Aging-Genomics: From Pharmacogenomics to Healthspan

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Project Summary / Abstract

Aging is increasingly understood as a dynamic, modifiable process rather than an inevitable decline. Behavioral, environmental, and socioeconomic forces shape *how long* and *how well* we live at least as powerfully as the genetic blueprint we inherit. Yet today's longevity landscape is saturated with expensive, unproven, and often outrageous "cures'' for aging — influencer protocols, supplement stacks, and biological reductionism dressed up as science. Distinguishing real scientific signal from this hype demands rigorous, evidence-based analytical tools, grounded in mechanism and validated in human cohorts.

This proposal extends the pharmacogenomics paradigm into "**aging-genomics**.'' Where 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?* The mechanistic premise is the mitochondrial-inflammaging vicious cycle: dysfunctional mitochondria release damage-associated molecular patterns (mtDNA, oxidized cardiolipin) and reactive oxygen species that activate the NLRP3 inflammasome, NF-κB, and chronic inflammatory cascades, which in turn drive cellular senescence, tissue damage, and accelerated biological aging. Conversely, beneficial behaviors — physical activity, optimal nutrition, restorative sleep, social engagement — drive a virtuous cycle of mitochondrial biogenesis, enhanced mtDNA repair, and dampened inflammation. A largely-overlooked dimension is the *maternal* inheritance of mtDNA, layered with *numts* (nuclear mitochondrial insertions, a process led by Ryan Mills) which are bi-parentally transmitted and may modulate cellular regeneration.

We propose a three-aim program to translate this mechanism into a clinically deployable readout. **Aim 1** develops the *Longevity & Cardiovascular Health Index (LCI)* integrating nuclear and mitochondrial whole-genome sequencing, cardiorespiratory fitness (CRF, METs — one of the strongest predictors of all-cause mortality), standard clinical risk factors, and continuous real-time physiology from the FDA-cleared BioIntelliSense BioButton wearable. The model trains on the

Michigan Genomics Institute (MGI, ∼90{,}000 recontactable patients) and the Multicenter Perioperative Outcomes Group (MPOG, millions of records across 85+ hospitals; founded by Sachin Kheterpal at UM), validates against military exercise-stress-test biorepositories (DoDSR, USAFSAM, Cooper Institute, VETS) and at scale against the Oracle Health 150-million-patient EHR via the Ellison Institute partnership. **Aim 2** develops the *Epigenetic & Mitochondrial Health Panel (EMHP)* — a clinically-practical blood-based panel of inflammatory and mitochondrial biomarkers (DNA methylation at key CpGs, targeted expression, circulating metabolites) calibrated against BioButton-captured behavioral and physiologic states. Phase 2 expands via genome-wide methylation and CRISPR Perturb-seq for causal-flow discovery in patient-derived iPSCs. **Aim 3** translates the platform into therapeutic targets and Precision Longevity Programs — individualized prioritization of lifestyle levers and candidate therapeutics with the same rigor that pharmacogenomics has brought to oncology and cardiology.

The deliverables are a CLIA/IVD diagnostic, an Oracle Cloud Infrastructure-hosted decision-support layer, and a pre-clinical drug target pipeline. The work is built on three decades of foundational mtDNA-atherosclerosis collaboration between the Ballinger and Runge laboratories, leverages UM's unique cohort assets, and is designed for clinical and commercial deployment through Oracle Health and Ellison Institute of Technology channels.

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 (∼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 → 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 → model → intervene → re-measure, with the same rigor that pharmacogenomics has brought to oncology and cardiology.

1 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.

References