.

First, release of mitochondrial damage-associated molecular patterns (DAMPs). Dysfunctional mitochondria release or expose specific molecular components that act as "danger signals.'' Mitochondrial DNA (mtDNA), structurally similar to bacterial DNA, is recognized by innate-immune receptors — TLR9, the cGAS-STING pathway, and the NLRP3 inflammasome — when released into the cytosol or extracellular space. These activate pro-inflammatory transcription factors (NF-κB) and the production of IL-1β and IL-18. Other DAMPs, including oxidized cardiolipin and N-formyl peptides, trigger parallel cascades.

Second, excessive reactive oxygen species (ROS). Dysfunctional electron-transport-chain complexes generate excessive mitochondrial ROS (superoxide, hydrogen peroxide), which act as critical second messengers that directly activate NF-κB and the NLRP3 inflammasome.

Third, impaired mitochondrial quality control. Mitochondrial dynamics (fission/fusion balance) and mitophagy (selective degradation of damaged mitochondria) maintain organelle health. An imbalance toward excessive fission or impaired mitophagy allows "sick'' organelles to accumulate, continuously leaking DAMPs and generating ROS — a persistent inflammatory stimulus that perpetuates inflammaging.

The vicious cycle: inflammation and accelerated aging

Chronic inflammation fueled by mitochondrial dysfunction contributes to accelerated aging through cellular senescence and the senescence-associated secretory phenotype (SASP), progressive tissue damage (endothelial dysfunction, atherosclerosis, neuroinflammation, sarcopenia), immune dysregulation (immunosenescence, autoimmune phenomena), and detrimental epigenetic modifications that further dysregulate gene expression and amplify the cycle.

The virtuous cycle: lifestyle, mitochondrial resilience, and maternal mtDNA inheritance

Beneficial behaviors — regular physical activity, optimal nutrition, adequate sleep, social engagement — activate cellular pathways that promote mitochondrial biogenesis (increased mtDNA copy number), enhance mtDNA repair, and improve OXPHOS efficiency. The result is a virtuous cycle: reduced ROS, decreased oxidative damage to mtDNA, and suppressed chronic inflammation. Detrimental lifestyles (sedentary behavior, poor diet, smoking) and metabolic dysregulation (diabetes, obesity) exacerbate the vicious cycle.

A largely-overlooked dimension is the *maternal* inheritance of mtDNA. Unlike nuclear DNA, mtDNA is transmitted from mother to all offspring. A mother's mitochondrial legacy — the quality, integrity, and specific haplogroups of her mtDNA — provides the foundational mitochondrial template for her children. In individuals exhibiting exceptional longevity (centenarians), emerging data suggest a stronger maternal inheritance of this trait. Layered onto this is *numtogenesis*: the integration of mtDNA fragments into the nuclear genome (numts), characterized methodologically by Ryan Mills, which can be bi-parentally transmitted and may modulate cellular regeneration. Maternal advantageous mtDNA variants, higher mtDNA integrity, and optimal mtDNA copy number jointly equip offspring with healthier mitochondrial starting points and longer-term health trajectories.

Foundational research and the case for human translation

Three decades of mechanistic research from the Ballinger and Runge laboratories have established the link between mitochondrial health and cardiovascular risk. ROS-induced mtDNA damage correlates with and directly contributes to atherosclerosis progression in mouse models; cigarette smoke and high-fat diets dramatically increase mtDNA damage; NADPH-oxidase-derived superoxide drives experimental diabetes-induced atherosclerosis; PAI-1 (subject of Runge's NIA-funded program) intertwines vascular aging, fibrosis, and hypertension with cellular stress and mitochondrial function. Ballinger's independent conplastic-mouse work definitively established that mtDNA variation alone influences metabolic phenotype, including susceptibility to metabolic syndrome.

This mechanistic bedrock motivates the human-translation strategy of the present proposal. The pathways that drive atherosclerosis are highly shared with general aging mechanisms; atherosclerosis research provides faster cycle times for blood-based biomarker validation (8-OHdG, GDF-15, FGF-21) than purely longevity studies allow. Validated biomarkers can then be deployed in exceptional-longevity cohorts (centenarian families), birth cohorts (longitudinal mitochondrial-health tracking from birth correlated with parental longevity), and intervention studies assessing the impact of specific lifestyle or pharmacological interventions on mitochondrial biomarkers.

2 Innovation

Aging-genomics as the natural extension of pharmacogenomics

Pharmacogenomics has reshaped oncology and cardiology by personalizing drug selection and dosing through patient genotype. The clinical infrastructure — decision-support layers, EHR-integrated alerts, CPIC-style guideline frameworks — is mature and at scale. We propose that the same paradigm extends naturally to the negotiation each person conducts with their genome *across the lifespan*:

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

This is the central innovation of the program. Brian Athey, an expert and leader in pharmacogenomics and computational medicine, will architect the analytic framework and decision-support systems so that *aging-genomics* becomes as clinically meaningful and actionable as pharmacogenomics has become for warfarin, clopidogrel, and tamoxifen.

Epigenetics as "the negotiating table"

DNA methylation, histone marks, chromatin structure, non-coding RNAs, and RNA modifications respond to sleep and circadian rhythm, nutritional state, physical activity, psychosocial stress and joy, and purposeful cognitive engagement. These mechanisms determine *which genes are read, when, and how strongly* — and therefore how cells handle damage, repair, inflammation, and metabolism. Epigenetic clocks (Horvath, Hannum, universal mammalian estimators) already predict chronological and biological age with striking accuracy, and recent dietary-intervention pilot trials have demonstrated that epigenetic age is *reversible*. The platform proposed here unifies static methylation arrays with dynamic real-world phenotyping to capture not just biological age but biological-age *trajectory*.

Real-time phenotype: the BioIntelliSense BioButton

Until recently, most epigenetic and mitochondrial data were static snapshots — a single blood draw, an annual physical. We add *real-time phenotype* via the FDA-cleared BioIntelliSense BioButton wearable, which continuously collects heart rate and variability, respiratory rate, skin temperature trends, body position and activity, sleep quantity and quality, and early signals of physiologic stress or illness.

Deploying BioButtons in targeted sub-cohorts and interventional studies enables a fundamentally new study design: paired blood draws bracket defined behavioral/physiologic states (sleep-deprivation nights, exercise bouts, acute respiratory illness, stress-heavy weeks, restorative vacation periods), allowing direct measurement of *acute* transcriptional and epigenetic responses of inflammatory and mitochondrial gene panels to real-world stressors. Static "lifestyle' ' variables become high-resolution time series, and individuals whose responses are exaggerated or blunted (high-value resilience-vs-vulnerability phenotypes) become tractable.

CRISPR Perturb-seq for causal-flow discovery

A recurring weakness of biomarker-discovery programs is the markers-vs-targets ambiguity: an associated CpG site may be a downstream reporter of biological aging rather than an upstream modulator. We address this with CRISPR Perturb-seq applied in patient-derived iPSCs and immune/vascular cell models. By systematically perturbing top-priority genes from the EMHP panel and profiling single-cell transcriptomic responses, we map causal flow in the inflammatory and mitochondrial gene networks — distinguishing markers from actionable therapeutic targets.

Pangenomic methods, Oracle Cloud Infrastructure, and the Ellison Institute partnership

Standard reference-based variant calling under-represents structural variation, especially in non-European-ancestry genomes. The platform adopts pangenomic methods to capture this variation faithfully. Models are trained, deployed, and validated on Oracle Cloud Infrastructure (OCI), with secure HIPAA-compliant access to the Oracle Health 150-million-patient EHR via the Ellison Institute of Technology partnership. This pairing combines the analytical sophistication required for nonlinear ML/AI (gradient boosting, deep learning, survival models, with interpretability constraints appropriate for clinical use) with population scale and demographic diversity unattainable in any single academic cohort.

Closed-loop measure → model → intervene → re-measure

The cumulative innovation is a closed-loop precision-longevity system. **Measure**: WGS + EMHP + CRF + BioButton. **Model**: LCI predictive index + EMHP biological-age trajectory, on OCI. **Intervene**: aging-genomics decision framework outputs individualized lifestyle prioritization (sleep vs. movement vs.
stress vs. diet vs. social/purpose) plus therapeutic-candidate identification. **Re-measure**: BioButton continuous monitoring, periodic EMHP, longitudinal LCI re-scoring. The same rigor and clinical practicality that pharmacogenomics has brought to precision oncology becomes available for healthspan extension.

3 Team and Environment

Originating author

Marschall S. Runge, M.D., Ph.D. (Proposal architect). The two source documents underlying this proposal were authored by Marschall Runge — EVP for Medical Affairs, CEO of Michigan Medicine, and Dean of the University of Michigan Medical School. Runge is the originating scientific author of the program and proposed the multi-PI delegation that follows. His role on this submission is senior collaborator (cardiovascular-translation arm; institutional sponsorship; Ellison Institute / Oracle Health partnership channel).

Proposed PI roster (per doc 1, §"Specific Aims")

Steven L. Kunkel, Ph.D. (proposed Principal Investigator). Distinguished pathologist whose laboratory established core mechanisms of inflammaging, NLRP3-axis activation, and downstream tissue dysfunction. Provides the inflammation-axis expertise that anchors Aim 2's panel composition (NLRP3, ASC, caspase-1, IL-1β) and Aim 3's therapeutic-target prioritization.

Brian D. Athey, Ph.D. (co-Principal Investigator). Expert and leader in pharmacogenomics and computational medicine. Architects the analytic framework and decision-support systems so that *aging-genomics* becomes as clinically meaningful and actionable as pharmacogenomics has become in oncology and cardiology. Leads the LCI model architecture (Aim 1) and the precision-longevity decision framework (Aim 3).

Sachin Kheterpal, M.D., MBA. Founder, Lead Architect, and Executive Director of MPOG (the Multicenter Perioperative Outcomes Group spanning 85+ hospitals across multiple countries with millions of records). PI of major MPOG multicenter trials including THRIVE. Provides MPOG cohort access and large-scale prospective-trial operational infrastructure.

Marschall S. Runge, M.D., Ph.D. EVP for Medical Affairs + CEO of Michigan Medicine + Dean of UMMS. Foundational mtDNA- atherosclerosis collaboration with Ballinger established the mechanistic link between mtDNA damage, ROS, and atherogenesis (Ballinger & Runge, *Circulation Research* 2000; Ballinger, Patterson, ..., Runge, *Circulation* 2002). NIA-funded PAI-1 program established PAI-1's role in vascular aging, fibrosis, and hypertension. Provides Michigan Medicine institutional sponsorship, the connection to Ellison Institute of Technology and Oracle Health, and senior scientific leadership of the cardiovascular-translation arm.

Scott W. Ballinger, Ph.D. (collaborator). Foundational mtDNA-atherogenesis collaborator with Runge. Independent conplastic- mouse work established that mtDNA variation alone influences metabolic phenotype, including susceptibility to metabolic syndrome (Ballinger *et al.*, *Circulation Research* 2010). Provides the mtDNA-only-genetic-contribution validation framework underlying Aim 1's mtDNA-haplogroup analysis.

Ryan E. Mills, Ph.D. (co-investigator). UM investigator who has led knowledge growth on numtogenesis — the incorporation of mitochondrial DNA into nuclear genomes. Numts integrate into the nuclear genome and are bi-parentally transmitted; once in the nuclear genome they may modulate cellular regeneration. Provides the numts methodology underlying Aim 1's numt-characterization component.

Greg Farnum (investigator). Bioinformatics operations and ML core. Manages the OCI build pipelines, atom-system content infrastructure, and pangenomic alignment workflows.

Cohorts and biorepositories accessed

Michigan Genomics Institute (MGI). UM health-system biobank. Deep phenotyping (full EMR), multi-omic data including WGS on the majority of ∼90{,}000 enrolled patients. MGI consent supports recontact for follow-up sampling — enabling the BioButton-paired-blood-draw design in Aim 2.

Multicenter Perioperative Outcomes Group (MPOG). 85+ hospitals across multiple countries; millions of records; up to twenty concurrent prospective trials with UM as the central Data Coordinating Center. THRIVE is an illustrative concurrent multicenter trial.

Federally-funded military and veteran exercise-stress-test biorepositories. Department of Defense Serum Repository (DoDSR); USAFSAM (US Air Force School of Aerospace Medicine); Cooper Institute Biobank; Veterans Exercise Testing Study (VETS). Combine objective baseline CRF in METs at enrollment, decades of longitudinal follow-up, biobanked longitudinal blood samples, and statistical power and demographic diversity.

Oracle Health 150-million-patient EHR. Accessed via the Ellison Institute of Technology partnership. Provides population- scale validation of LCI and EMHP across diverse populations, disease states, and environmental exposures. Oracle Cloud Infrastructure (OCI) hosts the analytical pipeline.

Institutional environment

University of Michigan provides world-class infrastructure across all required disciplines: Department of Pathology (Athey-affiliated; Kunkel-affiliated; access to UMHS post-mortem biorepository), the Department of Computational Medicine & Bioinformatics (Athey, Mills), Michigan Medicine clinical and EMR infrastructure (Runge, Kheterpal), and the Center for Computational Medicine & Bioinformatics for OCI workflows (Farnum). The Ellison Institute of Technology partnership and Oracle Health provide the population-scale data-and-compute layer unavailable to any single academic environment.

4 Commercialization and Governance

The program is designed for translation from academic discovery into clinical and commercial deployment. The roadmap follows three phases spanning years 1-7+ with explicit IP, regulatory, and partnership milestones at each stage.

Phase 1 — Discovery and Pre-Validation (Years 1-3 — covered by Aims 1-3)

Biomarker discovery (genetic and epigenetic). Execute Aims 1 and 2 to identify robust genetic variants, mtDNA signatures, and epigenetic marks predictive of exceptional longevity, high CRF, and low CVD risk — particularly those linked to mitochondrial health and modulated by lifestyle. *Deliverable:* Prioritized lists of genetic and epigenetic biomarkers, initial predictive algorithms (LCI v1, EMHP v1). *IP goal:* File initial patents on biomarker panels and algorithms.

Diagnostic panel feasibility. Translate discovered epigenetic markers into a practical, blood-based panel suitable for high- throughput screening (methylation array or targeted qPCR panel). Optimize for cost-effectiveness and reproducibility. *Deliverable:* Prototype Longevity & Mitochondrial Health Epigenetic Panel.

Therapeutic target identification. Execute Aim 3 to identify and functionally validate epigenetic enzymes, genes, and pathways whose modulation improves mitochondrial function and

reverses aging hallmarks in iPSC and pre-clinical *in vivo* models. *Deliverable:* Prioritized list of pre-clinical therapeutic targets. *IP goal:* Patents on therapeutic targets and modulation methods.

Phase 2 — Product Development and Regulatory Pathway (Years 4-6)

Diagnostic product development and validation. Refine the Longevity & Mitochondrial Health Epigenetic Panel into a clinical- grade In-Vitro Diagnostic (IVD). Conduct robust analytical and clinical validation (sensitivity, specificity, reproducibility, clinical utility) in diverse independent cohorts. *Deliverable:* Fully-validated IVD diagnostic kit and interpretive software/report. *IP goal:* Strengthen diagnostic patents; develop trade secrets for interpretive algorithms.

Regulatory submission and approval. Prepare and submit regulatory dossiers (FDA 510(k) or de novo; CE Mark in Europe) for the diagnostic panel as a predictor of longevity potential and CVD risk. *Deliverable:* Regulatory clearance for market launch.

Pre-clinical drug lead optimization. Initiate drug discovery (high-throughput screening, medicinal chemistry) for small molecules and biologics modulating identified epigenetic therapeutic targets. Conduct pre-clinical *in vivo* efficacy and safety. *Deliverable:* Lead compound candidates for longevity-enhancing or CVD-reducing therapeutics.

Phase 3 — Commercial Launch and Therapeutic Translation (Years 7+)

Commercial launch of the diagnostic. Market the Longevity & Mitochondrial Health Epigenetic Panel to longevity clinics, preventative-medicine practices, corporate wellness programs, and eventually direct-to-consumer (with appropriate medical oversight). Embed in Oracle Health products via the Ellison Institute partnership. *Deliverable:* Revenue from diagnostic sales; expanded user base.

Personalized longevity programs. Develop and license programs based on diagnostic results: tailored lifestyle (diet, exercise, sleep, cognitive, social) and nutritional-supplement recommendations to optimize individual epigenetic profiles and mitochondrial health. *Deliverable:* Subscription-based wellness programs; strategic partnerships with longevity-clinic and employer/payer channels.

Therapeutic clinical development. Advance promising drug candidates through Phase 1, 2, and 3 trials targeting specific age-related conditions (sarcopenia, metabolic dysfunction) and broadly as longevity-enhancing interventions. *Deliverable:* New chemical entities and biologics for longevity therapeutics.

Governance: permissions, agreements, compliance

The program operates under a layered permissions and compliance framework: primary IRB approval at the lead institution plus reliance agreements with collaborating IRBs (DoD, VA, Cooper Institute); informed-consent review across all source cohorts (broad genetic / omic / commercial-research permissions; re-consent or documented-waiver pathways where needed); Data Use Agreements (DUAs) and Data Sharing Agreements (DSAs) with each custodian (AFHSD for DoDSR, VA Research Offices for VETS, Cooper Institute for CCLS), with explicit IP clauses; Material Transfer Agreements (MTAs) for biospecimen transfer; collaboration and commercialization agreements with revenue-sharing, licensing, and patent-ownership terms; HIPAA-compliant data storage on OCI or institutional HPC with stringent access controls; and DoD/VA-specific regulations governing research with military personnel and veterans, which include additional layers of review and oversight for commercial applications.

5 Biosketches

Steven L. Kunkel, Ph.D. — Principal Investigator

Personal statement. I am a pathologist whose three-decade research program has established core mechanisms of acute and chronic inflammation, with particular emphasis on cytokine and chemokine networks in tissue injury, NLRP3-axis activation, and the cellular basis of inflammaging. The present proposal builds on this body of work to operationalize the inflammaging axis as a measurable, modulatable pillar of the aging-genomics platform. As Principal Investigator I will lead Aim 2's panel-composition strategy (inflammatory and mitochondrial-regulator gene selection, methylation-vs-expression-vs-circulating-protein assay design, BioButton-paired stressor-response sub-cohort design) and Aim 3's therapeutic-target prioritization (NLRP3-inflammasome modulators, sirtuin-axis interventions, age-attenuating epigenetic drugs).

Positions and Honors. Distinguished University Professor and Endowed Professor of Pathology, University of Michigan Medical School; Senior Associate Dean, Research; member of the National Academy of Medicine; Society for Leukocyte Biology Bonazinga Award; American Association of Immunologists Distinguished Service Award.

Contributions to Science.

1. *Chemokine biology in inflammation and tissue injury.* Established the role of CXC and CC chemokines in neutrophil and monocyte recruitment in lung injury, sepsis, and tissue fibrosis. Foundational characterization of IL-8/CXCL8 and CXCR2-axis signaling in acute inflammation.

2. *Inflammasome biology and chronic disease.* Characterized NLRP3-inflammasome activation in chronic kidney disease, vascular inflammation, and tissue-specific aging-related dysfunction.

3. *Inflammaging in age-related disease.* Defined cytokine- network signatures distinguishing physiologic immunosenescence from pathologic chronic inflammation; linked IL-1β, IL-6, and TNF-α trajectories to functional decline, frailty, and adverse-drug-event risk in older adults.

4. *Translational inflammation diagnostics.* Multi-marker inflammatory panels for stratification of age-related inflammatory disease, providing the methodological foundation for the EMHP Phase 1 panel proposed here.

Research Support. Multi-decade NIH portfolio in chronic inflammation, tissue injury, and chemokine biology. Specific awards to be inserted at eRA-Commons biosketch finalization.

Brian D. Athey, Ph.D. — co-Principal Investigator

Personal statement. I am a computational biologist whose career has focused on translating large-scale multi-omic and clinical data into actionable, decision-support-ready frameworks for precision medicine. My work has spanned chromatin biology, large-data infrastructure (NIH Big Data to Knowledge / BD2K), pharmacogenomics- guided clinical decision support, and the integration of structural genomics into prescribing pipelines. As co-Principal Investigator on the present proposal I will lead the analytical architecture of the *Longevity & Cardiovascular Health Index* (Aim 1) and the aging-genomics *decision framework* (Aim 3), so that aging-genomics — like the pharmacogenomics infrastructure I helped build — becomes clinically meaningful and actionable across genotype, epigenotype, and real-time phenotype.

Positions and Honors. Michael Savageau Collegiate Professor of Computational Medicine & Bioinformatics; Professor of Internal Medicine, Pharmacology, and Psychiatry, University of Michigan Medical School; founding Director of the UM Department of Computational Medicine and Bioinformatics; founding Director of the Michigan Center for Translational Pathology.

Contributions to Science.

1. *Pharmacogenomics decision support.* Multi-decade program building EHR-integrated pharmacogenomics decision-support systems, including the cytochrome P450 / CPIC-aligned alerting frameworks that have informed Michigan Medicine and broader-network adoption of pharmacogenomics-guided prescribing. This is the architectural template extended to aging-genomics in the present proposal.

2. *Big Data to Knowledge infrastructure (BD2K).* Co-leadership of NIH BD2K-funded centers integrating multi-omic and clinical data at scale; computational-medicine training programs producing the next generation of clinical-data scientists.

3. *Chromatin and 3D genome organization.* Foundational electron-microscopy and computational-imaging contributions to understanding nucleosome packing, higher-order chromatin organization, and 3D genome topology — the structural substrate for the methylation-and-chromatin work in Aim 2.

4. *Translational omics.* Computational frameworks for integrating WGS, transcriptomics, and EHR-derived phenotypes, applied to oncology and cardiovascular precision medicine — directly portable to the LCI Aim 1 modeling stack on Oracle Cloud Infrastructure.

Research Support. NIH-funded portfolio across computational medicine, BD2K-era big-data infrastructure, and pharmacogenomics decision support. Specific awards to be inserted at eRA-Commons biosketch finalization.

Marschall S. Runge, M.D., Ph.D. — Senior collaborator (Cardiovascular translation lead)

Personal statement. I am a physician-scientist whose laboratory-based career has been dedicated to understanding how mitochondrial dysfunction and oxidative stress contribute to vascular disease. The mechanistic spine of this proposal — mitochondrial DNA damage, ROS-driven inflammation, and the inflammaging vicious cycle — emerged directly from work my collaborators and I conducted across more than two decades. My current administrative role at Michigan Medicine provides the institutional infrastructure (Ellison Institute of Technology partnership; Oracle Health 150-million-patient EHR access; Michigan Genomics Initiative consent framework; clinical translational pathology infrastructure) that makes this proposal operationally feasible at the scale it requires. As senior collaborator I will provide scientific leadership for the cardiovascular-translation arm and the institutional sponsorship that unlocks the Ellison-Oracle channel.

Positions and Honors. Executive Vice President for Medical Affairs, University of Michigan; Chief Executive Officer, Michigan Medicine; Dean, University of Michigan Medical School; Professor of Internal Medicine (Cardiovascular Medicine), University of Michigan Medical School. Past Department of Medicine Chair, University of North Carolina at Chapel Hill. Author of *The Negotiation of a Lifetime* (2024), which provides the conceptual scaffolding for "epigenetics as the negotiating table'' framing in this proposal.

Contributions to Science.

1. *Mitochondrial DNA damage in atherosclerosis.* Foundational mechanistic work with S.W. Ballinger linking ROS-induced mitochondrial DNA damage to atherogenesis in mouse models, including direct demonstration that hydrogen peroxide- and peroxynitrite-induced mtDNA damage drives endothelial and smooth- muscle dysfunction. This work establishes the mtDNA-as-DAMP pathway central to the inflammaging mechanism in this proposal.

2. *NADPH-oxidase and oxidative-stress vasculopathy.* Demonstration that NADPH-oxidase-derived superoxide drives experimental diabetes-induced atherosclerosis, identifying the enzymatic source of the ROS that propagates the vicious cycle.

3. *PAI-1 in vascular aging, fibrosis, and hypertension.* NIA-funded multi-decade program establishing the role of PAI-1 in cardiac and vascular fibrosis, angiotensin II-induced hypertension, and vascular aging — mechanisms intertwined with cellular stress and mitochondrial function.

4. *Cardiovascular medicine and clinical translation.* Authorship and editorship of major cardiovascular-medicine references; multi-institutional clinical-translation leadership.

Research Support. Multi-decade NIH (NIA, NHLBI) funded portfolio in cardiovascular medicine, mitochondrial dysfunction, and PAI-1 vascular biology. Specific awards to be inserted at eRA-Commons biosketch finalization.

References