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

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Candidate Vision — HHMI Investigator

HHMI funds people, not projects. This statement positions the proposed candidate (Brian D. Athey, Ph.D., Michael Savageau Collegiate Professor of Computational Medicine & Bioinformatics, University of Michigan) and the long-horizon scientific vision that would benefit from HHMI Investigator support.

The candidate

Brian D. Athey is a computational biologist whose career has spanned chromatin biology, large-data infrastructure (NIH BD2K), and pharmacogenomics-guided clinical decision support. He founded the UM Department of Computational Medicine and Bioinformatics, leads the Michigan Center for Translational Pathology, and has architected the EHR-integrated pharmacogenomics decision-support framework that informed Michigan Medicine's institutional adoption of CYP450-guided prescribing. His work sits at the intersection of computational methodology, clinical-deployment infrastructure, and translational medicine — a combination uniquely positioned to deliver the next paradigm extension of precision medicine.

The 10-year vision

Pharmacogenomics has reshaped oncology and cardiology by turning genotype into prescribing decisions through EHR-integrated decision support, CPIC-style guidelines, and FDA companion-diagnostic regulation. The same paradigm extends naturally to healthspan: where pharmacogenomics asks *which drug 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?*

The candidate's 10-year vision is to architect, deploy, and validate the aging-genomics infrastructure — the predictive index (LCI), the biological-age-trajectory diagnostic (EMHP), the decision-support layer linking individual data to lifestyle and therapeutic recommendations — such that aging-genomics becomes as clinically meaningful and actionable as pharmacogenomics has become for warfarin, clopidogrel, and tamoxifen. This is not invention; it is the disciplined translation of mature mechanistic biology (mitochondrial-inflammaging axis from three decades of Ballinger-Runge work) and converged technical capability (long-read sequencing, continuous physiologic wearables, CRISPR Perturb-seq, pangenomic alignment, large-EHR validation) into deployed clinical infrastructure.

Why HHMI Investigator support specifically

HHMI's investigator-centric model is essential for this vision because the work crosses traditional grant-mechanism boundaries. The full arc — methodological development, multicenter cohort assembly, IVD diagnostic validation, decision-support deployment, regulatory engagement, commercial channel development — doesn't fit any single NIH mechanism on a single timeline. HHMI Investigator support provides the long-horizon flexibility to pursue the arc as a single coherent program rather than fragmenting it across mechanism-specific sub-grants. The candidate has already demonstrated this kind of sustained-program-leadership in the BD2K era; HHMI support extends the model into aging-genomics.

Collaboration and program leadership

The candidate's program operates through deep collaboration with Marschall S. Runge, M.D., Ph.D. (proposal architect; senior cardiovascular-translation lead; Michigan Medicine institutional sponsor; Ellison Institute / Oracle Health partnership channel), Steven L. Kunkel, Ph.D. (NLRP3 inflammasome and inflammaging biology lead), Sachin Kheterpal, M.D., MBA (MPOG multicenter-clinical-trial operations), Scott W. Ballinger, Ph.D. (mtDNA genetics; conplastic- mouse foundation), and Ryan E. Mills, Ph.D. (numts methodology, pangenome). The HHMI Investigator structure does not displace these collaborations; it consolidates the analytic-architecture and decision-support workstream under sustained candidate-led leadership while the broader program continues across all six investigators.

Track record relevance

The candidate's track record demonstrates the three capabilities the proposed vision requires. **Methodological depth**: founding-era chromatin and 3D-genome work establishes the structural-biology substrate for the methylation and chromatin-profiling components of EMHP. **Large-data infrastructure**: BD2K-era leadership demonstrates the ability to build, sustain, and scale multi-omic + clinical-data integrations of the kind aging-genomics requires. **Translational deployment**: pharmacogenomics decision support demonstrates the ability to take methodology to clinical impact — the durable test of any precision-medicine paradigm extension.

Specific Aims

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. Mechanistically, the mitochondrial-inflammaging axis (NLRP3 inflammasome activation by mtDNA damage and oxidized cardiolipin) drives accelerated aging, and lifestyle factors modulate this axis through epigenetic regulation. Maternal mtDNA inheritance and numts (Mills) layer a largely-overlooked genetic dimension onto this story.

Aim 1 — Longevity & Cardiovascular Health Index (LCI). Integrate nuclear and mitochondrial WGS, cardiorespiratory fitness (METs), standard clinical risk factors, and real-time BioIntelliSense BioButton physiologic data into a clinically-deployable predictive index. Train across MGI ($\sim$90{,}000 UM patients), MPOG (Kheterpal, millions of records), and federal exercise-stress-test cohorts (DoDSR, USAFSAM, Cooper, VETS); validate against Oracle Health 150 M EHR via Ellison Institute partnership.

Aim 2 — Epigenetic & Mitochondrial Health Panel (EMHP). Build a blood-based panel calibrated against BioButton-captured behavioral/physiologic states. Phase 1 = small inflammatory and mitochondrial-regulator gene set (NLRP3, sirtuins, GDF-15, FGF-21, etc.) with paired methylation + expression + circulating-protein assays. Phase 2 = genome-wide methylation (EPIC arrays $\rightarrow$ RRBS/WGBS where justified) and CRISPR Perturb-seq for causal-flow discovery in patient-derived iPSCs.

Aim 3 — Targets, Therapies, and Precision Longevity Programs. Pathway analysis across all data layers prioritizes epigenetic enzymes (DNMTs, TETs, HDACs, sirtuins) and mitochondrial regulators for therapeutic modulation. An aging-genomics decision framework (Athey) outputs individualized lifestyle prioritization and therapeutic-candidate identification, designed for Oracle Health clinical workflows and EIT-affiliated longevity clinics.

Closed-loop deliverable: measure $\rightarrow$ model $\rightarrow$ intervene $\rightarrow$ re-measure, with the same rigor that pharmacogenomics has brought to oncology and cardiology.

1 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.

2 Biosketches

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.

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.

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