Training Program in Aging-Genomics

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Project Summary / Abstract — Training Program in Aging-Genomics

This T32 institutional training grant will prepare a new generation of predoctoral and postdoctoral scientists at the intersection of inflammation biology, computational genomics, mitochondrial biology, and clinical decision support — the multidisciplinary skill set that the emerging field of *aging-genomics* (the natural extension of pharmacogenomics into healthspan-relevant interventions) demands at scale. The program is hosted at the University of Michigan and leverages institutional infrastructure spanning the Department of Pathology, the Department of Computational Medicine & Bioinformatics, the Michigan Genomics Initiative biobank, the Multicenter Perioperative Outcomes Group (MPOG), Michigan Medicine clinical operations, and the Ellison Institute / Oracle Health partnership.

The program supports four post-doctoral fellow lines and two predoctoral student lines, each co-mentored across the inflammation axis (Kunkel) and the computational-medicine axis (Athey), with additional specialty mentorship from senior collaborators (Kheterpal on multicenter clinical-trial operations; Mills on structural variation and numts methodology; Ballinger on mtDNA genetics; Runge on cardiovascular translation). Trainees rotate through the Oracle Cloud Infrastructure analytical environment, the wet-lab inflammation panels, the iPSC + CRISPR Perturb-seq screening platform, and the multicenter clinical-trial operations of MPOG.

Specific Aims of the Training Program

1. Recruit, support, and graduate trainees with cross-axis fluency: every trainee develops both wet-lab inflammation / mitochondrial biology skills *and* computational genomics / ML proficiency.

2. Sustain a high-quality training environment via formal courses in computational medicine, structural variation, single-cell genomics, and clinical decision support; quarterly individual development plan reviews; and seminar-series exposure to leaders across aging research, longevity translation, and regulatory affairs.

3. Build a pipeline of K99 / R00 transition awards and industry-research transitions, supporting senior fellows in their next career step at academic, biotech, and regulated-diagnostics companies.

4. Embed diversity recruitment as a structural program element through partnerships with the UM Rackham Diversity Recruitment Program, the Center for Computational Medicine Diversity Pipeline, and active outreach to MSI / HBCU institutions through Michigan Medicine.

Why this program is needed now

Aging-genomics is at the same alignment point that pharmacogenomics reached two decades ago: a tractable mechanistic biology, a clinical-decision-support infrastructure ready to extend, and a regulatory pathway converging on combined diagnostics. The field's limit is no longer technological — it is the supply of scientists who can bridge the wet-lab inflammation / mitochondrial biology axis, the computational-genomics-on-cloud-infrastructure axis, the clinical-decision-support and regulatory-affairs axis, and the multicenter clinical-trial operations axis. No existing training program covers this combination. This program does.

Public health relevance

The aging-related disease burden — cardiovascular disease, metabolic syndrome, frailty, polypharmacy adverse drug events, neurodegeneration — represents the leading driver of US healthcare costs and accounts for the majority of lost healthy life years. Healthspan extension delivered through evidence-based aging-genomics diagnostics and decision support, validated against rigorous clinical-translation infrastructure, is positioned to deliver substantial population health benefit. Training the next generation of aging-genomics scientists is the durable infrastructure investment that makes that translation possible.

Research Training Plan

The program is intentionally structured to produce a generation of trainees fluent at the intersection of inflammation biology, computational genomics, mitochondrial biology, and clinical decision support — the multidisciplinary skill set that aging-genomics will demand at scale.

Trainee positions

Four post-doctoral fellows (full-effort across the project period):

1. *LCI fellow* (Athey + Mills co-mentorship). Develops the Aim 1 LCI predictive model on OCI; pangenomic alignment; interpretable nonlinear ML.

2. *EMHP small-panel fellow* (Kunkel + Athey co-mentorship). Develops the Aim 2 Phase 1 inflammatory + mitochondrial-regulator panel and the BioButton-paired-blood-draw experimental design.

3. *Perturb-seq fellow* (Mills + Kunkel co-mentorship). Runs the CRISPR Perturb-seq screens in patient-derived iPSCs; causal-flow analysis distinguishing markers from actionable therapeutic targets.

4. *Therapeutic-target fellow* (Kunkel + Athey co-mentorship). Aim 3 network analysis, target prioritization, and small-molecule / biologic screen feasibility.

Two predoctoral students: one in computational medicine (Athey lab) and one in pathology (Kunkel lab), recruited through the relevant UM PhD programs.

Mentorship structure

Each trainee is *co-mentored* across the inflammation and computational axes. This is by design — the proposal's intellectual contribution requires fluency in both, and the co-mentorship pair ensures the trainee develops in both. The senior collaborators (Kheterpal, Runge, Ballinger) provide additional disciplinary mentorship in their respective domains as the trainee's project requires.

Skill development

Computational and analytical. OCI / Oracle Cloud Infrastructure proficiency (data engineering, ML pipelines, model deployment); pangenomic alignment and structural-variation calling; single-cell RNA-seq and Perturb-seq analysis; survival-analysis methods and interpretability-constrained ML.

Wet-lab and clinical. Inflammasome and inflammatory-cytokine assay execution; iPSC culture and CRISPR perturbation; multiplexed protein assays; phlebotomy-coordinated study design with the BioButton-paired sub-cohorts.

Translational and operational. IRB protocol design and amendment; multicenter consortium coordination through MPOG; data-governance and HIPAA-compliant workflow design; commercial- research and IP awareness.

Career-development infrastructure

Career milestones are tracked via the Michigan Medicine Office of Research trainee dashboard with quarterly individual development plan (IDP) reviews. Trainees participate in the UM Postdoctoral Association programming, the Computational Medicine & Bioinformatics training-program seminars, and the Department of Pathology trainee-development cohort. Senior fellows are supported in preparing K99 / R00 transition awards or industry-research transitions.

Diversity and inclusion

Recruitment across the four post-doctoral and two predoctoral lines prioritizes diverse candidate pools through the UM Rackham PhD Diversity Recruitment program, the Center for Computational Medicine Diversity Pipeline, and active outreach to MSI / HBCU institutions through Michigan Medicine partnerships. Quarterly DEI metrics are reviewed by the Steering Committee.

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

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